Journal of Pharmaceutical and Biomedical Analysis 54 (2011) 417–421

Contents lists available at ScienceDirect

Journal of Pharmaceutical and Biomedical Analysis

journal homepage: www.elsevier.com/locate/jpba

Short communication

A general static-headspace gas chromatographic method for determination of residual benzene in oral liquid pharmaceutical products

Hui Liu*, Qinglin Tang, Robert J. Markovich, Abu M. Rustum

Global Quality Services – Analytical Sciences, Merck & Co., Inc., Union, NJ 07083, USA

ARTICLE INFO

Article history:
Received 29 June 2010
Received in revised form 18 August 2010
Accepted 2 September 2010
Available online 15 September 2010

Keywords:
Benzene
Oral liquid pharmaceutical products
Headspace GC
DB-624 GC column

ABSTRACT

Sodium benzoate is used in oral liquid pharmaceutical products for its anti-microbial properties. The benzoate salts present in liquid pharmaceutical products can potentially generate residual levels of free benzene during manufacturing of the drug product and or during the shelf-life of the product under its storage conditions. To ensure the safety and quality of the pharmaceutical products (containing benzoate in the formulation), a selective and sensitive analytical method is required to monitor residual benzene in oral liquid pharmaceutical products. In this paper, we report the development and validation of a general static-headspace gas chromatographic (SH-GC) method to determine residual benzene in oral liquid pharmaceutical products. The liquid pharmaceutical drug product sample is dissolved in dimethylsulfoxide (DMSO) in a GC headspace vial. A DB-624 capillary column (30 m × 0.32 mm I.D. and 1.8 μm film thickness) was used under isothermal conditions with a flame ionization detection (FID). The benzene peak was well separated from all other volatile compounds that are present in the formulation of a number of liquid drug products. This method was successfully validated using a representative oral liquid pharmaceutical drug product. The limit of detection of the method for benzene is 0.5 ppm which met the 2 ppm limit of current ICH guideline for residual benzene in pharmaceutical products.

1. Introduction

Oral liquid pharmaceutical drug products (OLDPs) are formulated with various active pharmaceutical ingredients (APIs), flavoring agents, dyes, and preservatives. Each class (e.g., decongestants, cough suppressants, anti-histamines, etc.) of OLDP uses a specific API for its intended purpose. However, many OLDPs use same types/class of excipients and preservatives in the formulation. Benzoate salts are commonly used as preservatives in OLDPs for their bacteriostatic and fungistatic properties. Certain flavoring agents also uses benzoate salts as preservatives. Therefore, benzoate in a given OLDP can come from its formulation or from its flavoring agents or from both. Benzoate salts have been reported to form residual levels of free benzene under heat and acidic conditions in beverages and soft drinks [1–4]. Therefore, benzoate salts present in OLDP can also potentially generate residual levels of free benzene during manufacturing of the drug product and or during the shelf-life of the product under its storage conditions.

Benzene is a potential carcinogen that can cause or increase the risk of leukemia and benzene exposure is also associated with other types of blood cancers, and pre-cancers of the blood [5,6]. The International Conference on Harmonization (ICH) Guideline has set up a limit of 2 ppm for residual benzene in pharmaceutical drug products [7]. Therefore, a selective and sensitive analytical method is required to monitor the residual benzene in OLDPs to ensure the safety and quality throughout their shelf life.

The analysis of residual benzene in OLDPs is challenging due to the requirement of high sensitivity of the method and also due to the potential interferences from the formulation ingredients such as flavoring agents, dyes, preservatives, etc. as well as the API, its related impurities and degradants. The analysis of residual benzene in APIs and pharmaceutical products has been reported using gas chromatographic (GC) methods, flame ionization detection (FID) and different sampling techniques [8–14]. Analysis of drug product samples using a static-headspace gas chromatography (SH-GC) technique instead of direct injection gas chromatography technique has a great advantage in selectivity since only the volatile compounds from the sample are introduced onto the GC column [15].

A literature search revealed no available method for the determination of residual benzene in OLDPs at a level of 1–2 ppm. In this report, the development and validation of a general SH-GC method for determination of residual benzene in oral liquid pharmaceutical drug products is reported. The objective was to develop a sensitive

* Corresponding author. Tel.: +1 908 820 6098; fax: +1 908 820 6359.
E-mail address: hui.liu2@merck.com (H. Liu).

