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Liquid paraffin as new dilution medium for the analysis of high boiling point residual solvents with static headspace-gas chromatography

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ABSTRACT

Residual solvents are volatile organic compounds which can be present in pharmaceutical substances. A generic static headspace-gas chromatography analysis method for the identification and control of residual solvents is described in the European Pharmacopoeia. Although this method is proved to be suitable for the majority of samples and residual solvents, the method may lack sensitivity for high boiling point residual solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide and benzyl alcohol. In this study, liquid paraffin was investigated as new dilution medium for the analysis of these residual solvents. The headspace-gas chromatography method was developed and optimized taking the official Pharmacopoeia method as a starting point. The optimized method was validated according to ICH criteria. It was found that the detection limits were below 1 μg/vial for each compound, indicating a drastically increased sensitivity compared to the Pharmacopoeia method, which failed to detect the compounds at their respective limit concentrations. Linearity was evaluated based on the R^2 values, which were above 0.997 for all compounds, and inspection of residual plots. Instrument and method precision were examined by calculating the relative standard deviations (RSD) of repeated analyses within the linearity and accuracy experiments, respectively. It was found that all RSD values were below 10%. Accuracy was checked by a recovery experiment at three different levels. Mean recovery values were all in the range 95–105%. Finally, the optimized method was applied to residual DMSO analysis in four different Kollicoat® sample batches.

1. Introduction

Residual solvents (RS) are defined as volatile organic chemicals which were used during the manufacturing process of pharmaceutical products. At some stages in drug synthesis, organic solvents may be used to enhance yields or to obtain appropriate physicochemical properties such as crystal form and solubility [1]. However, RS have no therapeutic value and may even possess toxic properties for patients or environment. Therefore, appropriate limits for RS in pharmaceuticals have been proposed. For a complete list and permitted amounts of RS in pharmaceuticals, a guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is available [2]. For the identification and control of RS, an analytical method is described in the European Pharmacopoeia (Ph. Eur.) [3]. Owing the volatile nature of RS, the reported analytical technique is a static headspace-gas chromatography (sHS-GC) method. Theory and practical applications of this technique can be found in the reference work of Kolb and Ettre [4]. The use of sHS-GC for RS analysis has been extensively investigated and reviewed [5–8]. Recent advances in RS analysis generally deal with sensitivity improvement for selected RS. Modern developments include HS-solid-phase microextraction [9,10], HS-liquid-phase microextraction [11], thermal desorption [12] and purge-and-trap [13]. Separation based improvements comprise fast GC [14], programmed temperature vaporization injection [15] and the introduction of comprehensive two-dimensional GC [16].

A key factor for RS analysis with sHS-GC is the selection of a suitable dilution medium [17]. Commonly used matrix media include water, in case of water-soluble samples, and organic solvents such as N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and 1,3-dimethyl-2-imidazolidinone (DMI) in case of water-insoluble samples. However, these organic solvents used as dilution media can be present in pharmaceuticals as RS themselves. Moreover, due to their low vapor pressure, they possess high partition coefficients in most dilution media. Hence, sensitive detection may be challenging. Recently, ionic liquids were reported as suitable matrix

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media for the analysis of high-boiling point RS [18,19]. Ionic liquids have extremely low vapor pressures and can dissolve a wide range of compounds. However, background peaks can possibly interfere with analyte peaks [20]. Moreover, ionic liquids are relatively expensive and there are currently no selection criteria to use a particular ionic liquid for RS analysis [21].

In this study, the sHS-GC method described in the Ph. Eur. was evaluated for the analysis of some common RS with low vapor pressure such as DMF, DMSO, N,N-dimethylacetamide (DMA) and benzyl alcohol (BA). DMF and DMA belong to the group of Class 2 RS with limits of 880 ppm and 1090 ppm, respectively. DMSO and BA are Class 3 RS with a general limit of 5000 ppm. A new sHS-GC method, using liquid paraffin as new dilution medium, was optimized, validated and applied to the analysis of Kollicoat® samples.

