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Short communication

Headspace gas chromatography method for the analysis of volatile impurities in a hormone replacement transdermal patch

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Abstract

A headspace GC method was developed for the analysis of residual solvents in transdermal skin patches. These solvents could arise from the manufacture and process of the patch material. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Transdermal patch; Pharmaceutical analysis; Toluene; Isopropanol

1. Introduction

Transdermal delivery systems in hormone replacement therapy offer distinct advantages over other conventional dosage forms by combining the administration of female hormones with an advanced delivery system [1]. These advantages include bypassing the stomach and intestine where many problems related to the pH-instability and poor absorption of the drug compound could arise. Skin patches capable of delivering hormonal drugs transdermally are very attractive for the ease of their use. CombiPatch (estradiol/norethindrone acetate transdermal delivery system supplied by Rhône-Poulenc Rorer Pharmaceuticals, Collegeville, PA, USA) is an estrogen and progestogen replacement patch for constant optimal dose delivery in the treatment of postmenopausal symptoms and prevention/treatment of osteoporosis. The adhesive for the patch functions both as the drug delivery platform and as a means of attaching the patch to the skin. It is designed to be comfortable, cosmetically appealing, and easy to use resulting in a patch that is small, thin, flexible and translucent. However, the design of a proper transdermal patch offers a challenge in that small variations in the process of application of the adhesive and the drug could lead to a variation in dose delivery [2,3]. Therefore, a careful control and analysis of chemical constituents present in the delivery system is extremely important. Transdermal patches usually contain adhesive material which is coated onto the polymer sheet as a solution from which the solvent is then removed using appropriate drying processes. The active ingredient is similarly applied to the patch in the solution form either in the same application with the adhesive or subsequent to it. In any event, the knowledge and control of the levels of the volatile solvents left behind after the process and during stability/storage is extremely important to ensure product quality. In the preparation of CombiPatch, toluene and isopropanol are used as solvents. A sensitive method was required for their analysis in CombiPatch. Solvents have traditionally

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been analyzed in drug products by gas chromatographic methods [4–7]. Direct injection of a solution or extract of the CombiPatch will have the potential to contaminate the chromatographic flow path because of the presence of non-volatile materials and their potential thermal degradation products which could be formed in the hot injector. Guard columns have been used to stop non-volatile materials from entering the chromatographic columns. However, breakthrough volume of the guard column, its control, and the need to change the guard columns make it a less desirable approach. Ideally, after each injection and, if possible, at all times the flow path should be clean and free from residues from the previous injection. Built up charred material in the injector from multiple injections are detrimental to the reliability especially in the analysis of trace components.

We chose automated static headspace injection capillary gas chromatography (GC) to develop a method for the analysis of toluene and isopropanol in CombiPatch. For a high quality determination it is essential to ensure the homogeneity of the sample which cannot be adequately performed in the solid state due to matrix-trapping effects. It was, therefore, necessary to release all solvents in a homogeneous solution before headspace GC analysis. This was performed by extracting the contents of the patch with dimethylformamide (DMF) overnight. DMF is a strong solvent capable of solubilizing a wide range of organic compounds.

2. Experimental

2.1. Chemicals and materials

CombiPatches of different sizes containing coat masses of 9.5–10.5 mg/cm^2 were obtained from Noven Pharmaceuticals, Miami, FL, USA. The solvents, DMF, toluene and isopropanol were Omnisolve grade (VWR Scientific, West Chester, PA, USA) and were >99% pure by GC. DMF which was used to extract the patches and to make the standards was rendered free from trace level contaminants by purging with nitrogen gas for 2 h at a flow-rate of 5 ml/min. Thirty ml capacity headspace glass vials, septa and aluminium closures were all obtained from Hewlett-Packard (Wilmington, DE, USA).

2.2. Chromatographic system

Experiments were performed on a Hewlett-Packard Model 5890 Series II gas chromatograph equipped with a Model 19395A automated headspace autosampler. A flame ionization detector was used to obtain response data. Chromatographic data were collected and processed using the Waters Expertease Chromatographic Data Management System (Waters, Milford, MA, USA).