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doi:10.1016/j.jpba.2010.09.006

and selective SH-GC method that can be generally applied either "as-is" or with minor modification for determination of residual benzene in various OLDPs. A preliminary SH-GC method was first developed using a representative OLDP Product 1 Syrup (peach flavor). Samples from six other representative OLDPs namely Product 1 Syrup (fruit flavor), Product 1 Syrup (grape flavor), Product 2 Oral Solution, Product 3 Oral Solution, Product 4 Oral Solution and Product 5 Syrup were analyzed by the preliminary SH-GC method. The formulation of these six OLDPs has different excipients, APIs and flavoring agents and therefore represented a wide variety of dyes, flavors, and APIs. The objective of analyzing the samples of six other OLDPs was to find out if the preliminary SH-GC method has the required selectivity and sensitivity to be used as a general method to determine residual benzene in different OLDPs. The new SH-GC method for determination of residual benzene was successfully validated for its intended use, using a representative OLDP namely Product 1 Syrup (peach flavor).

2. Experimental

2.1. Reagents, chemicals, columns, and GC system

The drug products, Product 1 Syrup (peach flavor, fruit flavor, grape flavor), Product 2 Syrup, Product 3 Oral Solution, Product 4 Oral Solution, Product 5 Syrup, were provided by Merck & Co. Inc. Benzene was purchased from Sigma–Aldrich (Sheboygan Falls, WI, USA). Dimethylsulfoxide (DMSO) was purchased from Acros Organics (Fair Lawn, NJ, USA). Milli-Q Water (18.2 MΩ cm^{-1}) was obtained from an in-house Milli-Q System (Millipore, Billerica, MA).

The DB-624 column (30 m × 0.32 mm I.D. 6% cyanopropyl-phenyl, 94% dimethyl polysiloxane stationary phase with 1.8 μm film thickness) was purchased from Agilent (Wilmington, DE, USA).

Agilent 6890 gas chromatograph (GC) equipped with an Agilent G1888A headspace sampler with a 1.0 mL sample loop, a FID detector, and a Chemstation data acquiring and process software was purchased from Agilent Technologies (Santa Clara, CA, USA).

2.2. Standard and sample solutions preparation

Benzene standard solution was prepared by diluting benzene to the intended concentration with 1:1 (v/v) DMSO/water. The oral liquid pharmaceutical product sample solution was prepared by 1:1 (v/v) dilution of the sample with DMSO. A 1.0 mL aliquot of the standard and sample solutions were added to separate 10-mL headspace vial for analysis.

2.3. Gas chromatographic conditions and calculation

The SH-GC method conditions are listed in Table 1.

Eq. (1) shows the calculation of the residual benzene in the liquid oral pharmaceutical product:

$$\text{PPM (wt/wt) of benzene} = \frac{A_s}{A_{std}} \times \frac{C_{std} \times V_s}{W_s} \times CF \times 10^6 \quad (1)$$

where A_s and A_{std} are the areas of benzene in sample and standard chromatogram, respectively. C_{std} is the benzene standard concentration in mg/mL. V_s is the sample volume in mL. W_s is the sample weight in mg. CF is the correction factor for sample matrix effect. The 10^6 is the conversion factor for ppm.

2.4. Validation procedures

The method was validated for the determination of residual benzene in Product 1 Syrup (peach flavor), one of the oral liquid pharmaceutical drug products (OLDPs). The validation parameters including specificity, linearity/accuracy/precision (repeatability, intermediate precision)/range, detection limit (DL)/quantitation limit (QL), and robustness (solution stability and Headspace GC parameters). Linearity with and without the presence of Product 1 Syrup (peach flavor) were also evaluated for correction factor for the sample matrix effect.

Table 1
The GC method conditions.

