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Short communication

Static headspace gas chromatographic method for the determination of low and high boiling residual solvents in Betamethasone valerate

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ABSTRACT

Currently, there are no analytical methods available in the literature that can simultaneously separate and quantitate residual levels of acetone, methylene chloride, *n*-butyl ether and dimethylsulfoxide in Betamethasone valerate active pharmaceutical ingredient (API). This paper describes the development and validation of a simple, efficient, accurate and robust static headspace gas chromatography method for the determination of high and low boiling residual solvents, namely acetone, methylene chloride, *n*-butyl ether and dimethylsulfoxide, in Betamethasone valerate API. This method has been demonstrated to be accurate, linear, precise, reproducible, specific and robust for its intended purpose. Quantitation limits (QL) for acetone, methylene chloride and *n*-butyl ether are 20 ppm (20 μg/g of API) and 50 ppm (50 μg/g of API) for dimethylsulfoxide. Several other APIs (Loratadine and a few other corticosteroid compounds) were analyzed using the conditions of this method to evaluate and assess the versatility of this method for the purpose of residual solvents analysis for a wide range of APIs. The results of this evaluation strongly indicates that this method can be readily used (as-is or with minor modifications) to determine both low and high boiling residual solvents present in a wide range of APIs.

1. Introduction

Residual solvents (RS) in active pharmaceutical ingredients (API) encompass volatile organic compounds that are either used or produced during the manufacturing of an API. Depending on the type/class of solvent, high levels of RS in APIs can pose a potential safety risk to patients' health due to their toxicity and other undesirable adverse effects. It is a mandatory requirement by various health authorities in the world to accurately determine the levels of RS that are present in APIs. The presence of RS in an API could also play a critical role in the physiochemical properties (i.e., physical forms) and or physical appearance and other characteristics (e.g., color, odor, etc.) of the bulk API lots [1–3]. Hence, appropriate attempts are always taken in the manufacturing of APIs (such as drying) to eliminate and or minimize the presence of RS in the bulk lots of APIs. However, depending on the characteristics of the API, RS, and drying conditions/parameters of the API, various levels of RS can be retained in the final bulk lots of APIs.

According to the guidelines of International Conference on Harmonization (ICH), RS are divided into four different classes from most toxic solvents to solvents with insignificant toxicological effect on human health [4,5]. Excellent sensitivity and high selectivity of gas chromatography (GC) for volatile compounds makes it one of the most practical and popular techniques to determine RS in bulk APIs. In last decade, sampling techniques using static headspace gas chromatography (SHGC) gained preference and popularity over the direct injection GC because of various complications and disadvantages caused by the direct injection of the API into the GC system [6]. SHGC methods minimizes any potential interference caused by non-volatile substances (or by the degradation/decomposition products of the non-volatile components) as a result of direct injection into the GC system. Further, the direct injection method requires relatively high sample concentration, and this often leads to poor chromatography (for capillary columns) and limited injections of samples per sequence of sample analysis. Consequently, SHGC with FID detection has been widely used for the analysis of organic volatile ingredients present in the bulk lots of API and drug products [7–13].

Betamethasone valerate (BV) is a steroid with anti-inflammatory properties and is used to manufacture dermatological drug products for topical applications. Both low boiling (acetone and methylene chloride) and high boiling (*n*-butyl ether and dimethylsulfoxide (DMSO)) solvents are used in the final steps of BV synthesis. Though compendial methods such as the United States Pharmacopeia (USP), European Pharmacopeia (Ph. Eur.), etc., list procedures for the analysis of different types of organic solvents, this list does not cover all potential solvents such as *n*-butyl ether, one of the solvents used in the manufacturing of

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BV. The general procedure of Ph. Eur. and USP for RS determination in pharmaceutical products includes analysis of many solvents and hence a longer GC cycle time (~70 min) [14,15]. However since only a handful of the solvents were used in the manufacturing of BV our objective was to develop a simple, robust and efficient SHGC method that can accurately quantitate all the four RS present in commercial bulk API lots of BV.

