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New Chromatographic and Hyphenated Techniques for Hydrophilic Copolymers

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Summary: Most synthetic polymers are distributed in more than one parameter of molecular heterogeneity. For hydrophobic copolymers there are different chromatographic techniques available to analyse these distributions. As a result of the increasing interest in hydrophilic polymers and copolymers new chromatographic techniques are developed for the characterization of these polymers as well. However, very frequently these polymers contain highly polar or charged functional groups making them soluble only in aqueous mobile phases. There are several problems related to the use of aqueous mobile phases in polymer chromatography. Even the SEC analysis of such copolymers is not straightforward. As for HPLC in aqueous mobile phases, there are only a few applications in the literature so far. In addition to the fact that only a very limited number of stationary phases is available for aqueous HPLC of polymers, the interactions of polyelectrolytes in such chromatographic systems are not well understood.

The present paper addresses the problems related to the application of SEC and HPLC in aqueous mobile phases. For graft copolymers with a polyethylene oxide backbone, e.g. PEG-g-polymethacrylic acid and PEG-g-polyvinyl alcohol, it will be shown that methods can be developed that give accurate molar mass and chemical composition information. Two-dimensional chromatography where aqueous HPLC and SEC are coupled on-line will be shown to be the most powerful analysis tool for the analysis of such copolymers. The hyphenation of the chromatographic separation techniques with spectroscopic detection techniques provides further insight into the molecular complexity of these copolymers.

Keywords: hydrophilic copolymers; hyphenated techniques; liquid chromatography; two-dimensional chromatography

Introduction

Polymers are highly complex multicomponent materials. They are composed of macromolecules varying in chain length, chemical composition, and architecture. Depending on the composition of the monomer feed and the polymerization procedure, different types of heterogeneities may become important.

One very efficient approach for the analysis of the molecular heterogeneity of complex polymers is their chromatographic separation by combining different separation mechanisms. A typical experimental protocol includes the separation of the sample according to composition yielding fractions which are chemically homogeneous. These fractions are transferred to a size-selective separation method and analyzed with respect to molar mass. As a result of this two-dimensional (2D) separation, information on both types of molecular heterogeneity is obtained. Another useful approach is the combination of a selective chromatographic technique with a

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powerful spectroscopic method like NMR or MALDI-TOF mass spectrometry [1].

There are numerous selective modes for LC of polymers, including liquid chromatography at the critical point of adsorption (LC-CC) [2–4] and isocratic or gradient HPLC [5,6]. Using these techniques polymers can be separated selectively with regard to chemical composition or functionality, as has been shown for macromonomers, random and block copolymers, and polymer blends [6–9]. LC-CC and gradient HPLC are promising first dimensions in a 2D chromatography setup. These can be combined with size exclusion chromatography (SEC) in the second dimension that yields the corresponding molar mass distribution.

So far, 2D chromatography has been applied mostly to polymers that are soluble in organic solvents. Very typically, in the first dimension binary eluents are used, e.g. tetrahydrofuran-hexane, while in the second dimension THF is the eluent. At present we are not aware of any applications, where aqueous mobile phases are used in both dimensions when LC-CC and SEC are coupled in the 2D experimental setup.

There are several challenges related to the use of aqueous mobile phases in polymer chromatography. The types of polymers that are to be analyzed using such conditions are water-soluble polar or ionic copolymers. Even the SEC analysis of copolymers analyzed in aqueous mobile phases is not straightforward. In addition to the fact that only a very limited number of stationary phases is available for aqueous SEC, the experiments in most cases cannot be conducted in pure water. Due to the high polarity or the ionic nature of the polymers, electrolytes or ion-pairing reagents have to be added to the eluent to screen ionic interactions with the stationary phase, see for more details Mori and Barth [10]. Salt solutions, on the other hand, can cause severe problems for the detection in SEC, in particular, when an evaporative light scattering detector (ELSD) is used.

As for HPLC in aqueous mobile phases, there are only a few applications in the literature so far [11–16]. Regarding the analysis of water-soluble copolymers by HPLC methods and the determination of the chemical composition distribution of such copolymers the only publications relate to copolymers of ethylene oxide and propylene oxide [17], partially hydrolyzed polyvinyl acetate [18] polystyrene sulfonate and poly acrylic acid [19].

