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Short communication

Ion chromatography of methanesulfonic acid in pharmaceuticals ☆

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1. Introduction

Methanesulfonic acid (MSA) is used in the synthesis of SQ-26771, BMS-184718-01 and BMS-180680-01. SQ-26771 and BMS-184718-01 are drug intermediates and BMS-180680-01 is a final drug substance. SQ-26771 is an intermediate in the synthesis of Aztreonam. Aztreonam is a monobactam-type of beta-lactam antibiotic, which is used for managing gram-negative infections in patients [1]. It has been shown that Aztreonam can be used to treat urinary tract infections without having any adverse effect on renal function [2]. BMS-184718-01 is the penultimate compound in the synthesis of BMS-180448-01. BMS-180448-01 is a new potassium channel activator drug candidate [3]. It is indicated in the treatment of cardiac ischemia (angina) and post-myocardial infarction. BMS-180680-01 is a new antibiotic being developed at Bristol-Myers Squibb.

The monitoring of residual MSA in bulk drug substances or intermediates is necessary to prove its absence. Possible toxicity of MSA is an important concern above certain levels. Both organic and inorganic impurities are monitored at 0.1% levels for this purpose. Classically, GC has been used for the analysis of sulfonic acids [4–22]. These methods involve conversion of sulfonic acids into volatile derivatives with acids [4–6], alkali fusion [7–9], sulfonyl chlorination [10–12] or fluorination [13], sulfonyl esterification [10,14–18], trimethylsilyation [19], thio formation [20,21] and formation of sulfonamides [22]. However, the usefulness of these methods is limited by time-consuming derivatization processes.

Ion chromatography (IC) has been used for the analysis of MSA in environmental samples [23,24]. Saigne et al. [23] reported the analysis of MSA ions present in Antarctic ice. They analyzed MSA using an AS4 column with a sodium hydroxide mobile phase. The retention time was 5 min. Cheam [24] reported a method for the analysis of MSA in precipitation samples using ion chromatography. The column used was a polymeric anion exchange column (HPIC.AS5A) and the mobile phase was water–sodium hydroxide.

There are no reports in the literature of the analysis of MSA in pharmaceuticals using ion chromatography. In this paper, the use of IC in the analysis of trace levels of MSA in SQ-26771, BMS-184718-01 and BMS-180680-01 is presented. Fig. 1 shows the structure of SQ-26771, BMS-184718-01 and BMS-180680-01. The method is simple and based on direct injection of SQ-26771, BMS-184718-01 and BMS-180680-01 solutions into the ion chromatography system. The separations were achieved using a 10 μm PRP-X100 column and conductivity detection.

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2. Materials and methods

2.1. Reagents

SQ-26771, BMS-184718-01 and BMS-180680-01 were obtained from the Chemical Process Technology Group, Bristol-Myers Squibb, New Brunswick, NJ. Sodium hydroxide and methanesulfonic acid were purchased from Aldrich (Milwaukee, WI). HPLC grade acetonitrile (B&J brand) was obtained from Baxter Scientific (Edison, NJ). High purity, Baker-analyzed reagent grade sulfuric acid was obtained from J.T. Baker (Philipsburg, NJ). Certified grade sodium chloride was obtained from Fisher Scientific (Springfield, NJ) and 0.45 μm Nylon-66 filters were obtained from Schleicher and Schuell (Keene, NH).

2.2. Instrumentation

A Dionex ion chromatograph composed of a gradient pump module (GPM), eluent degas module (EDM-II), and pulsed electrochemical detector (PED-1) equipped with conductivity cell, all from Dionex corporation (Sunnyvale, CA), was used. The system was connected to a Thermo Separation Products (Freemont, CA) autosampler (model AS-3500). Data acquisition was performed with a VG multichrom data processor (VG Laboratory Systems, Cheshire, WA).

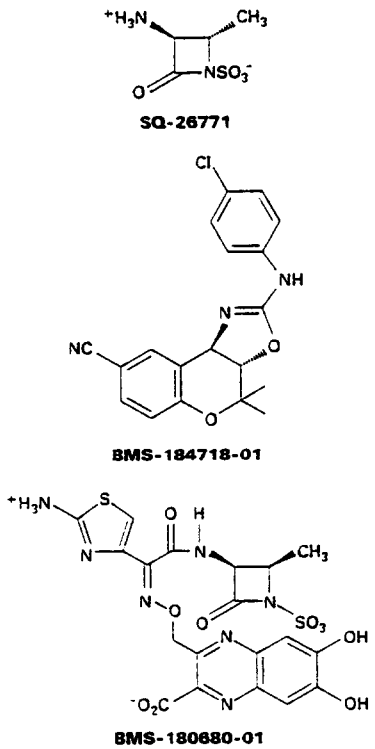

Fig. 1. Structural formulae of compounds studied.