1. GC parameter	
Column	DB-624 column (30 m × 0.32 mm I.D. 6% cyanopropyl-phenyl, 94% dimethyl polysiloxane stationary phase with 1.8 μm film thickness)
GC oven temperature	70 °C for 7 min, increase to 220 °C at 45 °C/min, held for 5 min
Carrier gas	Helium, 2.0 mL/min (constant flow)
Inlet temperature	250 °C
Inlet split ratio	40:1
FID detector	290 °C
2. Headspace parameter	
Sample loop size (mL)	1.0
Vial pressure (psi)	10
HS oven temperatures (°C)	90
Loop temperatures (°C)	115
Transfer line temperatures (°C)	120
Vial equilibration time (min)	11
Vial pressurization time (min)	0.5
Loop fill time (min)	0.2
Loop equilibration time (min)	0.1
Sample inject time (min)	1.0
Vial shaker mode	High

3. Results and discussion

3.1. Method development

The objective of the general method is to determine benzene at low level with high selectivity in OLDPs. SH-GC method has intrinsic superior selectivity because this analytical technique only analyzes compounds that are evaporated into the sample solution head space. Therefore, a SH-GC method was further explored for the determination of residual benzene in OLDPs. The capillary GC column DB-624 column (6% cyanopropyl-phenyl, 94% dimethyl polysiloxane) has been reported as suitable for the analysis of a wide range of common ICH residual solvents including benzene in pharmaceutical products [16], and thus, was selected for methods development. Typically, a GC method for residual solvents uses temperature programming for separation of residual solvents with different boiling points. Since this method is only targeted to analyze benzene, a simple isothermal column temperature program was explored as this would be preferred for general method robustness. The sample diluent, temperature program, split ratio, headspace oven temperature, and other headspace and GC parameters were investigated and optimized using benzene standard solution or benzene standard spiked Product 1 Syrup (peach flavor) sample solutions.

3.1.1. Diluent for sample and standard preparation

The sample diluent is important for a static Headspace GC method as it affects the sensitivity and accuracy by influencing the equilibrium between the analyte in the liquid phase and the analyte in the headspace [17]. Several sample diluents were evaluated including dimethylsulfoxide (DMSO), diethylamide (DMA), dimethylformamide (DMF) and water alone and in combination. The use of water alone as the sample diluent led to irreproducible results. Since the oral liquid pharmaceutical drug products are freely soluble in water and not soluble in organic solvents, a combination of water with the organic diluents (1 to 1 ratio) were studied

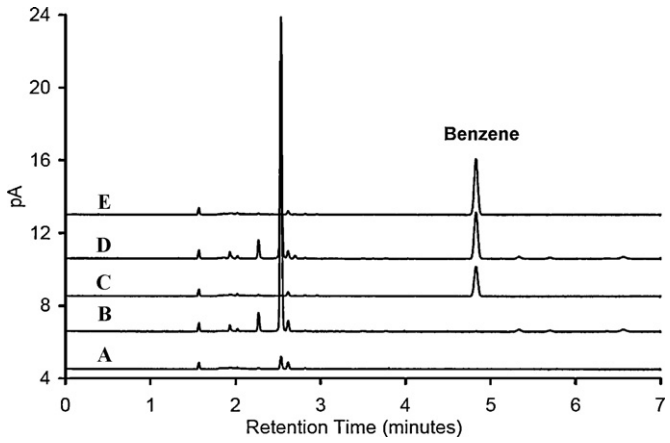

Fig. 1. The chromatograms of (A) diluent, (B) Product 1 Syrup (peach flavor) sample, (C) Limit of Quantitation solution for Benzene (1 ppm), (D) 2 ppm benzene spiked Product 1 Syrup (peach flavor) sample solution, and (E) Benzene standard solutions (2 ppm). The method conditions are the same as those in Section 2. Unlabeled peaks are from sample matrix/diluent.

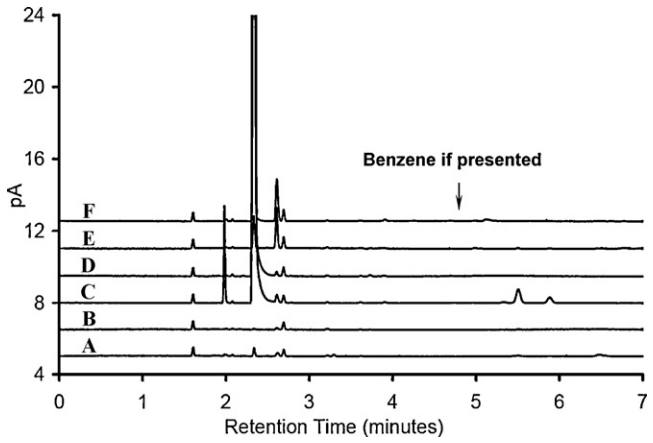

Fig. 2. The representative chromatograms of different oral liquid pharmaceutical drug products: (A) Product 2 Oral Solution, (B) Product 3 Oral Solution, (C) Product 4 Oral Solution and (D) Product 5 Syrup, (E) Product 1 Syrup Fruit Flavor and (F) Product 1 Syrup Grape Flavor. The method conditions are the same as those in Section 2. Unlabeled peaks are from sample matrix/diluent.

