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A generic static headspace gas chromatography method for determination of residual solvents in drug substance

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ABSTRACT

In order to increase productivity of drug analysis in the pharmaceutical industry, an efficient and sensitive generic static headspace gas chromatography (HSGC) method was successfully developed and validated for the determination of 44 classes 2 and 3 solvents of International Conference of Harmonization (ICH) guideline Q3C, as residual solvents in drug substance. In order to increase the method sensitivity and efficiency in sample equilibration, dimethylsulfoxide (DMSO) was selected as the sample diluent based on its high capacity of dissolving drug substance, stability and high boiling point. The HS sample equilibration temperature and equilibration time are assessed in ranges of 125–150 °C and 8–15 min, respectively. The results indicate that the residual solvents in 200 mg of drug substance can be equilibrated efficiently in HS sampler at 140 °C for 10 min. The GC parameters, e.g. sample split ratio, carrier flow rate and oven temperature gradient are manipulated to enhance the method sensitivity and separation efficiency. The two-stage gradient GC run from 35 to 240 °C, using an Agilent DB-624 capillary column (30 m long, 0.32 mm I.D., 1.8 μm film thickness), is suitable to determine 44 ICH classes 2 and 3 solvents in 30 min. The method validation results indicate that the method is accurate, precise, linear and sensitive for solvents assessed. The recoveries of most of these solvents from four drug substances are greater than 80% within the method determination ranges. However, this method is not suitable for the 10 remaining ICH classes 2 and 3 solvents, because they are too polar (e.g. formic acid and acidic acid), or have boiling points higher than 150 °C, (e.g. anisol and cumene). In comparison with the previous published methods, this method has a much shorter sample equilibration time, a better separation for many solvents, a higher sensitivity and a broader concentration range.

1. Introduction

Residual solvents are critical impurities in drug substances, drug products and excipients, because they may cause toxicity and safety issues, and affect physicochemical properties of drug substances and drug products. In order to control residual solvent contents in drug substances, products and excipients, ICH Q3C guideline provides specific criteria for class 1 solvents (5) – known or suspected human carcinogens or environmental hazards, class 2 solvents (26) – suspected of other significant but reversible toxicities, and class 3 (28) solvents – low toxic potential to man [1]. Therefore, determination of residual solvents becomes a necessary procedure for quality control of drug substances and drug products to meet regulatory expectations and ensure patient safety.

Developing and validating an efficient and sensitive generic analytical method for the determination of residual solvents may significantly increase productivity of an analytical laboratory in the pharmaceutical industry. Determination of residual solvents using GC with a flame ionization detector (FID) is the most common technique in the pharmaceutical industry, because of its high separation efficiency and sensitivity for volatile organic compounds. GC analysis may be performed by either direct injection or HS sampling [2]. The advantage of the direct injection mode is that all analytes in a sample solution are directly injected into the GC, leading to a lower sample load or sample requirement and a simpler analytical procedure. But, the high boiling/melting point or polar components of the sample may not be eluted through a GC column, and they may contaminate the GC injection port and/or column. In contrast, HS sampling can prevent this from occurring, but it limits the analysis to those solvents being evaporated from the HS only, and it requires a larger sample load. In addition, the analysis time can be longer due to sampler equilibration prior to injection on column.

There are two types of HS sampling techniques, static HS and dynamic HS sampling. The static HS sampling is more easily automated. Dynamic HS sampling with purge and trap is less suitable for automation but has a higher sensitivity [2,3]. Currently, static

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Table 1
HSGC parameters for the method development and validation.

Parameter	Evaluated settings for development	Optimized settings for validation
HS		
Equilibration temperature	125, 140, 150 °C	140 °C
Transfer line temperature	135, 140, 150 °C	140 °C
Loop temperature	125, 140, 150 °C	140 °C
Vial pressure	9 psi	9 psi
Vial equilibration time	8, 10, 15 mim	10 mim
Vial pressurization time	0.4 min	0.4 min
Loop size	1 mL	1 mL
Loop equilibration time	0.5 min	0.5 min
Loop fill time	1 min	1 min
GC		
Inlet temperature	200 °C	200 °C
Carrier (He) flow rate	1.5, 1.8, 2.0 mL/min (28–40 cm/s)	1.8 mL/min (constant flow, approximately 30–33 cm/s)
Inlet split ratio	1:0, 1:1, 1:2, 1:5	1:1 at the split flow of 1.9 mL/min
Oven temperature gradient	Hold 0, 1, 3, 5 min at 35 °C	0–3 min at 35 °C
	Ramping at 2, 3, 4, 5, 8, 10 °C/min	3–21.75 min, ramping to 110 °C at 4 °C/min,
	Ramping to 240–280 °C at 10, 20, 30, 40 °C/min	21.75–25 min, ramping to 240 °C at 40 °C/min
	Hold at 240–280 °C for 2–10	25–30 min at 240 °C
FID temperature	260, 280, 300 °C	260 °C
Detector gas flows	Hydrogen 30–40 mL/min, air 300–400 mL/min	Hydrogen, air, make up at 35, 350, 23.2 mL/min, respectively