An anion micromembrane suppressor, reagent pump and anion regenerant cartridge were all obtained from Dionex Corporation (Sunnyvale, CA). A 10 μm PRP-X100 column (4.1 mm i.d. × 150 mm) from Hamilton Co., (Reno, NV) was used for separations.

2.3. Preparation of standard MSA solutions

A standard stock solution of MSA was prepared by accurately weighing approximately 100 mg of methanesulfonic acid and dissolving it in 100 ml of the mobile phase (as described in the chromatographic conditions) to give a final concentration of approximately 1 mg ml^{-1}. This was further diluted to give 10, 20, 40 and 100 μg ml^{-1} MSA solutions.

2.4. Preparation of SQ-26771 samples spiked with MSA

A 2 mg ml^{-1} stock solution of SQ-26771 in the mobile phase was prepared (100 mg of SQ-26771 was dissolved in 50 ml of the mobile phase). A 5 ml portion was added to eight different 10 ml volumetric flasks. These solutions were spiked with standard MSA solutions to give spiked samples in the range of 0.1–2.0% w/w of MSA.

2.5. Preparation of BMS-184718-01 samples spiked with MSA

A 2 mg ml^{-1} stock solution of BMS 184718-01 was prepared in acetonitrile. A 5 ml portion was transferred to ten different 10 ml volumetric flasks. These solutions were spiked with MSA standard solutions to give spiked samples in the range of 0.03–2.0% w/w of MSA.

2.6. Preparation of BMS-180680-01 samples spiked with MSA

These were prepared in the same way as samples of BMS-184718-01.

2.7. Chromatographic conditions

A 10 μm PRP-X100 (4.1 mm i.d. × 150 mm) Hamilton column was used. The mobile phase was acetonitrile–sodium hydroxide (60 mM) (20:80, v/v). The flow rate was set at

2.0 ml min^{-1}. The column temperature was 30°C. An anion micromembrane suppressor was used before the detector to suppress the eluent conductivity. The regenerant solution was 50 mN sulfuric acid and it was changed every day. The injection volume was 20 µl.

2.8. System suitability test

A system suitability test was performed with each analysis by injecting a mixture of chloride and methanesulfonic acid. The elution order was MSA followed by chloride. A resolution of 1.7 or greater between MSA and chloride was indicative of proper system performance.

3. Results and discussion

In SQ-26771, trace levels of chloride may also be found with MSA, as another impurity. For the assay development, it was necessary to resolve MSA from both chloride and SQ-26771. Initially, an IC Pak column from Waters Associates (Milford, MA, USA) was investigated for the separation of MSA and SQ-26771. The mobile phase used was 10 mM NaOH (flow rate = 1.0 ml min^{-1}). By decreasing the NaOH concentration from 10 to 5 mM, the retention time of MSA increased from 3.9 to 6.0 min. SQ-26771 eluted in 35 min. The flow rate was increased to 2.0 ml min^{-1} and it was observed that the SQ-26771 retention changed to 16 min. Under all of these conditions, the chloride peak was coeluting with MSA. No further work was done using the IC Pak column.

Based on these observations, the column was changed to PRP-X100. The effects of flow rate (1.0–2.0 ml min^{-1}), ionic concentration (5 mM NaOH to 60 mM NaOH) and organic modifier concentration (5–20% acetonitrile) were studied. It was observed that under the conditions described in Section 2, the separation of MSA from chloride and SQ-26771 can be achieved. In aqueous solutions, methanesulfonic acid ionizes into methanesulfonate and hydronium ions. Under alkaline conditions, methanesulfonate is the species observed chromatographically. The results were reported as percentage methanesulfonic acid, since that was the potential residual impurity in the bulk drug substance or intermediates. Fig. 2 shows the typical chromatogram of methanesulfonate (Rt, 3.0 min), chloride (Rt, 4.8 min) and SQ-26771 (Rt, 33.5 min). The objective of the experiment was to quantify MSA only, and therefore, the data acquisition was programmed only for 10 min for method validation and routine analysis (run time = 60 min).

