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CHARACTERIZATION OF POLYMERS USED AS PHARMACEUTICAL EXCIPIENTS BY DYNAMIC HEADSPACE GAS CHROMATOGRAPHY - MASS SPECTROMETRY

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ABSTRACT

The use of dynamic headspace, a continuous gas extraction technique, for the analysis of volatile compounds in polymers is discussed. The present work presents the principles of dynamic headspace and its use in combination with capillary gas chromatography - mass spectrometry. The merits of dynamic headspace sampling in comparison to static headspace, the predominantly used headspace sampling method, are also discussed. To illustrate the technique, analyses of volatile compounds in three different carbohydrate polymers, commonly used as pharmaceutical excipients, are carried out.

INTRODUCTION

Polymers, which as such are non-volatile compounds, can contain substantial amounts of occluded volatile

compounds. The volatile compounds may be present due to incomplete polymerization or substitution reactions e.g. monomers and oligomers. Thermal and thermo-oxidative degradation of the polymer , as well as the conditions used at storage and in the manufacturing process, e.g. solvents and processing agents, can also generate a number of volatile compounds. These compounds are generally present only at a trace level. However, for another major group of volatile constituents in polymer, i.e. additives, the concentration may be in the percent range. Volatile compounds may thus have a substantial influence on the properties of the polymer, ranging from mechanical performance to chemical properties including stability. Moreover, the toxicologic aspects of volatile impurities are evidently also of importance.

Analysis of volatile compounds in polymers can be performed in a variety of ways, such as, direct analysis of the polymer by infrared spectroscopy (1) or thermal volatilisation analysis mass spectrometry (2). If the polymer is soluble, various chromatographic techniques, apart from spectroscopic techniques, also become feasible. Liquid extraction of volatile compounds from insoluble polymers can also be employed. Such methods are commonly based on various refluxing techniques.

During the last decade headspace (HS) techniques have been increasingly used in the studies of volatile compounds in liquid and solid samples (3). Headspace techniques are basically gas/liquid and gas/solid extraction techniques, generally performed in such a way that the gas phase is in equilibrium with the condensed phase (static HS). Recently, the

non-equilibrium counterpart to static headspace i.e. dynamic HS, has been introduced as a sampling method of volatile compounds in polymers. By combining the dynamic headspace with capillary gas chromatography-mass spectrometry (GC/MS), a high resolution separation of the extracted volatile compounds and an unambiguous identification is made possible (4-6).

For technical polymers as polyethylene and poly(vinyl chloride) dynamic headspace gas chromatography - mass spectometry has been shown to be a powerful analysis method (4-6), whereas for carbohydrate polymers no such data are available. In the present work three different carbohydrate polymers commonly used as pharmaceutical excipients are analyzed by means of dynamic headspace gas chromatography - mass spectrometry.

EXPERIMENTAL

The following polymers were studied: Three different grades of ethyl hydroxyethylcellulose (EHEC), supplied by Berol Kemi AB, Stenungsund, Sweden. The EHEC samples had the following specifications; sample A, degree of substitution of ethyl [DS(ethyl)] = 1.4, molar substitution of ethylene oxide [MS(EO)] = 0.9, and molecular weight (MW) = 30000 daltons; sample B, DS(ethyl) = 0.9, MS(EO) = 0.9, and MW = 60000 daltons; sample C, DS(ethyl) = 1.5, MS(EO) = 0.7, and MW = 80000 daltons: Three different qualities of hydroxypropyl methylcellulose (HPMC) supplied by Colorcon, Ltd., Orpington, England and Shin-Etsu Chemical Co., Ltd., Tokyo, Japan. The HPMC samples had a metoxyl group substitution in the range of 28.6-29.4 %, and a hydroxypropoxyl group substitution in the range of 7.4-8.7 % . For HPMC sample A the apparent viscosity

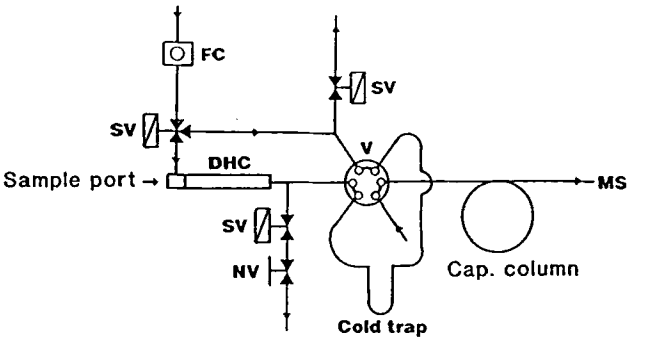

FIGURE 1

Schematic diagram of the dynamic headspace gas chromatograph - mass spectrometer. DHC = Dynamic headspace chamber; FC = flow controller; MS = mass spectrometer; NV = needle valve; SV = solenoid valve; V = Valco six-port valve.

was 50 cP; for sample B 4380 cP, and for sample C 9922 cP: Three forms of carrageenans, i.e. kappa, iota, and lambda, were supplied by Sigma Chemicals Co., St. Louis, U.S.A.