HSGC with FID is more popular for analyzing residual solvents in drug substances [4–8] and drug products [9–11] in the industry. Static HS sampling is based on thermostatic partitioning of volatile compounds in a sealed vial between the sample diluent and the gas phase. Sample diluent is a critical factor affecting HSGC method sample load, sensitivity, HS equilibration temperature and time. A good sample diluent for analyzing residual solvents in drug substances or drug products should have a high capability for dissolving a large amount of samples, a high boiling point and a good stability. There are a number of commonly used sample diluents for HSGC analyses, such water, DMSO, N, N-dimethyformamide (DMF), N, N-dimethylacetamide (DMA), benzyl alcohol (BA), 1,3-dimethyl-2-imidazolidinone (DMI), and mixtures of water–DMF or water–DMSO [12].

Water is a good diluent for water soluble samples and analytes, because it is clean, stable and inexpensive. However, many organic synthetic drug substances and drug products have low water solubilities, which would limit the sample load. Meanwhile, using water as a diluent may also lead to a lower method precision than organic solvent, like DMF [5]. When a mixture of water–DMF or water–DMSO is used as a sample diluent, it may increase the solubility of many drug substances or drug products, and decrease the partition coefficient of the analytes, resulting in better transfer of analytes from the diluents to the gas phase, and improved method sensitivity [4,6,10]. If the sample diluent uses these aqueous mixtures, two other important factors, HS equilibration temperature and time, must be taken into consideration for obtaining HS equilibration efficiency. It is required that the HS equilibration temperature should be lower than the boiling point of the sample diluent. Otherwise, if the sample was equilibrated at or above the boiling point of the sample diluent, e.g. water at 100 °C, a large amount of sample diluent may be vaporized (at 100 °C), resulting in a dangerously high sample vial pressure, and a flood of the sample diluent and analytes to the GC system. This means that if water or water–organic mixture is chosen as the sample diluent, the HS equilibration temperature must be lower than 100 °C, i.e. 75–80 °C [4–6,12]. However, more than half of the organic solvents listed in ICH guideline Q3C may not be fully vaporized below 100 °C, because their boiling points are higher than 80 °C. In order to increase method sensitivity, equilibration at a low HS oven temperature requires a longer equilibration time, e.g. 30–90 min [4–6,12], to obtain a good phase distribution of the volatile compounds between the gas phase and the sample diluent.

In contrast, those organic solvents, e.g. DMSO (b.p. 189 °C), DMF (b.p. 153 °C), DMA (b.p. 166 °C), BA (b.p. 204 °C), and DMI (b.p. 105 °C), may provide better solubilization of sample, and they also have higher boiling points than water. When they are used as the sample diluents for HSGC, higher method sensitivity due to better solvent recoveries and improved method precision were observed [3,12,13]. However, DMF, DMA and BA are not very stable at high temperature and are susceptible to degradation when exposed to ultrasonic wave energy during sample preparation. The degradants from high HS equilibration temperature or sonication process during sample preparation may interfere with the analyses of the residual solvents [12]. Since DMSO is more stable at high temperature than the other solvents, e.g. DMF and BA, and has a higher capacity of dissolving drug substances and drug products, as well as a higher boiling point than water, it is a better sample diluent for HSGC analyses.

A number of parameters may affect GC method sensitivity and separation efficiency, such as sample injection split ratio, GC carrier gas linear velocity or flow rate and oven temperature program (isocratic or gradient). The typical GC parameters for a generic separation of residual solvents in previous publications are: split ratio 1:5–20; carrier gas linear velocity 20–36 cm/s; oven temperature at 40 °C isocratic, or with gradient programming from 40 to 90–160 °C at 5–10 °C/min [3–7,12,13]. These parameters may be optimized for separation efficiency and detection sensitivity for determining specific ICH Q3C solvents.

The objective of this study was to develop and validate generic HSGC method which has a shorter sample equilibration time, a better separation for most of the interested solvents, a higher sensitivity and a broader concentration range. We selected 4 mL of DMSO as the sample diluent for 200 mg of drug substance in order

Table 2
ICH classes 2 and 3 solvents unsuitable for this HSGC method.

Number	Solvent	FW (g/mol)	b.p. (°C)
1	Anisole	108	154
2	Cumene	120	152
3	Tetralin	132	206–208
4	Ethylene glycol	62	197
5	N, N-dimethylacetamide	87	164–166
6	Formamide	45	210
7	Sulfolane	120	285
8	N-methyl pyrrolidone	99	202–204
9	Formic acid	46	101
10	Acetic acid	60	118