under different head space oven temperature at 80 °C, 90 °C and 100 °C (constant transfer line temperature at 120 °C). Under these GC headspace conditions, the reproducibility of benzene spiked (1 ppm) OLDP, Product 1 Syrup (peach flavor) was evaluated and the results demonstrated that the DMSO/water 1:1 (v/v) sample diluent at a headspace temperature of 90 °C showed the best sensitivity and selectivity.

3.1.2. Chromatographic and Headspace parameters optimization

For optimal method robustness, an isothermal column temperature program was targeted for the elution of residual benzene followed by a temperature ramp to 220 °C to clean the column. Since the boiling point of Benzene is 80.1 °C, the GC column oven temperature was evaluated at 40 °C, 50 °C, 60 °C, and 70 °C using a benzene (1 ppm) spiked oral liquid pharmaceutical product [Product 1 Syrup (peach flavor)]. The retention time of Benzene is 19.1, 6.5, 8.1 and 4.9 min at the GC column oven temperature 40 °C, 50 °C, 60 °C, and 70 °C, respectively. The sensitivity of the 1 ppm standard response was adequate (signal-to-noise ratio of 49 or higher) for all conditions studied. The 70 °C GC oven temperature was selected for additional optimization studies since this condition provided the shortest run time (4.9 min), appropriate selectivity and the greatest sensitivity.

One of the key objectives of the method development was to achieve adequate sensitivity for low level benzene analysis. The benzene method sensitivity was further optimized by the evaluating the effect of spilt ratio on the noise level and S/N value of a 1 ppm benzene standard solution. Several GC injection split ratios including 3:1, 10:1 and 40:1 were studied. The optimal noise level and adequate signal was observed using the 40:1 spilt ratio injection parameter.

The other GC parameters are summarized in Table 1 including the flow rate, column oven temperature, detector (FID) temperature, vial equilibration time, vial pressurization time, vial pressure, loop fill time, and injection time. These parameters were also optimized for better sensitivity and selectivity using 1 ppm benzene spiked OLDP, Product 1 Syrup (peach flavor). Under the optimized SH-GC conditions listed in Table 1, benzene eluted at 4.9 min which was well resolved from any potential drug product interfering peaks. Fig. 1 shows the representative chromatograms of the diluent blank, quantitation limit solution (QL, 1 ppm benzene standard solution), benzene standard solution (2 ppm), Product 1 Syrup (peach flavor) sample solution, and 2 ppm benzene standard spiked Product 1 Syrup (peach flavor) sample solution.

3.2. Selectivity for the residual benzene in six other oral liquid pharmaceutical drug products

The method is intended to be a general method for residual benzene on OLDPs that can be used either “as-is” or with minor modification. Six representative OLDPs that have different APIs, flavors, dyes and preservatives were tested use this method “as-is”. These six OLDPs are Product 1 Syrup fruit flavor, Product 1 Syrup grape flavor, Product 2 Oral Solution, Product 3 Oral Solution, Product 4 Oral Solution and Product 5 Syrup. Fig. 2 shows the chromatograms of those six OLDPs. The region of the benzene peak in the chromatograms was free from any interference, which demonstrated that the method has adequate specificity and selectivity for those six OLDPs. Based on the chromatographic data, there was no detectable benzene in any of the six OLDPs. Since those six OLDPs tested have a wide variety of dyes, flavors, APIs and excipients, the good selectivity of this method for those six OLDPs indicated that this method can be a general method for residual benzene in OLDPs that can be used either “as-is” or with minor modification.