The dynamic headspace GC/MS analysis was performed by an in-house constructed dynamic headspace sampling apparatus connected to a Shimadzu QP 1000 GC/MS (Shimadzu, Kyoto, Japan), see figure 1. The dynamic headspace apparatus has been described elsewhere (5). Throughout this work the following sample conditions have been used: the polymer sample was heated to 100°C, and the volatile compounds were extracted during 10 min at a flow of helium of 20 ml/min. The DHS interface and sampling valve were kept at 200 and 220°C, respectively. The compounds that were collected in the liquid nitrogen cooled trap were reinjected, after removal of the cooling medium, at a temperature of approx. 200°C, onto the capillary column at flow rate

of 4 ml/min. Prior to the capillary column a glass splitter was placed, allowing approx. 1 ml/min to enter into the column. The column was temperature programmed as follows; isothermal at 50°C for 1.0 min then programmed with a ramp of 10°C/min to 250°C. The capillary column (15.4 m * 0.24 mm) was a DB-5 (filmthickness 0.25 μm), supplied by J&W Scentific, Folsom, USA. The column was directly interfaced to the ion source of the mass spectrometer. The mass spectrometer was scanned in the interval 35 - 400 m/z at a cycle time of 1.2 s. Electron impact ionization at 70 eV and a source temperature of 250°C was used. Mass data was collected and stored on an IBM personal computer (model 50 Z).

RESULTS AND DISCUSSIONS

The use of static and dynamic headspace analysis in nonenvironmental applications has been reviewed by McNally and Grob (3). The method of static headspace is based on the principle that, after that equilibrium has been obtained for the volatile compound between the gas phase and the condensed phase in a closed vial, the concentration of the volatile compound in the gas phase reflects the concentration in the condensed phase. For samples in solution, quantification is normally performed with the standard addition method, although internal standard and external standards techniques are also used. For solid samples, however, these quantification methods are less applicable. A feasible method for the quantification of volatile compounds in solid samples is the multiple headspace extraction method (7). This method is based on the assumption that the extraction follows first order kinetics; however, this is not always the case. Moreover, for solid

samples the time to reach equilibrium of the volatile compound can take from hours to days, depending on the solid sample geometry and the diffusion coefficient of the compound under study. If small volumes of the solid sample are at hand, then a de facto dilution of the volatile compound occurs. And since generally only a minor proportion of the gas phase is sampled, which restricts the analytical sensitivity of the method. Due to these reasons, static headspace is normally only carried out for highly volatile compounds such as ethylene oxide and methanol and for concentrations of the volatile compound in the ppm-range or above. With the introduction of dynamic headspace (DHS), the non-equilibrium counterpart to static headspace, some of the limitations of static headspace are cirumvented. Dynamic headspace is basically a continuous gas extraction technique performed in an open system with on-line enrichment of the extracted volatile compounds prior to the chromatographic separation step. The degree of extraction is primarily governed by the flow characteristics of the extraction gas, the diffusion coefficient of the volatile compound and the solid sample geometry (8).

In the review of McNally and Grob (3) the vast majority of the reviewed articles concern target analysis with only a few articles dealing with the generation of chromatographic profiles and multicomponent analysis being taken up. For characterization of polymers, our approach is to generate as much data as possible from an analytical study in combination with multivariate data analysis, in order to not miss any information inherent in the polymer under study (9). For practical and theoretical reasons this is best provided by dynamic headspace sampling (6,8), since the