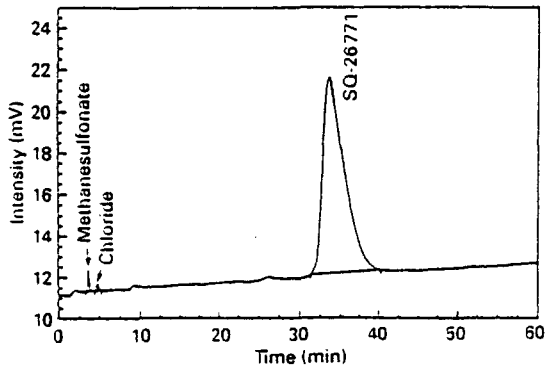

Fig. 2. Full length chromatogram of methanesulfonate, chloride and SQ-26771 on a PRP-X100 column. Other conditions: mobile phase, acetonitrile–60 mM sodium hydroxide (20:80, v/v); detector, conductivity; column temperature, 30°C; flow rate, 2.0 ml min^{-1}.

The limit of detection obtained was as low as 0.3 µg ml^{-1} MSA (corresponding to 0.03% w/w). The anion micromembrane suppressor after the column converted the sodium hydroxide eluant into water, thereby reducing the background conductivity. The reduction in background conductivity helped to enhance the sensitivity. Fig. 3 shows the typical chromatogram of methanesulfonic acid at the limit of detection in the presence of SQ-26771. One of the advantages of the present method is the direct injection of SQ-26771, dissolved in the mobile phase, into the ion chromatograph. This totally eliminates extensive sample cleanup steps normally associated with trace ion assays.

The linearity of the method was studied from 1 to 20 µg ml^{-1} (corresponding to 0.1–2% w/w

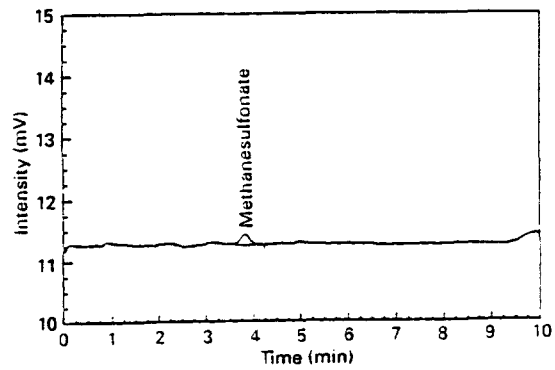

Fig. 3. Typical chromatogram of methanesulfonate at the limit of detection (0.3 µg ml^{-1}) in the presence of SQ-26771 (1 mg ml^{-1}). Other conditions as in Fig. 2.

Table 1
Day-to-day reproducibility for MSA detection in SQ-26771

Batch	Date prepared	Date of analysis	% MSA
16893-700	Day 1	Day 2	0.93 [a]
16893-700	Day 2	Day 2	0.88
16893-700	Day 2	Day 2	0.92
		$\hat{x}$	0.91
		SD	0.027 [b]
		RSD (%)	2.9
16894-706	Day 1	Day 2	0.54
16894-706	Day 1	Day 2	0.50
16894-706	Day 2	Day 2	0.51
		$\hat{x}$	0.52
		SD	0.021
		RSD (%)	4.0

[a] Based on duplicate injections.
[b] $n = 12$.

MSA). The correlation coefficient was found to be >0.999 ($n = 10$). The intercept was 446.8 and the slope was 2828.3. The precision of the method was determined by six individual weighings of SQ-26771 spiked with 0.5% MSA. The precisioin obtained was 0.51 ± 0.016 (RSD = 3.2%). The day-to-day reproducibility was found to be in the range of 2.9–4.0%. Table 1 shows the day-to-day reproducibility of the method.

The recovery and accuracy of the method were determined by spiking a batch of SQ-26771 at various levels with MSA. The recovery of MSA at levels ranging from 0.1 to 2.0% was 98–107%. Table 2 illustrates the recovery and accuracy data.

The method was also applied to MSA determination in BMS-184718-01 and BMS-180680-01. Both BMS-184718-01 and BMS-180680-01 have no conductivity. Therefore, their elution did not cause interference with MSA detection.

Table 2
Recovery of MSA from SQ-26771

Added (%	Found (%) [a]	Recovery (%)
0	NE ($n = 3$)	–
0.100	0.098	98
0.200	0.215	107
0.400	0.407	102
0.800	0.844	105
1.000	1.068	107
1.600	1.644	103
2.000	2.044	102

[a] Based on duplicate injections.

