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Short communication

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

Jayalakshmi Somuramasami*, Yu-Chien Wei, Emad F. Soliman, Abu M. Rustum

Merck & Co., Inc., ACDS-Supply Analytical Sciences, 1011 Morris Avenue, Union, NJ 07083, USA

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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

* Corresponding author at: Merck & Co., Inc., ACDS-Supply Analytical Sciences, U-22-1-1200 Laboratories, 1011 Morris Avenue, Union, NJ 07083, USA.
Tel.: +1 908 8206664; fax: +1 908 8206359.
E-mail address: jaya.somruamasami@merck.com (J. Somuramasami).

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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.