The present paper addresses the problems related to the application of SEC and HPLC in aqueous mobile phases. For graft copolymers with a polyethylene oxide backbone, e.g. PEG-g-PMAA PEG-g-PVA, it will be shown that methods can be developed that give accurate molar mass and chemical composition information. Two-dimensional chromatography where aqueous HPLC and SEC are coupled on-line will be shown to be the most powerful analysis tool for the analysis of such copolymers. The hyphenation of the chromatographic separation techniques with spectroscopic detection techniques provides further insight into the molecular complexity of these copolymers.

Experimental

Chromatographic System

A Shimadzu LC-10AD-VP HPLC system comprising a pump, an autosampler and a RI detector was used. For 2D experiments an evaporative light scattering detector ELS 1000 (Polymer Laboratories, UK) and an additional pump were added. The transfer of the fractions was carried out with a 8-port-2-position switching valve type ET8GW (Valco Instruments Co. Inc.) with two 100 μL sample loops. For data collection and processing the software package 'WinGPC-Software' (Polymer Standards Service GmbH, Mainz, Germany) was used. Molar mass calibration was based on PEG. The stationary and mobile phases were used as indicated in the text.

Samples

All samples were laboratory products of BASF AG, Ludwigshafen, Germany.

Results and Discussion

SEC Methods for Anionic (Meth)acrylate Copolymers

Hydrophilic (meth)acrylate copolymers are extremely important precursors for surfactants, dispersing agents and drug carriers in the chemical and pharmaceutical industries. In particular, they are used as binders and coating materials. Very frequently these polymers contain hydrophilic and hydrophobic segments. In addition to the molar mass distribution they frequently exhibit a chemical composition distribution. Anionic methacrylic acid-(meth)acrylic ester copolymers belong to a group of pharmaceutical excipients that are primarily used as controlled release film coating agents in oral capsule and tablet formulations [20]. Their methacrylic acid content is up to 50 % by weight making them water soluble in some cases and water insoluble in other cases.

Due to the large variety in chemical composition and molar mass, up to now there was no reliable and robust size exclusion chromatography (SEC) method for the molar mass characterization of such copolymers. Commercial products, like the EUDRAGIT® range of copolymers produced by Röhm, Germany, were characterized only by solution viscometry. It was, therefore, most desirable to develop a robust SEC method for neutral and anionic (meth)acrylate copolymers to serve as a means of quality control that can be used by producers and users of such copolymers alike.

The copolymers under investigation were based on methacrylic acid (MAA) and different (meth)acrylic esters, such as methyl methacrylate, methyl acrylate and ethyl acrylate. The content of methacrylic acid ranged up to 50 % by weight, i.e. 30 (sample A), 50 (sample B), 50 (sample C), 0 (sample D), and 10 % by weight MAA (sample E). For a preliminary screening of different stationary and mobile phases, the chromatographic behaviour of the samples was first investigated on conventional SEC columns. The following combinations were tested: (1) styrene-divinylbenzene (SDV) stationary phase + THF + 0.2 % by volume of trifluoro acetic acid, (2) SDV + dimethyl acetamide (DMAC) + 0.1–0.9 % by weight LiBr, (3) HEMA 3000 stationary phase + DMAC + 0.5 % by weight LiBr. For the conventional SDV as well as for the hydrophilic HEMA 3000 (hydroxyethyl methacrylate based) stationary phases more or less deformed elution peaks were obtained. Some samples even eluted in bi- or multimodal distributions. This was a strong indication for non-ideal SEC behaviour.

As all samples are properly soluble in DMAC, in the following experiments, the chromatographic behaviour of the copolymers was investigated with using DMAC as the mobile phase. As is suggested by standard procedure DIN 55672-2, 5 g/L LiBr were added to DMAC. Due to the high viscosity of DMAC these measurements have been conducted at a column temperature of 80 °C.

As the stationary phase a new polyester-based material (commercial name GRAM) was selected that has been specifically designed for SEC of polar polymers by Polymer Standards Service GmbH, Germany. As can be seen in Fig. 1, there is a significant difference between the chromatographic behaviour of the different copolymers. At the present chromatographic conditions, only sample D exhibits a typical SEC elution profile. This is obviously because this sample is a neutral polymer and non-size exclusion effects cannot occur. Such effects could, however, clearly be observed when the concentration of carboxylic groups in the copolymers was increased, see samples E, A, and B. For sample E with 10 % MAA the elution peak of the polymer shifted towards higher elution volumes and overlapped partially with the salt peak. Obviously, adsorptive interactions start to disturb the SEC separation mechanism. As can be seen for sample B with 50 % MAA, no elution is observed.