2.3. Chromatographic method

A Supelco Nukol (Supelco, Bellefonte, PA, USA), acid-modified, bonded polyethylene glycol megabore capillary column (90 m×0.53 mm I.D.) with a 0.5 μm film thickness was utilized for the chromatographic separation of the solvents and matrix components. Chromatography was initiated with a non-split injection on a packed column injector at a flow-rate of 6 ml/min of helium as a carrier gas. A minimum flow-rate of 0.2 ml was received from the GC packed column injector to prevent the sample from backing up into the injector lines during injections from the headspace autosampler. The remainder of the helium flow was derived from the headspace autosampler. The packed column injector was maintained at 150°C. The flame ionization detector was heated to 280°C. Helium, at a flow-rate of 20 ml/min was used as a make-up gas. The temperature program used an initial oven temperature of 35°C which was then increased at 1°C/min to 65°C in ramp 1 followed by the rapid increase at the rate of 35°C/min to 190°C where it was held for 5 min. Total analysis time was 40 min. The headspace autosampler conditions were as follows: servo air pressure, 3.0 bar; auxiliary pressure 1.2 bar; bath temperature, 80°C; sample loop temperature, 120°C. The headspace autosampler program included a 10 s (second) pressurization time followed by a vent time of 10 s and subsequent injection for 10 s, during which the contents of the loop are flushed onto the GC column. These headspace autosampler events were separated by 7, 2 and 1 s delay times, respectively. The constant heating accessory of the head-

space autosampler was used to heat all samples for the same time. Each sample was heated in the heating bath for three analysis times (120 min). The actual equilibration waiting period for all samples in a run is 120 min because samples are automatically dropped by the constant heating time (CHT) accessory before time so that a constant heating time is maintained for all samples.

2.4. Sample and standard preparation, quantitation and calculations

2.4.1. Standard preparation

A standard containing approximately 10 mg/ml of toluene and 21 mg/ml of isopropanol is prepared by first filling a 25-ml volumetric flask with ~15 ml of DMF, weighing the two solvents accurately and then diluting the flasks to volume with DMF.

2.4.2. Sample extraction

The sample patches extracted in this method were of 9, 16, 20 and 30 cm^2 size. The number of patches used were 3, 2, 2, 1 and their total coat masses were 270, 320, 400 and 300 mg, respectively.

The analyte patches were cut into 2–4 pieces depending upon the diameter of the patch, the protective liner was then removed, and the patch introduced into a sample bottle containing 20 ml of DMF with the help of forceps premoistened with DMF to avoid sticking. The patch was extracted by rotating the contents of the bottle overnight on a mechanical rotator. The clear solution obtained was used to prepare the samples for analysis.

2.4.3. Sample preparation

Samples for analysis were prepared by placing four accurately measured 1-ml aliquots into separate headspace vials of 30 ml capacity. To these vials, 0, 5, 10 and 15 μl of the standard solution was added with the help of a 50-μl capacity syringe. The vials were labeled and closed with the septa, aluminium closures and a crimper. These vials were placed in the CHT accessory of the headspace autosampler.

2.4.4. Quantitation

Quantitation was performed by the standard addition method to eliminate any concerns due to the matrix effect. In this method four analyses were performed for each sample, one without any addition and the other three after the samples had received incremental addition of 5, 10 and 15 μl of the standard solution separately. The peak areas from these four injections are plotted on the *y*-axis and the analyte concentration on the *x*-axis. The concentration of the analyte in the solution is then calculated from the *y*-intercept and the slope of the linear regression line.

2.4.5. Calculation

The amount of residual solvent in the patch is calculated based on its coat mass which represents the total amount of adhesive and the drug substance applied on the polymeric patch liners. It is given by the following expression:

amount of solvent as percentage of coat mass

$$= \frac{Y}{S} \cdot \frac{C}{W}$$

where: Y=y-intercept of the fitted line for that solvent, S=slope of the fitted line for that solvent, C=concentration of the solvent in the standard in mg/ml and W=coat mass in mg.

An Excel (Microsoft, Redmond, WA, USA) spreadsheet (version 5.0) can conveniently be formatted to calculate the percentage of solvent based on the above expression and only requires entry of coat mass, standard addition concentrations, and corresponding peak areas to obtain the answer.