3.3. Headspace GC method validation

The optimized general residual benzene method was validated for OLDPs using Product 1 Syrup (peach flavor) as a representative. The method was validated for specificity, linearity/recovery/precision/range, quantitation limit/detection limit, and robustness including solution stability and GC parameter variation.

3.3.1. Specificity

The method specificity was validated for potential interference from diluent blank, and sample matrix and for identification of benzene peak by analyzing diluent blank, sample blank [Product 1 Syrup (peach flavor) without detectable benzene], 2 ppm benzene spiked Product 1 Syrup (peach flavor) sample solution, and 2 ppm benzene standard (Fig. 1). As shown in Fig. 1, there are no detectable peaks in the chromatograms of diluent blank and sample blank that would interfere with benzene in the chromatogram of 2 ppm benzene spiked Product 1 Syrup (peach flavor) sample solution. The Benzene peak in the chromatogram of 2 ppm benzene spiked Product 1 Syrup (peach flavor) sample solution is adequately resolved from all other peaks before and after the benzene peak. The retention time of Benzene in the chromatogram of 2 ppm benzene spiked

Table 2
Robustness results of GC and headspace parameters.

Parameter	Setting condition	QL(S/N ratios)	Retention time (min)	Tailing factor	%Difference of peak area vs. initial peak area
Procedural setting		71	4.8	1.0	0
Column lot	Lot 1	61	5.2	1.0	−3.8
	Lot 2	47	4.7	0.9	−6.0
Flow rate mL/min	1.8	65	5.2	1.0	1.5
	2.2	77	4.5	1.0	−3.7
Spilt ratio	36:1	65	4.8	1.0	7.5
	44:1	54	4.8	1.0	−8.8
Initial oven (°C)	65 °C	64	5.3	1.0	0.6
	75 °C	70	4.4	1.0	−3.6
Detector (°C)	280 °C	72	4.8	1.0	−1.4
	300 °C	57	4.8	1.0	2.7
Headspace temperature	85 °C	83	4.8	1.0	−11.4
	95 °C	59	4.8	1.0	9.1
Vial equilibration	10 min	63	4.8	1.0	0.0
	12 min	73	4.8	1.0	0.8
Pressurization time	0.4 min	64	4.8	1.0	−2.4
	0.6 min	59	4.8	1.0	1.0
Vial pressure	9 psi	64	4.8	1.0	1.4
	11 psi	60	4.8	1.0	5.5
Loop fill time	0.1 min	65	4.8	1.0	0.2
	0.3 min	55	4.8	1.0	2.4
Sample inject time	0.9 min	53	4.8	1.0	−0.2
	1.1 min	59	4.8	1.0	−0.9

Product 1 Syrup (peach flavor) sample solution matches well with that from 2 ppm benzene standard solution.

3.3.2. Detection limit (DL), quantitation limit (QL)

Replicate analysis ($n = 3$) of 0.5 ppm Benzene standard solution and 1.0 ppm benzene standard solution resulted in average of S/N ratios of 41 and 78, respectively. Therefore, the quantitation limit (QL) and the detection limit (DL) was thus set at 1.0 ppm and 0.5 ppm, respectively. These S/N ratios are much greater than ICH recommended S/N value for DL (S/N ~ 3) and QL (S/N ~ 10), which ensures the robustness of the method during its day-to-day use in the quality control laboratories.

3.3.3. Linearity/accuracy/precision/range

The linearity of benzene was evaluated from 1 ppm to 6 ppm (six levels with triplicate preparations at each level) in the absence and presence of the oral liquid pharmaceutical drug product [Product 1 Syrup (peach flavor)] sample matrix. The peak areas were plotted against the corresponding theoretical concentrations and the linear regression was performed. The correlation coefficients (r) of the linearity curves for benzene standards in the absence and the presence of OLDP, Product 1 Syrup (peach flavor), are 0.9993 and 0.9997, respectively. The y-intercept observed for benzene standards in the absence and the presence of OLDP, Product 1 Syrup (peach flavor), corresponds to 0.01% (~0.01 ppm) and 0.04% (~0.04 ppm) of QL response for standard solution, which suggest no significant bias. The slope of linearity curves for benzene standards in the absence and the presence of Product 1 Syrup (peach flavor) are 7.51 and 9.36. The matrix correction factor, 1.25, in Eq. (1) is experimentally established from the ratio of the slope of the linearity curve for benzene standards in the absence of OLDP, Product 1 Syrup (peach flavor), over the slope of linearity curve for Benzene standards in the presence of OLDP, Product 1 Syrup (peach flavor).