In this paper, we describe the development and validation of an efficient, accurate, sensitive and rugged SHGC method for quantitation of RS present in commercial bulk API lots of BV. In addition, we also presented validation data on two alternative columns and application of this method for the determination of RS in other APIs (namely Loratadine and other corticosteroid APIs).

2. Experimental

2.1. Materials

Betamethasone valerate, Betamethasone Sodium Phosphate, Mometasone Furoate Monohydrate, and Loratadine API was provided by ACDS-Supply Analytical Sciences group of Merck & Co., Inc. (Union, New Jersey, USA). Primary vendor for 1,3-dimethyl-2-imidazolidinone (DMI) and *n*-butyl ether was Acros (NJ, USA), acetone and methylene chloride was Fisher Chemicals (Fairlawn, NJ, USA) and dimethylsulfoxide (DMSO) was Burdick and Jackson (Muskegon, MI, USA). All solvents were either ≥98% pure or HPLC/GC grade wherever applicable.

2.2. Instrumentation

Analysis was performed using an Agilent GC system (Wilmington, DE, USA) equipped with an oven with temperature programming capability, a flame ionization detector (FID), a data system capable of performing data collection, integration, and processing of chromatography data (e.g., Agilent 6890N Series), and a headspace autosampler capable of housing 10-mL GC headspace vials (e.g., Agilent G1888). A 2 mm I.D. deactivated direct liner was used as an inlet liner.

2.3. Chromatographic conditions

Separation was performed on a 30 m × 0.32 mm I.D., 1.8 μm film thickness DB-624 (bonded 6% cyanopropylphenyl–94% dimethylpolysiloxane) capillary GC column manufactured by J & W Scientific (Agilent Scientific Technologies, Wilmington, DE, USA). The GC parameters, headspace parameters and temperature programming of the method are listed in Table 1. Two alternate columns, Supelco SPB-624 or Alltech AT-624 30 m × 0.32 mm I.D., 1.8 μm film thickness DB-624 (bonded 6% cyanopropylphenyl–94% dimethylpolysiloxane) were purchased from Supelco Analytical, Bellefonte, PA, USA or Alltech, Deerfield, IL, USA.

2.4. Sample preparation

Approximately 500 mg of BV sample was accurately weighed and transferred into a 10 mL headspace vial followed by addition of 1.0 mL of DMI. BV completely dissolves in the diluent/solvent at the sample oven temperature of 120 °C. The vial was loaded into the headspace oven and heated for 10 min to ensure liquid–gas equilibrium of the RS. The resulting headspace sample was injected into the GC system via a 1-mL sample loop.

2.5. Validation procedure

The linearity study for the four solvents was carried out both in the absence and presence of BV. The linearity study in the absence of BV was carried out from 20 to 6000 ppm for acetone and from quantitation limit (QL) to 1200 ppm for the remaining RS. The linearity/accuracy/precision study in the presence of BV (spiked API samples) was carried out from 250 to 6000 ppm of acetone and 50–1200 ppm for the remaining solvents. RS spiked API samples were prepared by pipetting in 1.0 mL of appropriate linearity standard solutions into 10 mL headspace vials containing 500 mg of BV API. The detection limit (DL) was set at 2 μg/mL (equivalent to 4 ppm) for acetone, methylene chloride and *n*-butyl ether and 5 μg/mL (equivalent to 10 ppm) for DMSO. The QL was set at 10 μg/mL (equivalent to 20 ppm) for acetone, methylene chloride and *n*-butyl ether and 25 μg/mL (equivalent to 50 ppm) for DMSO.

Robustness of the method was studied by deliberately varying both GC parameters such as flow rate, inlet split ratio, initial oven temperature, temperature slope time, detector temperature and headspace conditions such as headspace oven temperature, vial equilibration, vial pressurization time, vial pressure, loop fill time and sample inject time. The method robustness was assessed by evaluating the system suitability criteria such as S/N ratio of QL, resolution factor between *n*-butyl ether and DMSO, tailing factor of acetone and the % relative difference in assay values compared to the procedural method (as-is) for each one of the RS.