Another option to screen ionic and adsorptive interactions is the addition of

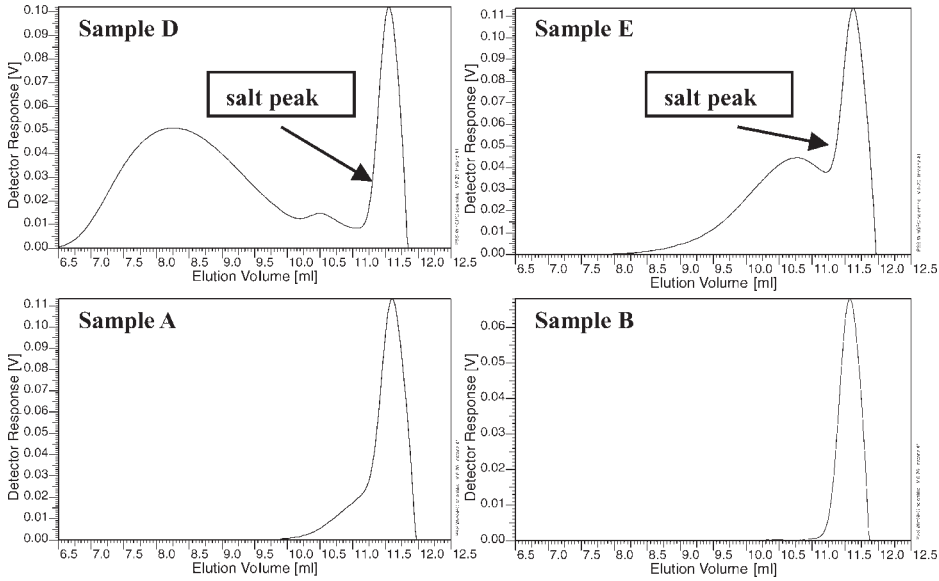

Figure 1.
SEC of copolymers, stationary phase: GRAM 3000 Å, mobile phase: DMAC + 5 g/L LiBr, detector: RI

an acid to the mobile phase to lower the pH. As compared to the behaviour without addition of acetic acid (AcOH), where elution did not occur, the addition of different amounts of acid promoted a proper elution of the samples. However, for a proper elution of all samples regardless of the MAA content, the addition of LiBr and AcOH was necessary. In order to improve the stability of the mobile phase, the column temperature was decreased to 60 °C. In another set of experiments different concentrations of LiBr and acetic acid in the mobile phase were tested in order to achieve optimum performance. Further, instead of only one column of 3000 Å, a second column of 100 Å was added. The better separation in the lower molar mass range enabled to separate the polymer peak from the salt peak. Consecutively, these columns were replaced by one and two linear columns GRAM XL, respectively, with a significantly broader separation range.

With respect to chromatographic behaviour of the samples and stability of the mobile phase, optimum performance was obtained for a mobile phase of DMAC with 6 g/L acetic acid and 3 g/L LiBr. The elution profiles indicate monomodal molar mass distributions for all samples as was expected. To check the validity of the results, the weight-average molar masses were determined by SEC coupled to laser light scattering. The measurements were conducted using a Wyatt EOS multi-angle laser light scattering instrument. Fig. 2 gives an overview of the molar mass distributions of the samples. As can be seen, the function $\log M = f(V_e)$ in all cases indicates typical SEC behaviour. This is additional proof for the finding that at the present experimental conditions the samples elute in the typical SEC mode. There are no indications for adsorptive or other non-SEC effects [21].

The final step of the present study was the investigation of the robustness and the reproducibility of the newly developed SEC method.

For a reproducibility test among three different laboratories, the one-column set was used. The reproducibility tests were conducted at Röhm GmbH (Röhm), Deutsches Kunststoff-Institut (DKI) and Polymer Standards Service GmbH (PSS) running the same samples at five consecu-