3. Results and discussion

In a closed system at a given temperature and pressure an equilibrium is reached between the components of the liquid phase and its vapor phase. At this equilibrium, the concentrations in the vapor phase are representative of the concentration in the liquid phase. It is, therefore, possible to know the concentration of the solution by analyzing the volatiles in the vapor phase by GC. It is, however, necessary to consider the factors which play a role in the liquid–vapor equilibrium which have been described in the literature [1–6]. In a solution of a complex mixture such as adhesive materials of a skin patch, the activity of the analyte can be influenced by

the nature and concentration of the matrix components. For accurate quantitation it is, therefore, necessary to have the sample solution and the standard as close as possible in their contents. The standard addition method of quantitation is an ideal solution for such quantitative work. The standard addition method also allows the use of headspace analysis under non-equilibrium conditions since the standard and the sample experience identical conditions. In the analysis of toluene and isopropanol, we utilized these approaches for quantitation. We chose a 90 m megabore Nukol (Supelco) column for its higher capacity and ability to separate the matrix interference from the toluene peak. Fig. 1 shows a chromatogram of a sample solution under the conditions described above. Fig. 2 shows a chromatogram of a sample solution which had been heated at 80°C for 24 h. Separation of the isopropanol and toluene peak from the matrix interference/thermal degradation products is shown which establishes the specificity of the method. Validation studies were carried out to demonstrate precision, linearity, accuracy and ruggedness of the method. System precision was established by making six replicate injections of a solution containing approximately 210 μg/ml of isopropanol and 109 μg/ml of toluene in DMF prepared from the standard solution. This corresponds to 0.07% of the isopropanol and 0.04% of toluene in the sample solution based on 300 mg of approximate total coat mass. The relative standard deviations (RSDs) for isopropanol and toluene were 1.7 and 2.3%, respectively. Method precision is determined by adding 10 μl of standard solution 1 to six separate 1-ml aliquots of the placebo solution and analyzing them. RSD for both the isopropanol and toluene was found to be 1.1%. Method precision was determined by one analyst on one day. For transdermal patches, recovery of the analyte is an important consideration because of the complexity of the matrix which could lead to the trapping of the analytes. The use of a strong solvent like dimethylformamide is necessary to ensure release of all matrix contents into a homogeneous sample solution. In an ideal recovery experiment, the analyte should be introduced in the sample under conditions as identical to the actual process as possible. Therefore, in our recovery experiments we spiked the analyte isopropanol and toluene directly onto the coating of the placebo patches and allowed these solvents to be matrix-trapped for some time instead of adding the solvents directly to the DMF extracts. Recovery studies were performed at 0.31%, 0.15% and 0.06% levels for toluene and 0.58%, 0.29% and 0.11% of isopropanol with respect to the coat mass of 360 mg

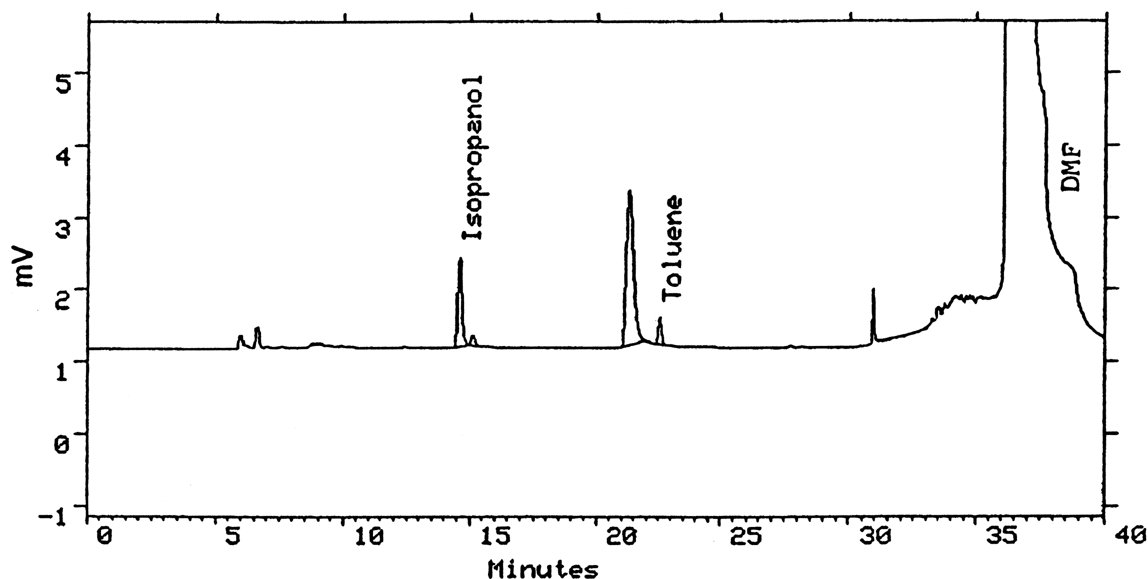

Fig. 1. Chromatogram of a sample solution.