Accuracy was determined by analyzing the triplicate preparation of benzene standards at low (1.0 ppm), middle (2.0 ppm), and high (6.0 ppm) levels in the presence of OLDP, Product 1 Syrup (peach flavor), as per the analytical method. The accuracy as % recovery was calculated from the experimental concentrations of benzene standards divided by the theoretical concentrations. The % recovery of ranged from 96% to 103% were obtained for the three concentration levels, which were well within the accepted range for residual solvents.

Precision (repeatability) was evaluated from the recovery data. Percent relative standard deviation (%RSD) of the recoveries from nine (9) samples (triplicates at the 1.0 ppm, 2.0 ppm, and 6.0 ppm) is 2.1%.

Intermediate precision was demonstrated by performing a test for two spiked samples using the experimental design [18] in which the variables tested include day of testing (days), analysts (analyst A, analyst B), instrumentation (instrument a, instrument b) and analytical columns (column α, column β). The intermediate precision as the %RSD of the pooled assay results from two analysts using two different instruments and columns on two different days is 3.0%.

The range 1–6 ppm was established by meeting the acceptable criteria of linearity, accuracy (recovery), and precision (repeatability and intermediate precision) for the entire concentration interval study.

3.3.4. Robustness

Robustness was validated by studying the stability of solutions and the effect of deliberately varied GC and headspace parameters on the change of specificity and response of the method.

The stability of QL, standard, and standard spiked sample solutions were prepared in duplicated and stored at refrigeration (2–8 °C), ambient laboratory conditions (25 ± 5 °C), respectively. Since the sample had no quantifiable benzene, standard spiked sample was used to represent the sample for sample solution stability study. They were analyzed against freshly prepared standard solutions at day 0, day 1, day 3, and day 7. The QL solution is stable

for 7 days at both room and refrigerated temperature conditions because the S/N ratios of benzene peak ranged from 53 to 74 at the time points. The %difference ranged from 2% to 7% for average assay of benzene in standard solutions and 2% to 4% for average assay of benzene in spiked sample solutions of the respective day 0 value for the solution stability time points. Therefore, the standard solution and the sample solution were stable for 7 days at both room and refrigerated temperature conditions.

Table 2 lists the robustness validation of varied GC and headspace parameters and their results. The QL and 2 ppm benzene standard spiked oral liquid pharmaceutical product [Product 1 Syrup (peach flavor)] sample solutions were tested by the approach of changing one parameter at a time. The S/N ratios of benzene peaks in QL chromatograms ranged from 53 to 83, all greater than 10 and met the criteria. The tailing factor of benzene was 1.0, which met the criteria. The benzene peak in the spiked sample solution had been adequately resolved from all other peaks before and after the benzene peak, which met the criteria. The retention times ranged from 4.4 to 5.3 min. The %difference of peak area obtained from different parameter settings against the peak area when obtained from the method setting are within 12%. All the results indicate that the method is robust and reliable during the method's normal usage.

4. Conclusions

The SH-GC method presented in this report, successfully achieved the main objective of method development, which was to obtain a method that can be used as a general method to determine residual benzene in various oral liquid pharmaceutical drug products. A total of seven different oral liquid drug products such as Product 1 Syrup (peach flavor), Product 1 Syrup (grape flavor), Product 1 Syrup (fruit flavor), Product 2 Oral Solution, Product 3 Oral Solution, Product 4 Oral Solution and Product 5 Syrup were tested using the new SH-GC method and was found to have good selectivity of benzene peak for all seven formulations regardless of the presence of different APIs and excipients in each product. Therefore, this new method can be used as a general method to determine residual benzene because it has a good potential to work either "as-is" or with minor modifications for other liquid pharmaceutical products. This method was successfully validated for its intended use with a 0.5 ppm limit of detection for benzene. To the best of our knowledge, the SH-GC method reported in this paper is the first known method that has been demonstrated to have the capability to separate and accurately quantitate residual levels of free benzene in multiple liquid oral pharmaceutical drug products containing different types of excipients, APIs, flavoring agents and dyes.

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