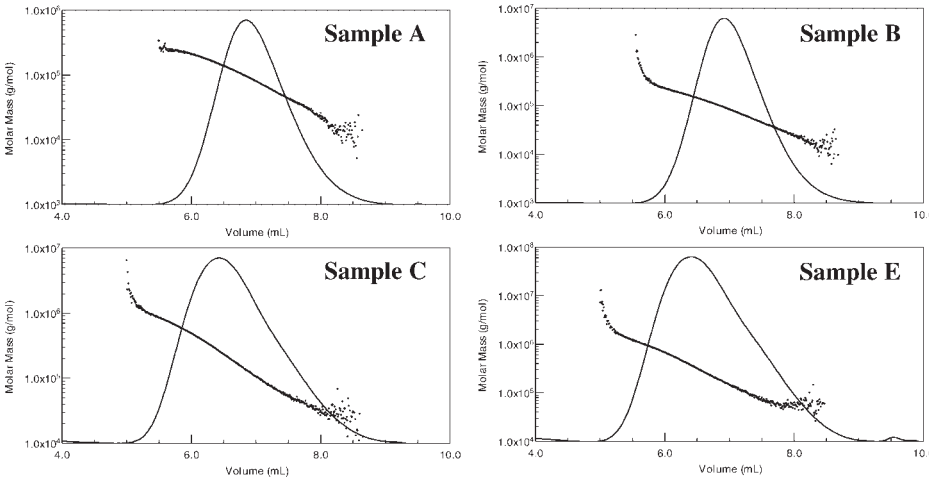

Figure 2.
Molar mass vs. elution volume functions of the copolymers A, B, C, and E stationary phase: GRAM XL, mobile phase: DMAC + 6 g/L AcOH + 3 g/L LiBr, detector: RI and MALLS

tive days on different equipment and with manual and automated injection. Selected results are presented as diagrams in Fig. 4. Overlays of molar mass distributions measured at the three laboratories are summarized in Fig. 3[21].

As can be seen, in all cases well reproducible results are obtained. To summarize, a robust and reproducible method for the molar mass analysis of neutral and anionic copolymers based on methacrylic acid and different (meth)acrylates has been developed.

Multidimensional Chromatography of Graft Copolymers of PEG and Polymethacrylic Acid

Copolymers of ethylene oxide and (meth)acrylic acid are used as dispersants and binders in cosmetics and in the building industry. Frequently, such copolymers are produced by grafting (meth)acrylic acid onto polyethylene glycol. The grafting reaction most likely takes place along the PEG polymer chain and not at the PEG endgroups. Thus, it can be assumed that true graft copolymers are formed.

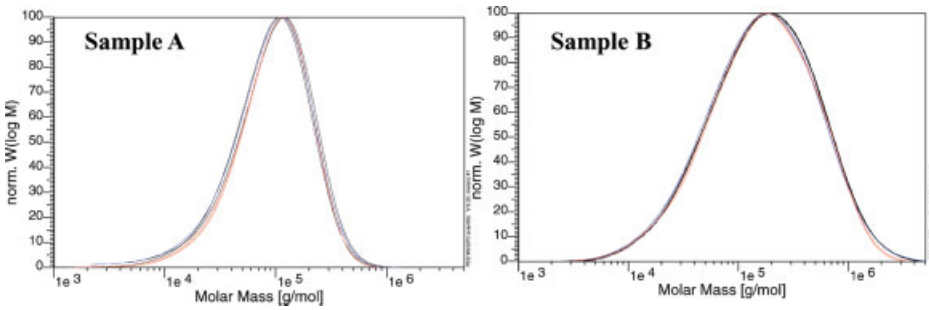

Figure 3.
Molar mass distributions of samples A and B determined in three different laboratories all measured as dual injections: DKI (black), PSS (blue), Röhm (red), stationary phase: GRAM linear XL, mobile phase: see Fig. 2, detector: RI, calibration: PMMA