2. Experimental

2.1. Reagents and materials

Analytical grade liquid paraffin, DMA and BA were purchased from Sigma–Aldrich (St. Louis, MO, USA). Analytical grade DMF was obtained from Fisher Scientific (Loughborough, UK) and GC-grade DMSO was from Merck (Darmstadt, Germany). Treated Kollicoat® samples were donated by Formac Pharmaceuticals (Leuven, Belgium). DMSO-free Kollicoat® was obtained from BASF (Antwerp, Belgium). Headspace vials (22 ml) and high-temperature resistant silicone/PTFE caps were obtained from Filter Service (Eupen, Belgium).

2.2. Preparation of solutions

2.2.1. Sample vials

According to Ph. Eur. prescriptions, the total sample amount in the vial should be 50.0 mg. However, due to limited sample availability, the sample amount was reduced to 25.0 mg/vial. The sample was directly weighed into a HS vial, to which 1.000 g of liquid paraffin was added.

2.2.2. Preparation of the stock reference solution

A stock reference solution was prepared by weighing 44.0 mg of DMF and 54.5 mg of DMA into a conical flask. Liquid paraffin was added until a total weight of 100.000 g was attained (=S1). Amounts of 50.0 mg of DMSO and BA were weighed in a second conical flask together with 20.000 g of S1. Liquid paraffin was added to obtain a total weight of 100.000 g (=S2). Finally, the stock reference solution was obtained by 1:1 dilution of S2 with liquid paraffin. Mixtures were always thoroughly stirred with a magnetic stirrer for 10 min. The stock reference solution thus contained DMF, DMA, DMSO and BA at concentrations of 44.0 $\mu g\,g^{-1}$, 54.5 $\mu g\,g^{-1}$, 250 $\mu g\,g^{-1}$ and 250 $\mu g\,g^{-1}$ in liquid paraffin, respectively. To the vials, 1.000 g of stock reference or an appropriate dilution was added. To all vials containing reference solution, 25.0 mg of DMSO-free Kollicoat® was added as sample matrix compensation.

2.3. Instrumentation

The GC instrument was a Delsi (Suresnes, France) DN200 equipped with flame ionization detection. The analytes of interest were separated on an AT™-Aquawax column (30 m × 0.53 mm × 0.5 μm) purchased from Grace (Deerfield, IL, USA). As carrier gas, helium 5.6 was used at a flow rate of 4.0 ml min^{-1}. The headspace sampler was a Turbomatrix HS40 from Perkin Elmer (Waltham, MA, USA). The optimized instrument settings versus the settings mentioned in Ph. Eur. are summarized in Table 1.

Table 1
Parameter settings of the optimized HS-GC method compared to the settings mentioned in Ph. Eur.

Parameter	Ph. Eur. setting (system B)	Optimized setting
HS		
Oven temperature	80 °C	90 °C
Needle temperature	–	180 °C
Transferline temperature	85 °C	190 °C
Equilibration time	60 min	45 min
Pressurization time	0.5 min	1.5 min
Injection volume/time	1 ml	0.08 min
GC		
Injector	140 °C	200 °C
Detector	250 °C	250 °C
Temperature program	50 °C for 20 min	100 °C for 5 min
	6 °C min^{-1}	20 °C min^{-1}
	165 °C for 20 min	200 °C for 5 min
Total analysis time	59.2 min	15 min

2.4. Validation

RS in the samples were quantified by the method of external calibration. The optimized method was validated by determining the limit of detection (LOD), limit of quantification (LOQ), linearity, precision and accuracy. The effect of sample matrix on the response was also checked.

2.4.1. LOD/LOQ

For each compound, a calibration curve was constructed in a range from 2.5 μg/vial to 12.5 μg/vial. Five quantity levels were prepared over this range and each level was repeated in quadruplicate. Total solution weight in each vial was 1.000 g. To each vial, 25 mg of DMSO-free sample matrix was added. LOD was calculated using the formula $(3.3^*\sigma)/S$, whereas this was $(10^*\sigma)/S$ for the LOQ. In these formulae, σ is the standard error of the intercept and S the slope of the calibration curve.