Column-to-column reproducibility was also checked by using two different lots of DB-624 and also two additional brands of columns, Supelco SPB-624 and Alltech AT-624 from other vendors. One additional source of DMI, acetone, methylene chloride, *n*-butyl ether and DMSO were tested for comparability study of solvents from different vendors.

Table 1
GC parameters, headspace parameters and temperature programming for GC column.

GC parameters			
Primary column	J&W Scientific DB-624, 30 m × 0.32 mm I.D., 1.8 μm film thickness		
Carrier gas	Helium, 1.0 mL/min (constant flow)		
Inlet temperature	160 °C		
Detector	Flame ionization detector (FID), 250 °C		
Hydrogen	30–40 mL/min or adjust to ensure the retention of the flame		
Air	400 mL/min or adjust to ensure the retention of the flame		
Make-up gas[a]	25–30 mL/min or adjust to ensure the retention of the flame		
Inlet split ratio	10:1 or adjust to pass the quantitation limit (signal-to-noise ≥10)		
Inlet liner	2 mm I.D. deactivated direct liner (e.g., Agilent Cat. #5181-8818)		
Sample loop size (headspace)	1 mL		
Headspace parameters			
Vial pressure	10 psi		
Sample oven	120 °C		
Loop temperature	135 °C		
Transfer line	150 °C		
GC cycle time	45 min		
Vial equilibration	10 min		
Vial pressurization	0.5 min		
Loop fill	0.2 min		
Loop equilibration	0.1 min		
Sample inject	1.0 min		
Vial shaker mode	High		
	Temperature (°C)	Hold (min)	Ramp (°C/min)
Temperature programming for the GC column			
Initial temperature	35	15	10
Temperature I	90	–	15
Temperature II	230	5	–

[a] Helium and nitrogen make up gas can be used.

2.6. Calculation

The concentration of individual RS in the sample solution was carried out using an external standard containing approximately 1000 μg/mL of acetone and 200 μg/mL of methylene chloride, *n*-butyl ether and DMSO. The sample solutions were bracketed between two external standard solutions and the experimental concentration was obtained from the following equation:

individual residual solvent (ppm)

$$= \frac{C_{smpl}}{W_{smpl}} \times 1 = \left(\frac{A_{smpl} C_{std}}{A_{std} W_{smpl}} \right) \times CF \times 1$$

where A_{smpl} is the peak area of the individual RS in the sample, A_{std} is the average peak area of the individual RS in adjacent bracketing standards, C_{smpl} is the concentration of the individual RS in the sample (in μg/mL), C_{std} is the concentration of the individual RS in the standard (in μg/mL) [C_{std} = (W_{std}/dilution factor); W_{std} is the weight of the individual RS in the stock solution (in μg), dilution factor = 2500 mL], W_{smpl} is the weight of the BV sample (in grams), 1 is the volume of diluent added (mL) to the BV in the headspace vial and CF is the correction factor which is caused by the API matrix in the sample solution. CF is the ratio between the slope (area counts vs. concentration) of the RS in the absence and in the presence of BV API. CF for acetone, methylene chloride, *n*-butyl ether and DMSO was found to be 1.03, 0.98, 1.03 and 1.30, respectively. The percent recovery for each RS was then determined by dividing C_{smpl} by theoretical RS concentration.

3. Results and discussion

3.1. Analytical method development

Critical elements of a new SHGC method development are: (i) identifying an appropriate diluent which would completely dissolve the API; (ii) determining suitable headspace parameters (i.e., headspace temperature, vial equilibration time, vial pressurization), GC parameters (i.e., inlet split ratio, inlet temperature) and GC temperature programming to improve the sensitivity of the method; (iii) determining the detection limit (DL) and QL levels based on the sensitivity of the method.