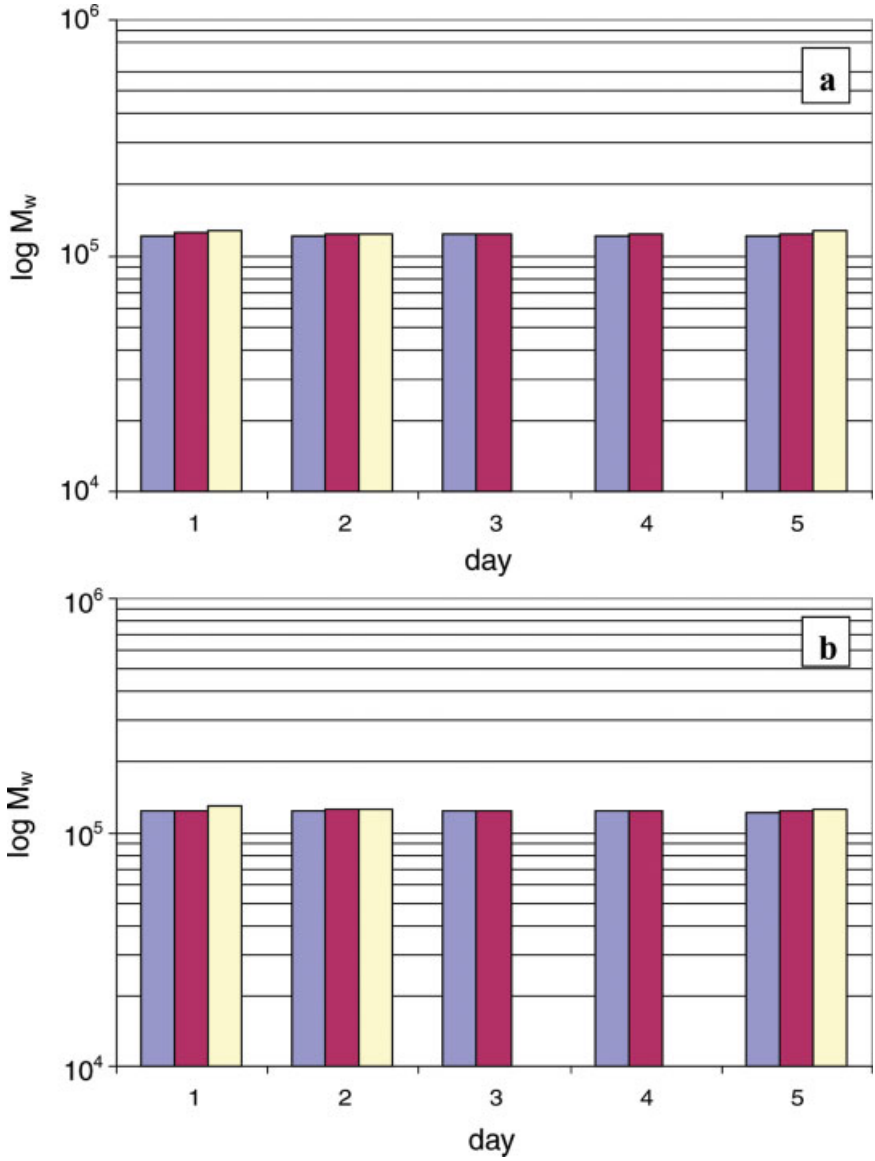

Figure 4.
Molar mass analyses of sample A at three different laboratories, stationary phase: GRAM linear XL, mobile phase: see Fig. 2, detector: RI, freshly prepared sample solutions (a) and solutions from the first day (b), PSS (blue), Röhm (red), DKI (yellow)

The free-radical grafting process of methacrylic acid (MAA) onto PEG is never complete. Considering the fact that during the grafting reaction the polymerization of MAA homopolymer can take place, very complex reaction products are obtained. Therefore, they consist of the real graft copolymer (PEG-g-PMAA) as well as non-grafted PEG and polymethacrylic acid (PMAA). Aiming at the preparation of graft copolymers of different molar masses and compositions that could be used as model compounds, a PEG with an average molar mass of 1,500 g/mol was grafted with MAA in different ratios. The MAA/PEG ratios were 15/85, 20/80, 25/75, and 30/70 %

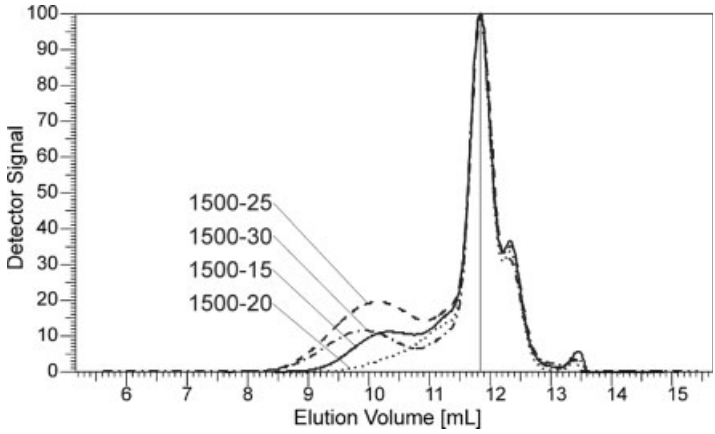

Figure 5.
SEC chromatograms of the graft products, stationary phase: Suprema linear M, mobile phase: water + 0,08 M TRIS + 0,15 M NaCl + 0,01 M NaN_3, pH 7, detection: RI, samples: 1500-15 (solid), 1500-20 (dotted), 1500-25 (dashed), 1500-30 (dotted-dashed)

by weight (i.e. samples 1500-15, 1500-20, 1500-25, 1500-30). For the characterization and the quantitative determination of the components in the potential mixture of the graft polymers and the by-products, the components must be separated from each other by means of liquid chromatography.