2.4.2. Linearity

For each compound, linearity was checked in a range from its LOQ to 125% of the reference concentration prescribed in the Ph. Eur. (corresponding to 1/20 of the compound's limit concentration). Over the specified ranges, six different concentration levels were prepared and each analyzed in quadruplicate. Also here, total solution weight was 1.000 g in each vial, in which 25 mg of DMSO-free sample matrix was added. Linearity was evaluated by calculating the coefficient of determination R^2 and inspection of residual plots.

2.4.3. Accuracy

Method accuracy was evaluated by carrying out recovery experiments at three concentration levels. As first quantity level, the respective LOQ amounts of the analytes of interest were spiked to vials containing 25 mg of DMSO-free Kollicoat®. Next, amounts corresponding to 1/40 of the official limit concentrations were spiked to 25 mg of DMSO-free Kollicoat®, which was the sample amount in this work. The third quantity levels were amounts corresponding to 1/20 of the official limit concentrations, as stated in the Ph. Eur., where a sample amount of 50 mg/vial is prescribed. Therefore, these amounts were spiked to vials containing 50 mg of DMSO-free Kollicoat®. For a clear overview, the real spiking amounts of each analyte at the various quantity levels are given in Table 2. The peak areas obtained with the spiked samples were compared with peak areas obtained with the stock reference solution. For the LOQ amounts however, a separate reference solution was prepared containing all analytes at their respective LOQ concentrations. Reference vials were prepared by adding 1.000 g of stock reference solution (or LOQ reference solution) to 25 mg (or 50 mg following literal Ph. Eur. prescription) of solvent-free Kollicoat®. The recov-

Table 2
Real spiking amounts of each analyte at three different quantity levels.

Quantity level	DMF (μg/vial)	DMA (μg/vial)	DMSO (μg/vial)	BA (μg/vial)
LOQ	0.8	1.1	1.6	1.1
Limit 1[a]	22	27.3	125	125
Limit 2[b]	44	54.5	250	250

[a] 1/40 of official limit concentration when 25 mg sample is used (as in this study).
[b] 1/20 of official limit concentration when 50 mg sample is used (Ph. Eur. prescription).

ery was calculated by comparing the measured concentrations with the known added amounts. The whole procedure was carried out in triplicate.

2.4.4. Precision

Instrument repeatability was assessed by evaluating the RSD of the peak areas obtained for each quantity level in the linearity experiment. Method precision was considered as the RSD of the recoveries obtained with the accuracy experiment.

2.5. Method application

The optimized method was applied to four sample batches of Kollicoat® which were treated with DMSO. These samples were first cooled with liquid nitrogen and milled for better dispersion into the liquid paraffin. For quantification, the method of external standard was used. Sample vials contained 25.0 mg of Kollicoat® to which 1.000 g of liquid paraffin was added. Reference vials contained 25.0 mg of DMSO-free Kollicoat® and 1.000 g of a 1:1 dilution of the stock reference solution.

3. Results and discussion

3.1. Ph. Eur. method

To evaluate the performance of the Ph. Eur. method for the analytes of interest, they were analyzed according to the exact Ph. Eur. prescriptions (see Table 1). Therefore, an aqueous reference solution containing a mixture of DMF, DMA, DMSO and BA, at concentrations of 1/20 of the analyte's respective official limit concentrations, was prepared. Hence, analyte amounts in the vial were 44.0 μg for DMF, 54.5 μg for DMA, and 250 μg for both DMSO and BA.