3.1.1. Selection of solvent for sample preparation

Several organic solvents were investigated, namely, formamide, N,N-dimethyl acetamide (DMAc), 1,3-dimethyl-2-imidazolidinone (DMI) and propylene carbonate (PC) to identify the most suitable solvent (diluent) for the intended purpose of this method. The initial GC oven temperature program used was 35 °C for 15 min, then to 90 °C at 10 °C/min ramp, then to 200 °C at 45 °C/min ramp and hold for 5 min. The headspace temperatures were set as 120 °C for oven, 135 °C for sample loop, and 150 °C for transfer line to aid the evaporation of the RS and to increase the sensitivity. Both formamide and DMAc diluent peaks co-eluted with either DMSO or *n*-butyl ether and were unsuitable for this method. On the other hand, DMI and PC showed much cleaner chromatograms with insignificant or no interfering peaks in the retention time window of the four RS in BV.

For DMI and PC, further studies were conducted to determine the critical elements such as dissolution of the API in DMI and PC, matrix effect (CF), sensitivity of the RS and the profile of DMI and PC blanks at higher headspace oven temperatures. BV API was completely soluble in both DMI and PC at the elevated sample oven temperatures. Though the RS exhibited similar sensitivities in both diluents, increasing the headspace sample oven temperature to improve the sensitivity of the high boiling DMSO resulted in a greater number of interfering impurity/degradation peaks from PC. Hence DMI was selected as the diluent for this method and all further studies were carried out only with DMI.

3.1.2. Selection of headspace oven temperature and other GC parameters

The headspace sample oven temperature has a profound effect on the sensitivity of the method because temperature has a direct impact on the equilibrium concentration of the RS in the headspace of the sample vial [16]. For these experiments, the transfer line was kept 10–15 °C higher than the sample loop temperature, and the loop temperature 20–25 °C higher than the sample oven temperature [17]. Several sample oven temperatures were evaluated from 120 to 160 °C with the loop and transfer line temperatures changed accordingly but maintained the GC inlet temperature at 200 °C and the split ratio at 40:1. Under these conditions, all the RS were detected with a S/N much greater than 10 except for DMSO. Increasing the headspace oven temperature showed a linear increase in signal of the RS. But, it resulted in a noisy chromatogram and therefore was not very helpful to enhance the sensitivity of DMSO.

Further experiments were conducted by changing the inlet split ratio from 40:1 to 30:1 to 20:1 and 10:1 to improve the sensitivity of DMSO. Decreasing the inlet split ratio would naturally inject higher amounts of samples into the column and would lead to an increase in sensitivity. As expected, decreasing the inlet split ratio lead to a significant improvement in the sensitivity of all the RS and especially DMSO. The optimum inlet split ratio was identified as 10:1 for this method.

3.1.3. Evaluation of different GC temperature programming

DMI is a high boiling solvent with a boiling point of 225 °C. During the preliminary evaluations the highest temperature used in the GC temperature program was only 200 °C. Under these conditions, one of the unknown impurities in DMI did not elute from the column within the runtime of the method and was carried over to the subsequent run. This carry over peak appeared around 22 min and interfered with the identification and quantitation of *n*-butyl ether. Therefore, higher column oven temperatures were explored to ensure the impurity peak from DMI is completely eluted from the column. Also, both *n*-butyl ether and DMSO eluted during the fast GC ramp of 45 °C/min. Due to this fast ramp, a very noisy baseline with an upward slope was obtained. Hence, a reliable and accurate determination of S/N ratio at the low DL and QL levels was extremely challenging. To overcome these challenges, the GC temperature programming was varied with respect to the final ramp, hold time and the final column/oven temperature. Under these conditions, the carryover peak from DMI was no longer observed when the final column temperature was raised to 240 °C. Also, the resolution between *n*-butyl ether and DMSO improved with decreasing slope of the temperature ramp and a cleaner baseline was obtained. Since the boiling point of DMI is 225 °C, a final temperature of 230 °C was considered sufficient to allow the DMI and its impurities to elute out within the run time of the method. Final GC parameters, headspace parameters and temperature programming of GC Capillary Column for the SHGC method presented in this report are listed in Table 1.