First, the samples were analyzed by aqueous size exclusion chromatography (SEC) to obtain a survey about the molecular heterogeneity. The separation was performed on a PSS Suprema column with a mobile phase of water + TRIS + NaCl + NaN_3. The pH-value was adjusted to a value of 7. This mobile phase composition has been proven to be particularly effective in screening polar and ionic intercations.

All samples exhibit similar SEC patterns: at high elution volumes a rather sharp and intense elution peak appears that indicates that the samples contain significant amounts of low molar mass material. Towards lower elution volumes peaks or shoulders of variable intensity are obtained that are characteristic for the graft copolymers. A comparison of the elution behaviour of the samples with the elution behaviour of the initial PEGs indicates that the sharp peaks in the chromatograms are due to remaining, non-grafted PEG. The position of the PEG peak is indicated by a vertical line.

The chromatograms show that there is a trend of increasing concentration and molar mass of the copolymer fractions with increasing MAA/PEG ratio. Unfortunately, an exact molar mass and concentration analysis of the samples by SEC cannot be conducted due to the co-elution of the different sample components.

Another technique to separate the reaction products PEG-g-PMAA and PMAA from residual non-grafted PEG is liquid chromatography at critical conditions (LC-CC) for PEG. At such LC-CC conditions separation takes place with regard to the chemical composition of the different species and PEG elutes in one chromatographic peak irrespective of molar mass. The reaction products PEG-g-PMAA and PMAA having a higher polarity than PEG should elute under these conditions prior the PEG peak. Fig. 6 summarizes the LC-CC chromatograms of the sample set [26].

As one can see, baseline separation of the graft products and non-grafted PEG is obtained. For a detailed analysis of the different species, the chromatographic system can be coupled with FTIR spectroscopy.

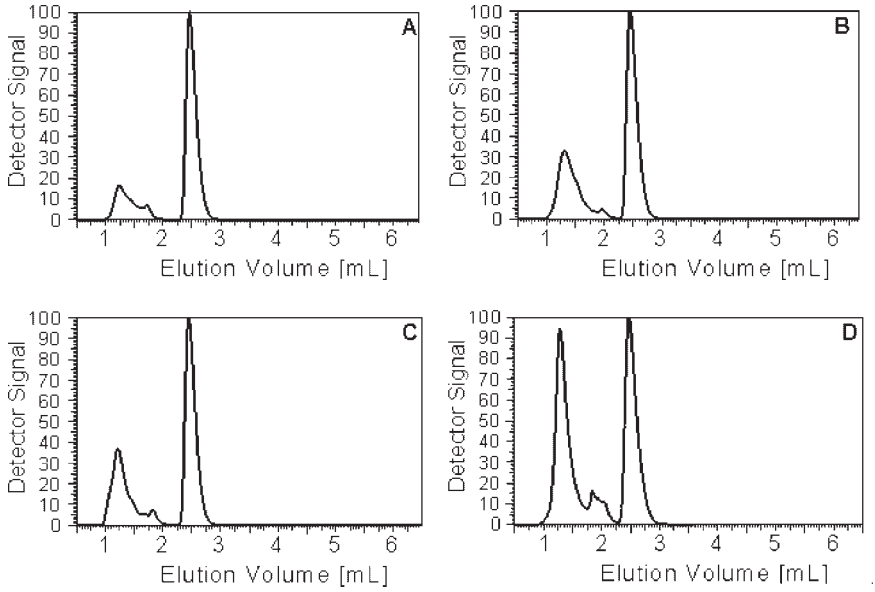

Figure 6.
LC-CC chromatograms of the graft products, stationary phase: Knauer Nucleosil RP18-100, mobile phase: methanol/water 81/19 (w/w), detector: ELSD; samples: 1500-15 (A), 1500-20 (B), 1500-25 (C), 1500-30 (D)

While the chemical composition of the graft copolymer samples can be analyzed in detail by LC-CC coupled to FTIR spectroscopy, the molar masses of the different sample components must be determined by size exclusion chromatography. This can only be done after the LC-CC separation because SEC alone is not capable of separating the non-grafted PEG from the graft products, as has been shown in Fig. 5. Preferably such molar mass analysis has to be conducted separately for each component to obtain full information. An investigation of the chemical heterogeneity in relation to the molar mass distribution of the sample components, is done by on-line two-dimensional chromatography which combines the two methods LC-CC and SEC that separate into diverging directions of molecular heterogeneity.