According to the Ph. Eur., a sample solution must be prepared by weighing 200.0 mg of sample in a volumetric flask and dissolving it in 20.0 ml of an appropriate dilution medium, resulting in a sample concentration of 10 mg/ml. The proposed sample dilution media include water, DMF or DMI, depending on the solubility properties of the sample and expected presence of DMF as RS. Sample vials are prepared by pipetting 5.0 ml of sample solution into a HS vial

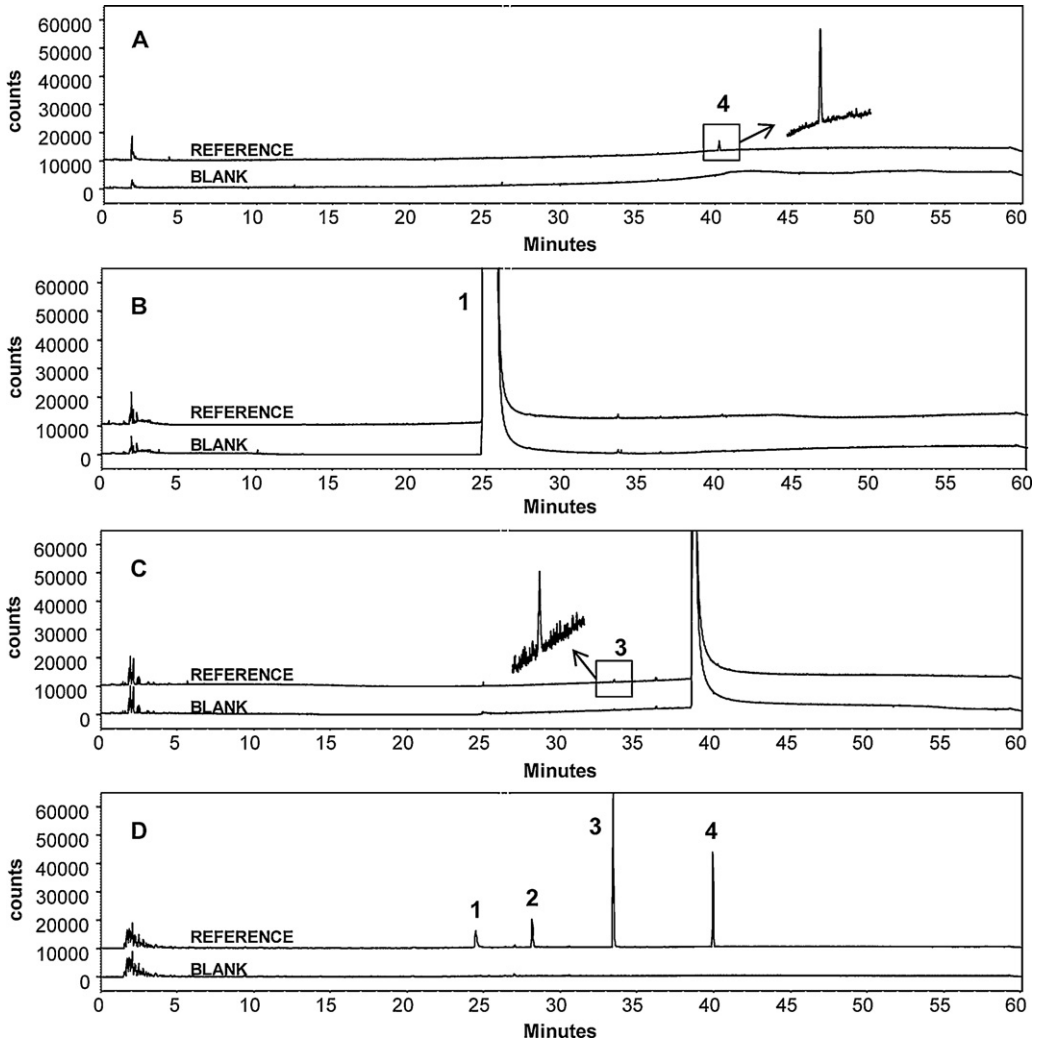

Fig. 1. Overlay of chromatograms of blank and reference solutions, containing the analytes at a concentration of 1/20 of the official limit concentrations, in four different dilution media: A, water; B, DMF; C, DMI; D, liquid paraffin. The assigned peaks are (1) DMF, (2) DMA, (3) DMSO and (4) BA.