3.1.4. Evaluation of S/N ratio value at the DL and QL level

QL refers to the lowest amount of a substance in a sample that can be quantitatively determined with suitable precision and accuracy. There are different approaches to determine the QL and DL. Typically the concentration level that generates a signal-to-noise (S/N) of 10 is regarded as the QL and the concentration level that generates a S/N of 3 is regarded as the DL. Practically, however, different substances can possess different QL and DL concentrations depending upon its sensitivity at a particular level. Hence, the S/N

Table 2
S/N ratio and peak heights in DL and QL standard solutions and DL and QL spiked API.

Homologous solvents	DL solution				QL solution			
	Peak height (pA)		S/N ratio		Peak height (pA)		S/N ratio	
	Absence of API	Presence of API	Absence of API	Presence of API	Absence of API	Presence of API	Absence of API	Presence of API
Methyl ethyl ketone	0.486	0.484	17.5	20.9	2.136	2.103	78.5	83.4
1,2-Dichloro ethane	0.484	0.492	17.4	21.3	2.757	2.793	101.4	110.8
Hexyl methyl ether	0.759	0.792	27.3	34.2	5.211	5.036	191.6	199.8

ratios can be very different at the selected QL and DL levels. Since it is already known that the sensitivity and relative abundance of the RS depend on the number of oxidizable carbons present when using a FID detector [18] and the boiling points of the RS of interests, the concentration levels for DL and QL were set at different levels for each one of the RS.

The presence of inherent RS in the BV API would interfere with the accurate determination of signal-to-noise (S/N) assessment in the DL and QL solutions. Hence several lots of BV API were tested to determine the levels of RS present in samples. A vast majority of the samples showed the presence of acetone, methylene chloride and *n*-butyl ether, and the absence of DMSO. In order to eliminate interference from the RS in the API, especially acetone (concentration of ~1000 ppm was found in the majority of the batches), drying of the API was carried out. The acetone content in the sample reduced by about 42% after 2 weeks of drying at 120 °C under vacuum suggesting that drying the API was not practical. Hence it was concluded that the S/N of the RS at DL and QL levels will be determined in the absence of API.

Preliminary studies on linearity for the four RS in the absence and in the presence of BV suggested that there is no significant matrix effect from BV. However, additional studies using the next homologous solvents (methyl ethyl ketone, 1,2-dichloroethane and hexyl methyl ether) to the RS (acetone, methylene chloride and *n*-butyl ether) were carried out to further confirm the claim. The homologous solvents gave comparable peak heights and S/N ratio in the absence and in the presence of API (Table 2). This provided further support that the S/N ratio of DL and QL of acetone, methylene chloride, *n*-butyl ether in the absence and in the presence of BV API should be comparable.

3.2. Analytical method validation

Method validation was performed with respect to parameters such as linearity, accuracy, QL, and DL, ruggedness and precision, specificity, robustness, sample stability, and equivalency between the primary and alternative columns.

3.2.1. Linearity and accuracy (recovery)

The slope, *y*-intercept, and coefficient of determination (r^2) for linearity study were obtained from linear regression analysis performed by the SAS system JMP® version 6.0.0. The peak areas (corrected peak areas in spiked API) of each individual RS were plotted against corresponding theoretical concentrations (μg/mL) obtained from each linearity solution for both in the presence and in the absence of BV API. Linear regression analysis showed that a coefficient of determination (r^2) of 1.00 from both analysts for all the four RS. The *y*-intercepts for both analyst in the absence of BV API were −15% and −24% for acetone, −6% and −11% for methylene chloride, 1% and −4% for *n*-butyl ether and −11% and −37% for DMSO respectively meeting the acceptance criteria of *y*-intercept no more than ±75% of the QL solutions. Table 3 lists the linearity equations for the RS in the presence and in the absence of BV API for both analysts.