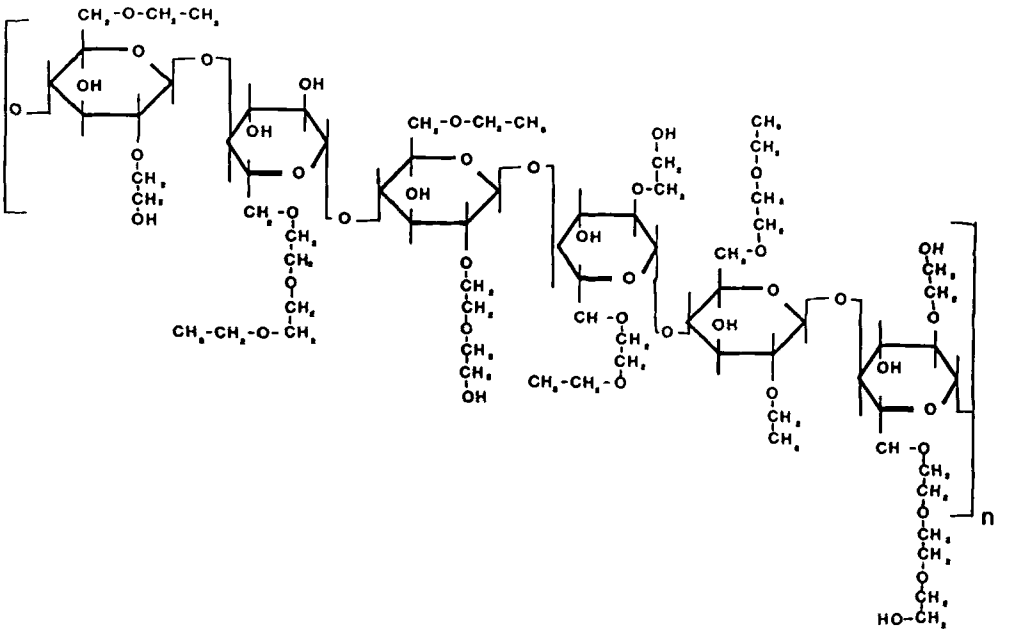

FIGURE 2

Possible structure elements in ethyl (hydroxyethyl) cellulose.

chromatographic profiles contain a larger number of peaks and over a more extended range of volatility in comparison with the chromatograms obtained by static headspace sampling.

The large number of structure elements in ethyl (hydroxyethyl) cellulose can be inferred from figure 2. Normally, the polymer is described in general terms such as the degree of substitution of ethyl groups (DS(ethyl)) and molar substitution of ethylene oxide (MS(EO). For the studied EHEC samples the average molecular weight, through viscosity measurements, were also given for the EHEC polymers by the supplier.

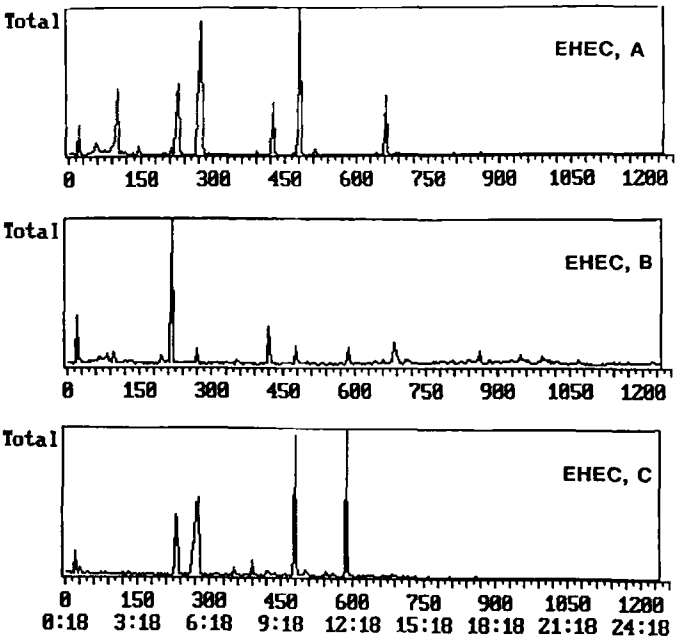

FIGURE 3

Chromatograms generated from EHEC samples by dynamic headspace GC/MS. (Integers represent scan no.; the lower scale is time in minutes)

DHS GC/MS analysis of the EHEC polymers generates different chromatographic profiles for each type of polymer, given in figure 3. As can be inferred from the mass spectrum of each peak, the volatile compounds present in the studied EHEC polymers to a large extent reflects incomplete substitution reactions. The volatile compounds are constituted to a greater part of oligomers of ehtylene oxide and ethyl moieties. Apart from the chromatographic profiles and assignment of mass spectral data to each peak, a positive identification of for example solvents present in the polymer is made possible. By use of the reconstructed selected ion monitoring technique the presences of for