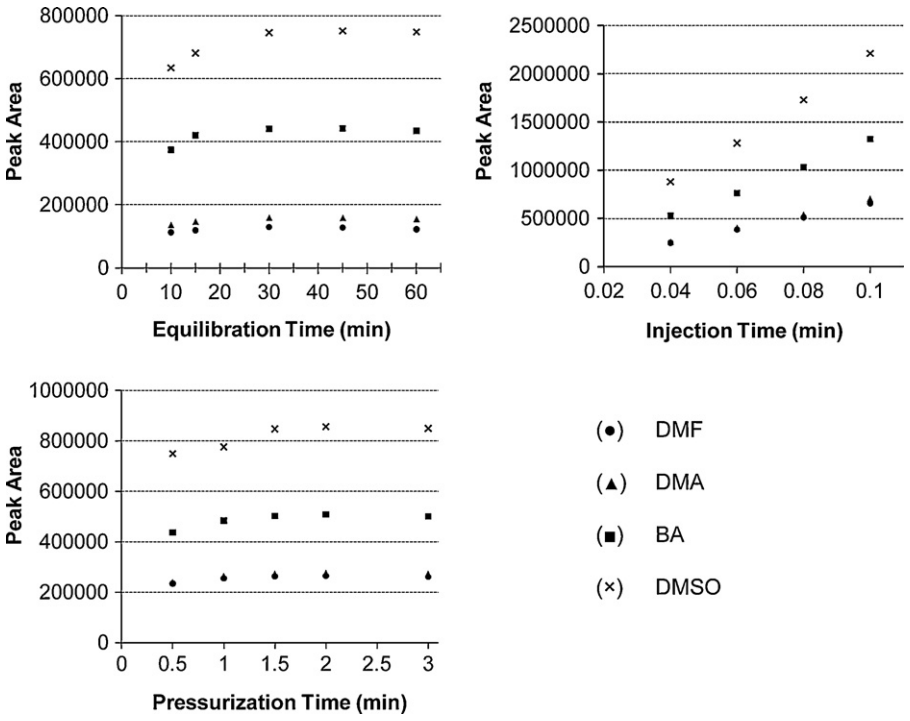

Fig. 2. Optimization of equilibration time, injection time and pressurization time of the HS system, using liquid paraffin as dilution medium.

and adding 1.0 ml of water, while reference vials are prepared by pipetting 5.0 ml of sample solution and adding 1.0 ml of reference solution. Hence, the sample amount in the vial is always 50 mg and the official limit for a particular analyte is exceeded if the peak area in the sample chromatogram is more than half the peak area in the reference chromatogram.

In the first experiment, the Ph. Eur. method was applied to vials which contained 1.0 ml of reference solution and 5.0 ml of pure dilution medium (thus without sample matrix) to check the system suitability in terms of sensitivity. Therefore, three possible combinations were tested: vials contained 1.0 ml of reference solution together with 5.0 ml of water, DMF or DMI, respectively. The obtained chromatograms are shown in Fig. 1A–C. When water was added to the reference solution, only BA was clearly detected. In the case of DMF as dilution medium, other analytes than DMF could not be detected. When adding DMI as dilution medium, only DMSO could be detected but, with a S/N ratio < 10. To conclude, the Ph. Eur. method did not offer enough sensitivity for the detection of the four analytes of interest at 1/20 of their respective official limit concentrations, as is prescribed in the Ph. Eur.