The slopes obtained from the linearity study in the absence and in the presence of BV were used to evaluate the matrix effect and to calculate the CF (Table 3). These CFs were applied in the calculation of the percent recovery values (Table 4). Based on the recovery data shown in Table 4, the method has been demonstrated to be linear and accurate for routine analysis.

3.2.2. Method precision and ruggedness

The data obtained from the recovery study was used for the evaluation of the method reproducibility. The %RSD of the recoveries obtained for each RS from nine samples prepared as triplicates at the low (250 ppm, 50 ppm, 50 ppm and 100 ppm for acetone, methylene chloride, *n*-butyl ether and DMSO), middle (4000 ppm for acetone and 800 ppm for all other RS), and high (6000 ppm for acetone and 1200 ppm for all other RS) were calculated for precision repeatability. The intermediate precision was evaluated based on the difference in the average recoveries and the absolute difference in the %RSD of recoveries between analyst 1 and analyst 2. The results for all the tested compounds are listed in Table 4, which reveal that the method has acceptable reproducibility and intermediate precision.

3.2.3. Detection limit (DL) and quantitation limit (QL)

At the selected DL, an average S/N of 74, 14, 158 and 8 for acetone, methylene chloride, *n*-butyl ether and DMSO were obtained for analyst 1 and an average S/N of 42, 8, 84 and 5 were obtained for analyst 2. For the QL solutions (Fig. 1A), the S/N were 353, 66, 730, and 39 for acetone, methylene chloride, *n*-butyl ether and DMSO for analyst 1 and an average S/N of 192, 50, 533 and 18 were obtained for analyst 2. All S/N for QL were larger than 10 and all the S/N for DL were larger than 3.

3.2.4. Method specificity

The method specificity was demonstrated by injecting the individual RS to demonstrate the ability of the method to unequivocally resolve the RS (acetone, methylene chloride, *n*-butyl ether and DMSO) from each other and from diluent or API related peaks (Fig. 1B). In addition, the diluent blank (DMI) has no interfering peaks that will affect the quantitation of the RS in the sample.

3.2.5. Method robustness: GC and headspace sampler parameters variation

The assay values at different variations of GC parameters and GC headspace sampler parameters were all within ±2% relative difference for acetone, methylene chloride, and *n*-butyl ether, and were within ±9% for DMSO. In addition, the system suitability criteria were met for all the variations. The tailing factors of acetone were 0.9–1.1, and the resolution factor between *n*-butyl ether and DMSO were 13.2–13.6. The S/N ratios of QL were all above 10. The retention times of the RS acetone, methylene chloride, *n*-butyl ether and DMSO obtained from parameter variations were within ±1 min of the retention time obtained from the procedural conditions. This

Table 3
Summary of the average correction factors and the linearity equations for the residual acetone, methylene chloride, *n*-butyl ether and DMSO in Betamethasone valerate from the linearity/accuracy studies.

Residual solvent	Analyst 1			Analyst 2			Average CF
	Slope from linearity study without API	Slope from linearity study with API	CF	Slope from linearity study without API	Slope from linearity study with API	CF	
Acetone	5.66	5.53	1.02	7.40	7.13	1.04	1.03
Methylene Chloride	1.23	1.26	0.98	1.64	1.66	0.99	0.98
n-Butyl Ether	4.08	3.98	1.02	5.35	5.14	1.04	1.03
DMSO	0.14	0.12	1.20	0.19	0.14	1.39	1.30