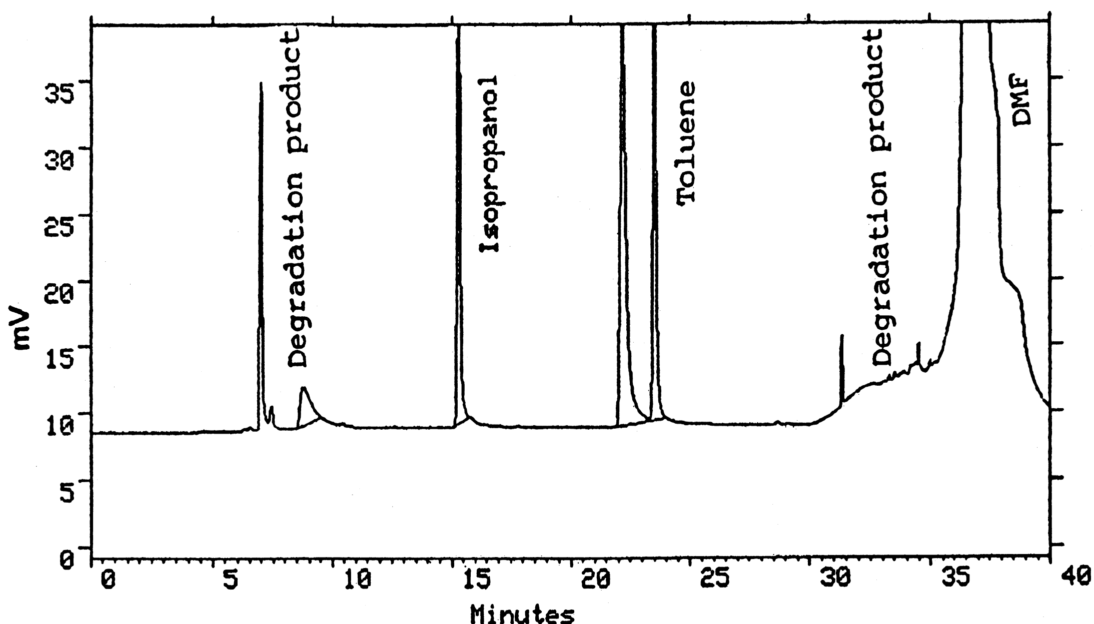

Fig. 2. Chromatogram of a sample solution after heating at 80°C for 24 h.

Table 1
Recovery of toluene and isopropanol from CombiPatch

Sample No.	Amount added (μg)		Amount recovered (μg)		Recovery (%)	
	Toluene	Isopropanol	Toluene	Isopropanol	Toluene	Isopropanol
Level 1, 0.31% toluene and 0.58% isopropanol						
1	1091.2	2100	1159.2	195	106	93
2	1091.2	2100	1191.3	1785.6	109	85
3	1091.2	2100	1188.5	2102	109	100
4	1091.2	2100	1004	1751.1	92	83
				Mean, $n=4$ (RSD)	104 (7.8)	90 (8.5)
Level 2, 0.15% toluene and 0.29% isopropanol						
5	1050	545.6	1110.8	611.8	106	112
6	1050	545.6	997.5	602	95	110
7	1050	545.6	998.9	602.1	95	110
8	1050	545.6	925.8	505.2	88	93
				Mean, $n=4$ (RSD)	96 (7.6)	106 (8.6)
Level 3, 0.06% toluene and 0.11% isopropanol						
9	218.2	420	220.3	426.2	100.9	101
10	218.2	420	209.3	399.2	95.9	95
11	218.2	420	215.6	417.2	98.8	99
12	218.2	420	214.4	114.8	98.2	98.7
				Mean, $n=4$ (RSD)	98.5 (2.1)	99 (2.7)

in quadruplet. This covers a range of 206% to 40% of the target 0.15% limit specification for toluene. The recovery data is summarized in Table 1. The recoveries ranged from 90.4% to 106.3% for both solvents, and the relative standard deviations were in the 2.7–8.6% range for all these determinations. The linearity of the detector response was demonstrated in the range 0.01 to 0.3% for toluene and 0.03 to 0.6% for isopropanol by sample coat mass. The correlation coefficients of 0.9995 were obtained for both the solvents.

4. Conclusion

Adhesive material of hormonal skin patches can be effectively extracted in DMF using a simple sample preparation method. The DMF extracts can be analyzed by headspace GC using a megabore capillary column. Quantitation by a standard addition technique eliminates any possible matrix effects and the need to establish equilibrium quantitation which can be time consuming. This method of analysis of residual solvents in transdermal patches is sensitive, precise, accurate and automated. A simple sample preparation is required.

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