3.2. Method optimization

3.2.1. Liquid paraffin

As a first optimization step, liquid paraffin was introduced as new dilution medium. Because water and liquid paraffin are not miscible, the stock reference solution was immediately prepared in liquid paraffin. Since liquid paraffin is too viscous for pipetting, the solutions were weighed into the vials. Similarly to the exact Ph. Eur. method, 1.000 g of stock reference solution and 5.000 g of pure liquid paraffin were added to the HS vials. The settings of all other parameters were kept identical to those prescribed in the Ph. Eur. The obtained chromatogram is shown in Fig. 1D. Here, contrary to the dilution media used before, all analyte peaks were clearly detected and thus sensitivity was improved remarkably.

3.2.2. HS optimization

For additional sensitivity improvement, sample was directly weighed into the vials, to which 1.000 g of liquid paraffin was added. Hence, RS are more concentrated in the liquid phase of the vial. Further optimization was done by optimizing several HS parameters such as equilibration temperature, equilibration time, pressurization time and injection time. The HS parameters were optimized using 1.000 g of stock reference solution in all vials. Vials were analyzed in triplicate at each variable. The equilibration temperature could be raised to 90 °C without any interference from the paraffin matrix. Higher temperatures can be used, but then blank peaks could appear in the chromatogram. Curves demonstrating the influence of the equilibration time, pressurization time and injection time are shown in Fig. 2. Equilibration time was investigated at 10, 15, 30, 45 and 60 min. Although the peak area reached a plateau at 30 min, repeatability was better at 45 min with all RSD values equal to or lower than 1.0%. Hence, 45 min was selected as optimal value. The pressurization time was checked at 0.5, 1.0, 1.5, 2.0 and 3.0 min. According to the graph, 1.5 min was chosen as best value. Finally, the influence of the injection time was verified at 0.04, 0.06, 0.08 and 0.10 min. Here, it was decided to choose 0.08 min because the peak shape deteriorated when using an injection time of 0.10 min.

3.2.3. GC optimization

The temperature program of the Ph. Eur. method takes a total analysis time of about 60 min (see Table 1). For the analysis of DMF, DMA, DMSO and BA, a higher initial temperature, a faster ramp and shorter hold times were selected. This way, the analysis time of the optimized temperature program was reduced to 15 min.

3.3. Method validation

Several validation parameters such as specificity, LOD/LOQ, linearity, precision and accuracy were evaluated.

Table 3
Validation results obtained with the optimized HS-GC method.

	LOD (μg/vial)	LOQ (μg/vial)	Range (μg/vial)	Equation	R^2	RSD (%)
DMF	0.3	0.8	0.8–52.8	$y = 4976.5x - 999.4$	0.9994	0.4–4.2
DMA	0.4	1.1	1.1–65.4	$y = 3740.2x + 585.2$	0.9977	0.3–7.1
DMSO	0.5	1.6	1.6–300	$y = 4750.2x - 20373.7$	0.9992	1.1–5.4
BA	0.4	1.1	1.1–300	$y = 3315.5x - 11785.0$	0.9978	0.6–8.7

3.3.1. Specificity

To evaluate specificity, peak separation and possible interferences from DMSO-free Kollicoat® were checked. Therefore, all four analytes were spiked to 25 mg of DMSO-free Kollicoat® at a fixed concentration of 10 μg/vial each. A blank chromatogram was also recorded representing 25 mg of DMSO-free Kollicoat® to which 1.000 g of liquid paraffin was added. The obtained chromatograms are shown in Fig. 3. A peak with a retention time of 4.8 min was observed in the blank chromatogram. The retention times of the analyte compounds were 3.7 min, 4.5 min, 6.8 min and 10.1 min for DMF, DMA, DMSO and BA, respectively. A critical peak separation was observed between the peaks of DMA and the unknown blank peak. The resolution (calculated according to Ph. Eur.) between those two peaks was calculated and was found to be 1.65.