Analyst 1	Analyst 2
Linearity equation in the absence of BV API for	
Acetone, $y = -8.2731 + 5.6619484x$	Acetone, $y = -17.0655 + 7.4002997x$
Methylene chloride, $y = -0.685051 + 1.2295594x$	Methylene chloride, $y = -1.6815 + 1.6362034x$
n-Butyl ether, $y = 0.5299183 + 4.076636x$	*n*-Butyl ether, $y = -1.9456 + 5.3480421x$
DMSO, $y = -0.3416 + 0.1397539x$	DMSO, $y = -1.5643 + 0.1928913x$
Linearity equation in the presence of BV API for	
Acetone, $y = -20.34141 + 5.5260946x$	Acetone, $y = -29.9944 + 7.1301487x$
Methylene chloride, $y = -1.882131 + 1.2598182x$	Methylene chloride, $y = -2.1448 + 1.6562083x$
n-Butyl ether, $y = -3.879895 + 3.9834631x$	*n*-Butyl ether, $y = -8.1614 + 5.1437967x$
DMSO, $y = -0.499437 + 0.1158247x$	DMSO, $y = -1.1508 + 0.1383923x$

Note: The data in this table was rounded off from the full precision data.

study demonstrated that the proposed method is robust for quantitation analysis.

3.2.6. Comparability of columns and solvents from different vendors

In this study, all system suitability criteria with respect to S/N, tailing factor, resolution and the relative % difference in assay values were met. Also, the retention times of the RS acetone, methylene chloride, *n*-butyl ether and DMSO obtained from the columns of other vendor were within ±1 min of the retention time obtained from the column of the primary vendor.

3.2.7. Evaluation of application of this method for RS analysis of other APIs

This method was evaluated to assess if it would also work for the determination of RS in other APIs. For this study, two APIs were selected from the family of corticosteroid and one API was selected that is vastly different compared to the chemical and physical properties of corticosteroid APIs. The two corticosteroid APIs were Betamethasone Sodium Phosphate and Mometasone Furoate Monohydrate (MMF) and the third API was Loratadine. The RS present in Loratadine API are isopropyl alcohol, methylene chloride, and toluene, in Betamethasone Sodium Phosphate are methanol, acetone, ethyl acetate and tetrahydrofuran (THF) and in MMF are methanol and methylene chloride. As is evident from the chromatogram of standard mixture (Fig. 2), all the RS that are present in these three APIs are well resolved from each other using the final method conditions. Therefore, this method can be readily used for RS analysis of these three APIs. However, appropriate validation must be conducted for each of these three APIs if the method is intended for use of formal testing for the purpose of batch release or if the method is used to conduct formal stability studies for regulatory filings. The data generated in this study strongly indicates that the method presented in this report has a high potential to work "as-is" or with minor modifications for a wide range of APIs for the analysis of RS.

Table 4
Summary of accuracy, precision /repeatability and precision intermediate results.

Solution #	Acetone % recovery		Methylene chloride % recovery		*n*-Butyl ether % recovery		DMSO % recovery	
	I	II	I	II	I	II	I	II
1A	96	98	95	98	97	94	N/A	N/A
1B	95	98	96	98	96	97	N/A	N/A
1C	99	98	96	98	98	95	N/A	N/A
2A	N/A	N/A	N/A	N/A	N/A	N/A	98	111
2B	N/A	N/A	N/A	N/A	N/A	N/A	91	109
2C	N/A	N/A	N/A	N/A	N/A	N/A	92	103
3A	100	100	100	100	99	99	98	112
3B	99	100	101	100	100	99	100	108
3C	100	100	101	101	99	100	96	111
4A	100	100	101	101	100	100	103	110
4B	98	101	101	102	99	101	97	115
4C	100	101	101	102	100	100	99	112
Precision repeatability	2.0%	1.3%	2.6%	1.6%	1.5%	2.5%	3.9%	3.3%
Precision intermediate	1%		1%		−1%		1%	

Note: The data in this table was rounded off from the full precision data.
(I) Analyst 1.
(II) Analyst 2.
(1) Solution containing 250 ppm acetone and 50 ppm of other RS.
(2) Solution containing 500 ppm acetone and 100 ppm of other RS.
(3) Solution containing 4000 ppm acetone and 800 ppm of other RS.
(4) Solution containing 6000 ppm acetone and 1200 ppm of other RS.
A, B and C indicate triplicate preparation at a particular concentration level.