In the present case, 2D-chromatography is conducted by connecting the LC-CC in the first dimension with the SEC in the second dimension. The operation of the system is explained in the experimental part and in Refs.[22–25]. The results of the two-dimensional separation of samples 1500-15 and 1500-30 are presented as contour plots in Fig. 7.

As compared to the LC-CC and SEC measurements, the 2D experiments yield much more detailed information on the molecular complexity of the samples. Information on the chemical heterogeneity is presented in the ordinate direction of the contour diagram. The molar mass distribution is plotted in the abscissa direction. As can be seen for both reaction products in Fig. 7, three different fractions are detected in the contour plots. By comparison with the starting material, one fraction can be assigned to non-grafted PEG. The molar mass analysis of this fraction gives 1,200 g/mol and 1,400 g/mol for samples 1500-15 and 1500-30, respectively. The fractions coded with Product 1 and Product 2 belong to reaction products of PEG and MAA, i.e. the graft copolymers PEG-g-PMAA. The two products exhibit different elution volumes in the ordinate direction and different molar masses. The lower elution volume of Product 2 indicates that it contains more MAA units than Product 1. This is in agreement with the higher

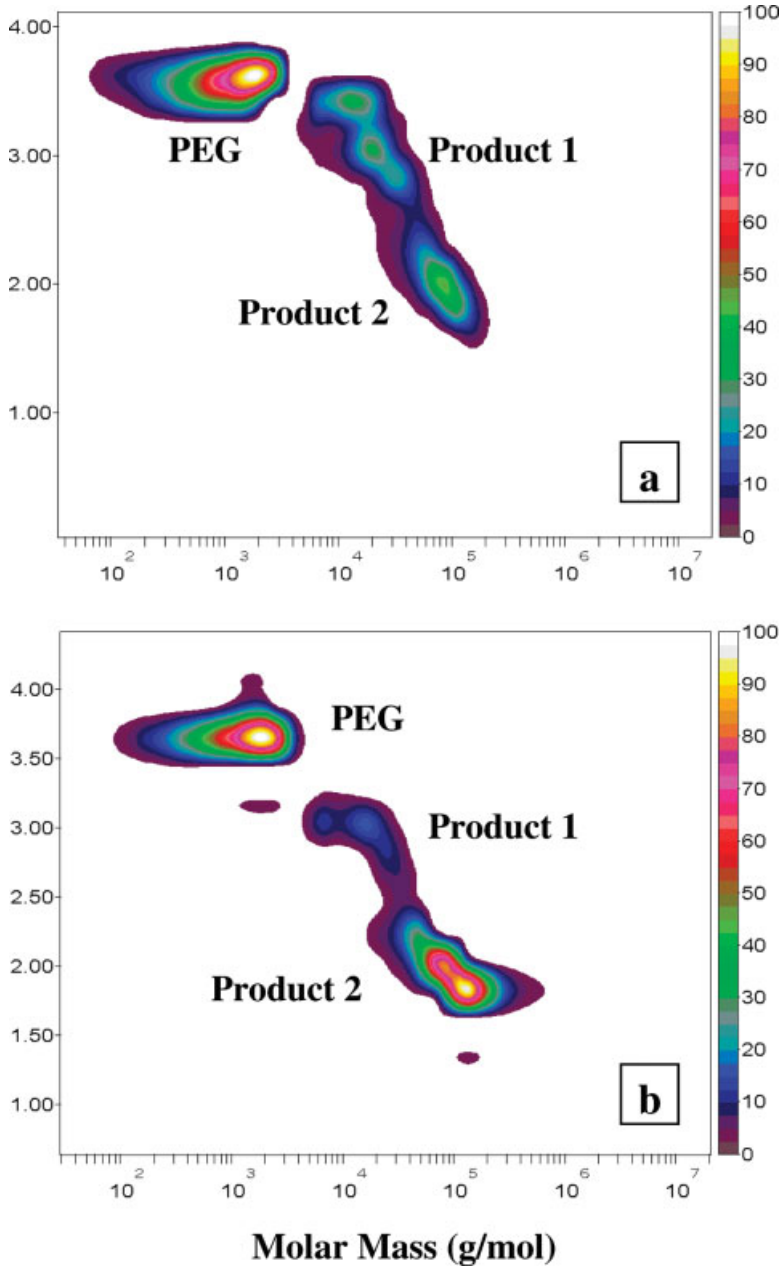

Figure 7.
Contour plots of the 2D-LC separations of samples 1500-15 (a) and 1500-30 (b), 1st dimension: LC-CC, 2nd dimension: SEC, detector: ELSD, calibration: PEO

molar mass of Product 2. Obviously, the grafting reaction results in a bimodal graft copolymer distribution where Product 2 is the more advanced reaction product with a higher amount of grafted MAA and a higher molar mass [26].

Multidimensional Analysis of Graft Copolymers of PEG and Vinyl Alcohol

The preferred and easiest intake of medicines is by oral ingestion in the form of tablets. Tablets contain a combination of an active pharmaceutical ingredient and a

(polymer) excipient – the ''inactive'' ingredient that delivers the pharmaceutical active compound [27,28]. A tablet coating has many functions and requirements, such as to protect the contents of the tablet during transport and storage, to ease the identification by the use of a coloured coating, to mask the taste, and to enhance the swallowability. Another important function of a tablet coating is to obtain a controlled release of the active pharmaceutical