3.3.2. LOD/LOQ

First, LOQ was estimated based on a manual S/N calculation. It was found that S/N was 10 at an amount of about 2.5 μg for each compound. Subsequently, a calibration curve was constructed in a range from 2.5 μg to 12.5 μg, considering five concentration levels. Each concentration level was analyzed in quadruplicate. All obtained peak areas were subject to regression analysis. LOD was calculated using the formula $(3.3^*\sigma)/S$, whereas this was $(10^*\sigma)/S$ for the LOQ. In these formulae, σ is the standard error of the intercept and S the slope of the calibration curve. As can be seen in Table 3, all LOD amounts were equal to or below 0.5 μg/vial. Hence, sensitivity was drastically improved compared to the Ph. Eur. method, where 1/20 of the official limit levels (being 44 μg/vial for DMF, 54.5 μg/vial for DMA and 250 μg/vial for both DMSO and BA) could not be detected.

3.3.3. Linearity

For each compound, the range in which linearity was investigated started at its respective LOQ amount. The highest amounts in the investigated range were 125% of the reference amounts as prescribed in Ph. Eur. (corresponding to 1/20 of the official limit amounts). Hence, the reference amounts used in this study (corresponding to 1/40 of the official limit amounts) are also included in the investigated range. Six quantity levels were prepared over these ranges. The linearity was evaluated by calculating the coefficients of determination (R^2) and plotting the residual values. All R^2 values were >0.997 (Table 2) and residuals were randomly distributed, as demonstrated in Fig. 4.

Table 4
Recovery values (%) for each compound at three different concentration levels.

Quantity level	DMF	DMA	DMSO	BA
LOQ	103.0	92.8	107.7	103.4
	103.2	98.3	115.9	91.6
	104.6	88.4	114.5	102.1
Limit 1[a]	95.3	96.7	95.4	97.9
	89.7	91.9	90.2	95.0
	87.9	91.9	97.6	97.6
Limit 2[b]	106.1	103.4	93.7	98.3
	104.2	101.9	99.3	101.0
	101.8	102.7	96.1	101.7
Mean	99.5	96.4	101.2	98.7
RSD % ($n = 9$)	6.9	5.7	9.2	3.8

[a] 1/40 of official limit concentration when 25 mg sample is used (as in this study).
[b] 1/20 of official limit concentration when 50 mg sample is used (Ph. Eur. prescription).

3.3.4. Accuracy

To examine accuracy, a recovery experiment was performed. Therefore, known analyte quantities were spiked to vials containing solvent-free Kollicoat®. Three quantity levels were tested: LOQ amounts, limit amounts with respect to a sample amount of 25 mg used in this study and limit amounts with respect to a sample amount of 50 mg according to the Ph. Eur. prescriptions. Each quantity level was analyzed in triplicate. The obtained recovery values are shown in Table 4. Mean recoveries ($n = 9$) were found to be between 95% and 105% for all analytes, which are acceptable values for sHS-GC. Single recovery values fell into the range of 80–120%.

3.3.5. Precision

Instrument repeatability was checked by calculating the RSD values of the peak areas obtained for each quantity level of the linearity experiment. The lowest and highest RSD value for each compound are given in Table 3. All RSD values were below 10%, which is acceptable for a HS-GC method. Method precision was evaluated by calculating the RSD values of the recoveries obtained with the accuracy experiment. Also here, all RSD values were below 10%.

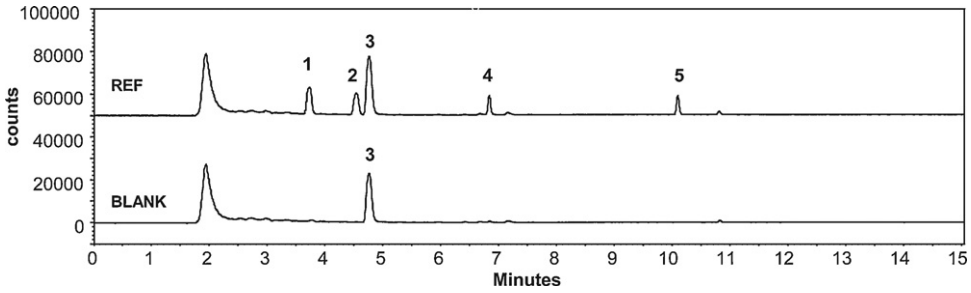

Fig. 3. Overlay of chromatograms of DMSO-free Kollicoat® (BLANK) and a reference solution containing all four analytes at a concentration of 10 μg/vial each (REF). The assigned peaks are (1) DMF, (2) DMA, (3) *unknown blank peak*, (4) DMSO, and (5) BA.