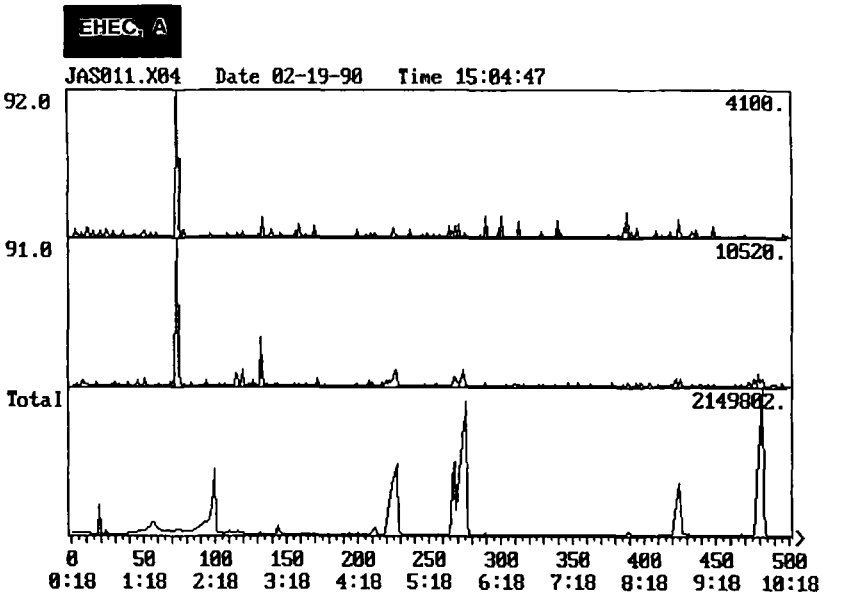

FIGURE 4

Reconstructed selective ion monitoring of ions m/z 91 and 92. The peak at the retention time of 1.6 min corresponds with toluene. (Integers represent scan no.; the lower scale is time in minutes)

example solvents even in very complex chromatograms could be detected, as shown in figure 4. In this EHEC sample low amounts of toluene was found. The presence of toluene may reflect the storage conditions of that particular sample.

The three hydroxypropyl methylcellulose that have been analyzed differed only in the viscosity measurements but were approximately substituted in the same manner. DHS GC/MS analysis generates three different chromatograhic profiles for the HPMC samples too as shown in figure 5. The HPMC sample B and C were from the same supplier. Since the chromatographic profiles are unique for each HPMC sample, this could then

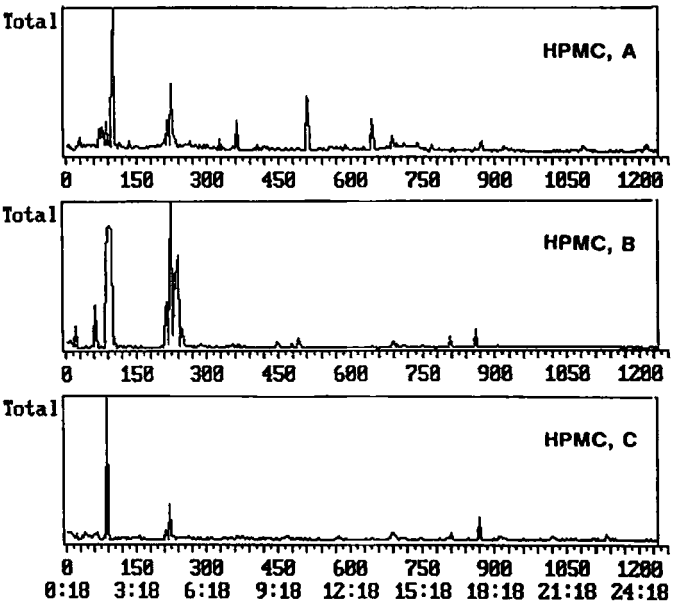

FIGURE 5

Chromatograms generated from HPMC samples by dynamic headspace GC/MS. (Integers represent scan no.; the lower scale is time in minutes)

constitute a base for correlation studies on e.g. viscosity as well as discrimination between different suppliers of HPMC. Furthermore, since the DHS GC/MS analysis is very sensitive to changes of volatile compound content in polymers, batch variations could be closely followed.