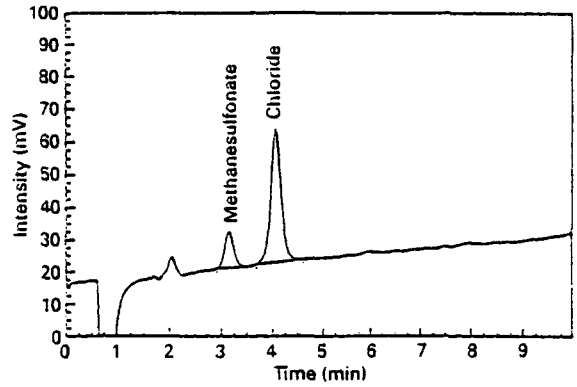

Fig. 4. Typical chromatogram of BMS-184718-01 spiked with 0.1% MSA standard. Other conditions as in Fig. 2.

Fig. 4 shows the typical chromatogram of BMS-184718-01 (Rt = 4.0 min) spiked with 0.1% MSA standard. The peak at 5 min is the chloride peak, which is also found in BMS-184718-01. Fig. 5 shows the typical chromatogram of BMS-180680-01 at 1 mg ml^{-1}.

It can be noted from Figs. 3–5 that the separation conditions used are powerful enough that there are no interferences from other impurities for MSA analysis. These three samples originated from three distinctly different synthetic processes. The precision of the method for MSA in BMS-184718-01 was determined by spiking 1 mg ml^{-1} of BMS-184718-01 with 0.1% MSA. The precision of the method obtained was 0.103 ± 0.002 ($n = 12$, RSD 1.9%). The precision of the method for MSA in BMS-180680-01 was determined by injecting a batch of BMS-180680-01 containing 0.26% MSA eight times. The precision of the method obtained was 0.26 ± 0.012 (RSD 4.6%, $n = 8$). The recovery of the MSA was determined by spiking BMS-184718-01 and BMS-

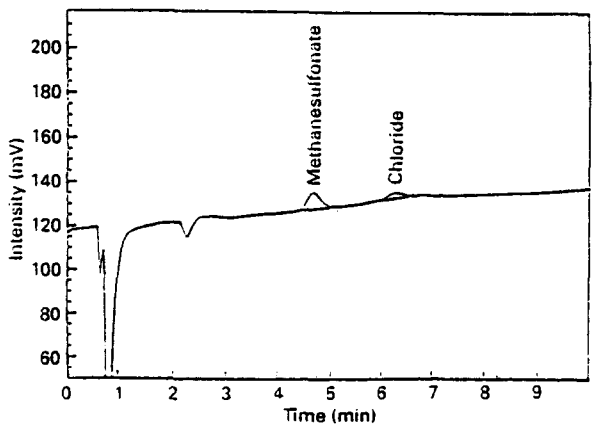

Fig. 5. Typical chromatogram of BMS-180680-01 at 1 mg ml^{-1}. Other conditions as in Fig. 2.

Table 3
Recovery of MSA FROM bms-184718-01

% MSA added	% MSA found [a]	% Recovery
0	NE ($n = 4$)	–
0.101	0.099	98.0
0.202	0.210	104.0
0.403	0.446	110.7
0.504	0.503	99.8
0.605	0.653	107.9
0.806	0.845	104.8
2.016	2.114	104.9

[a] Based on duplicate injections.

Table 4
Recovery of MSA from BMS-180680-01

% MSA added	% MSA found [a]	% Recovery
0	0.276 ($n = 4$)	–
0.099	0.368	98.1
0.198	0.495	98.1
0.396	0.680	101.2
0.495	0.774	100.4
0.594	0.901	103.6
0.693	0.100	103.2
0.792	1.054	98.7
0.990	1.252	98.9

[a] Based on duplicate injections.

180680-01 with 0.1–2.0% of MSA. The recovery obtained was within 110–113% for BMS-184718-01 and 97–104% for BMS-180680-01. Tables 3 and 4 show the accuracy and recovery of the method for MSA determinations in BMS-184718-01 and BMS-180680-01, respectively.

In summary, ion chromatography has been shown to be successful in the analysis of MSA as an impurity in drug substances and their intermediates. The method can also be adopted for the simultaneous determination of chloride as an impurity.

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