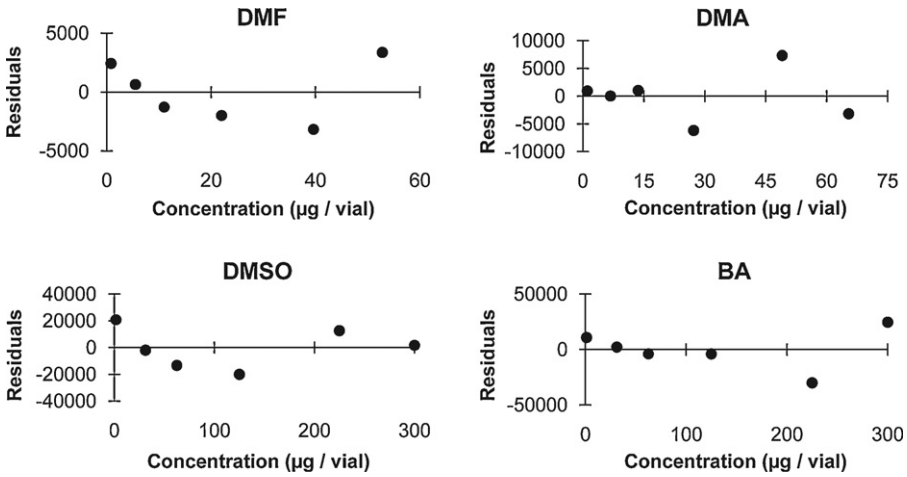

Fig. 4. Residual plots of the four analytes over the investigated linearity range.

Table 5
DMSO contents in four different Kollicoat® sample batches.

Sample batch	Content DMSO		RSD (%)
	µg/vial	ppm	
A	63.3	2532	4.6
B	60.3	2410	10.0
C	110.1	4406	1.5
D	69.0	2758	11.3

3.4. Method application

Four sample batches were analyzed with the procedure mentioned in Section 2.5. The obtained contents are summarized in Table 5.

The results indicated that residual DMSO could be successfully quantified below the official limit concentration of 5000 ppm (or 125 µg/vial). However, the RSD ($n = 3$) of the contents found in samples B and D was rather high with values of 10% and 11.3%, respectively. This may be explained by the possibility that residual DMSO was not homogenously distributed in the Kollicoat® polymer, as pre- and post treatment procedures of the sample batches differed.

4. Conclusion

In this work, liquid paraffin was introduced as new dilution medium for HS-GC determination of high boiling point RS such as DMF, DMA, DMSO and BA. Although the application range of liquid paraffin as dilution medium is rather small with respect to general RS analysis due to limited sample or analyte compatibility, it may demonstrate some strong advantages for some applications. First, apart from a system peak indicating the holdup time, no peak appears in a chromatogram at HS temperatures below 100 °C, ruling out interference with potential analyte peaks. Another advantage is the enormously increased sensitivity for the investigated high boiling point RS. The detection limits were below 1 µg/vial and the quantification limits below 2 µg/vial for each compound. As a consequence, these solvents could be quantified far below their respective limit concentrations. Other validation aspects such as linearity, precision and accuracy were within acceptable limits for HS-GC methods. Since high purity liquid paraffin is easy to obtain and relatively cheap, it is suitable for routine HS-GC analysis of particular sample types. Finally, the developed method was successfully applied to residual DMSO analysis in Kollicoat® samples. DMSO could be quantified below its limit concentration of 5000 ppm.

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