Carrageenans, are, sulfated polysaccharides, characteristically built up from residues having the galacto configuration linked alternately α-(1->3) and ß-(1->4) and, typically, have masked repeating structures. In figure 6 the generalized structures of the kappa- and iota-forms of carrageenans are given.

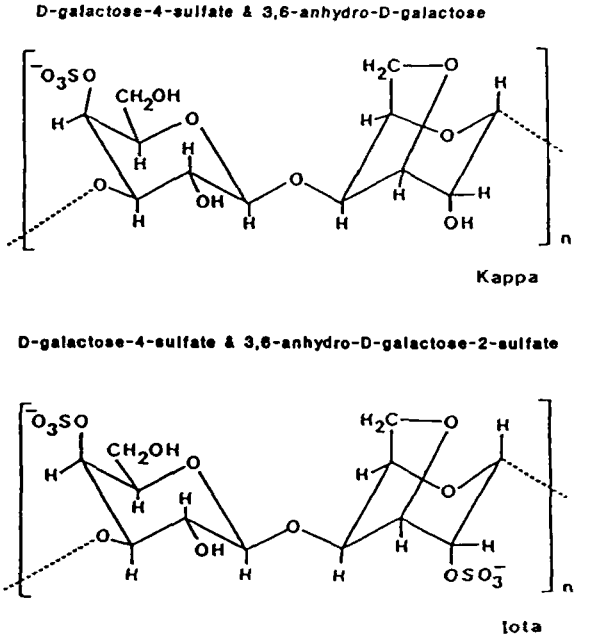

FIGURE 6

Generalized structures of kappa and iota carrageenan.

The corresponding chromatograms generated by DHS GC/MS analysis are shown in figure 7. Even for these polymers differences are obtained in the chromatographic profiles as well as in the distribution of different fragment ions. The volatile compounds sampled from the carrageenans, eluted from the chromatographic column at a relative high temperature, i.e. above 150°C. These compounds would be inaccessible for analysis if static headspace sampling had been used, due to low concentrations and large distribution coefficients. However, owing to the efficient extraction of dynamic headspace sampling, even compounds with low volatility could analyzed. We have also studied a common third form i.e. lambda-carrageenan, which had substantially

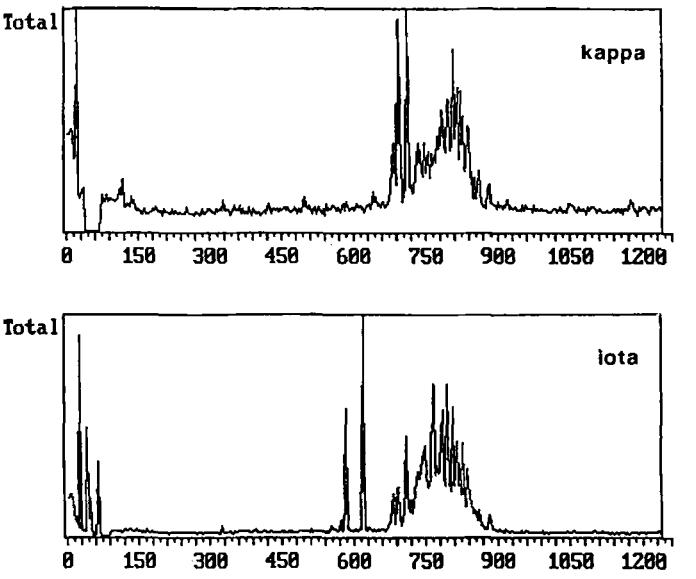

FIGURE 7

Chromatograms generated from carrageenan samples by dynamic headspace GC/MS. (Integers represent scan no.)

less volatile compounds occluded in the polymer. This apparently restricts the applicability of DHS for the characterization of the carrageenans samples that were employed in this study.

CONCLUSIONS

If the polymer under study contains volatile compounds in the ppb-range or above, characteristic chromatographic profiles could be generated for that polymer by use of dynamic headspace sampling in combination with gas chromatography. By use of a mass spectrometer in the detection step, the chromatographic peaks could be assigned with a mass spectrum and, thus, unambiguous identification is made possible. The

chromatographic profiles, which could be quantitatively reproduced, together with the peak identification, constitute a sound base for chemometric approaches. In our experience dynamic headspace gas chromatography-mass spectrometry is especially valuable in the studies of batch variations, and changes in processing and handling conditions. They could also be to some extent used for studies of changes of the polymer on the molecular level e.g. differences in the substitution pattern.

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