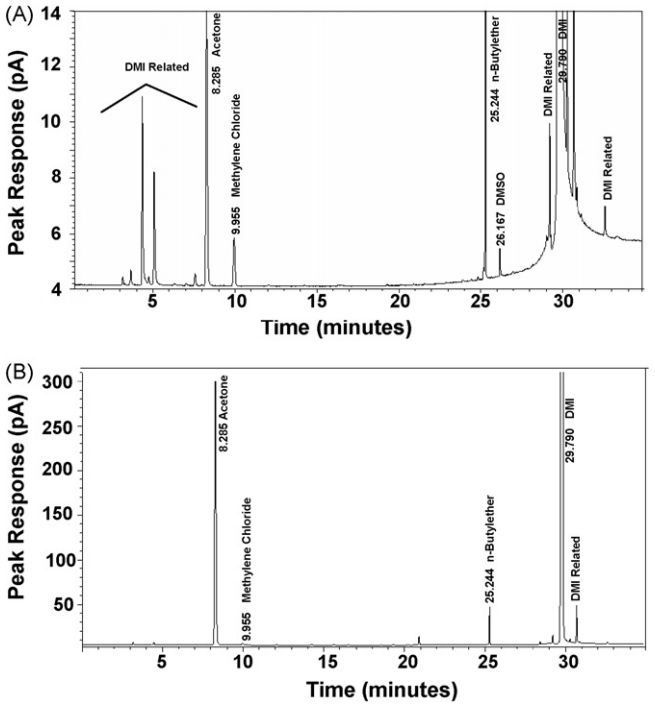

Fig. 1. (A) GC-FID chromatogram of the QL standard solution. (B) GC-FID chromatogram of Betamethasone valerate API Blank.

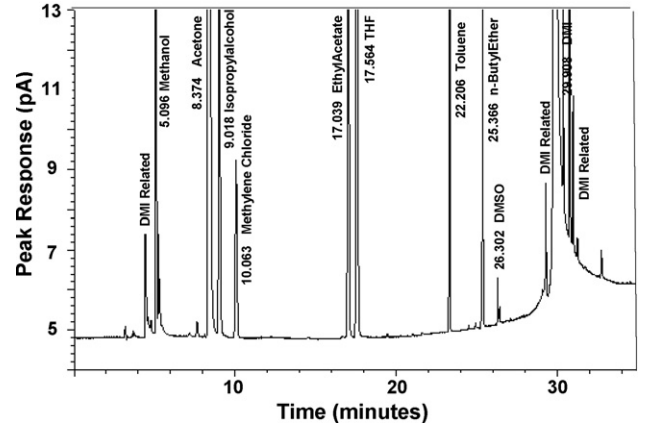

Fig. 2. GC-FID chromatogram of standard solution containing mixture of high and low boiling solvents.

4. Conclusions

The SHGC method developed for the identification and quantitation of residual acetone, methylene chloride, *n*-butyl ether and DMSO in the samples of BV API has been successfully validated. This is the first reported headspace GC method for *n*-butyl ether. This method has been shown to have a high sensitivity since it has a low DL and QL of 4 ppm and 20 ppm for acetone, methylene chloride, and *n*-butyl ether. The DL and QL for DMSO are 10 ppm and 50 ppm, respectively. This method has also been demonstrated to be accurate, linear, precise, reproducible, repeatable, specific, and robust. Two alternate columns have also been identified and validated to enhance the method endurance in case the column from the primary vendor cannot be obtained on time or is unavailable in the lab when sample analysis of BV is conducted. It has also been demonstrated that this method can be readily used to determine both high and low boiling residual solvents in Loratadine and other corticosteroid APIs. Therefore, this method may also work for a wide variety of other APIs for RS analysis.

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