ingredient in the stomach or intestine. An instant release system is generally used in the stomach, whereas both ''instant'' and sustained release systems are used in the intestines. Instant release systems are used to obtain a fast effect of an active pharmaceutical compound. This can be achieved by using sugar, hydroxypropyl methyl cellulose, poly(vinyl pyrrolidone-*co*-vinyl acetate), or poly(vinyl alcohol) as a material for the tablet coating. The polymers dissolve readily and the tablet content is released.

Recently, a new class of excipients based on ethylene oxide-vinyl alcohol copolymers has been developed (PEO-g-PVA). The combination of PVA and PEO should result in an excellent instant-release tablet coating. One way to obtain a copolymer of PVA and PEO is the grafting of vinyl acetate (VAc) onto PEO and subsequent hydrolysis of the acetate groups. The grafting reaction of VAc onto PEO is hardly known and very little details are given in literature [29,30]. The most similar reaction described is the grafting of acrylic acid onto EO-PO copolymers [31,32]. Assuming an analogous reaction sequence [33], the following mechanism is proposed for the formation of the PEO-*g*-PVA copolymers, see as depicted in Fig. 8.

For analysing structure-property relationships a variety of PEO-*g*-PVA copolymers were prepared, differing in the VAc-to-PEO ratio and the molar mass of PEO. The analysis of the copolymers by IR and ^{1}H- and ^{13}C-NMR showed the presence of both PEO and PVA. A small C=O absorption was still present and was explained by a non-quantitative saponification. SEC

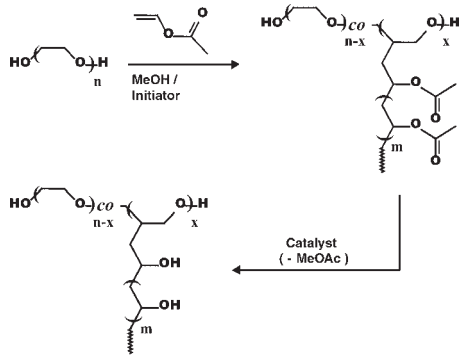

Figure 8.
Synthetic route for the preparation of PEO-g-PVA copolymers

showed polydispersities (M_w/M_n) of around 5, with a small tailing to the low molar mass side. The latter was probably caused by the relatively low molar mass PVA homopolymer formed by the chain transfer reaction of VAc, both to the PEO and its acetate functionality.

One of the main requirements of the PEO-*g*-PVA copolymers used in tablet coatings is that no free (non-grafted) PEO is present. Free PEO can be determined by liquid chromatography and mass spectrometry. Gradient HPLC measurements were performed, using a THF-water eluent, however, by using this experimental setup complete separation of PEO and PEO-*g*-PVA could not be obtained [34]. However, liquid chromatography under critical conditions (LC-CC) resulted in the desired separation [34]. The critical point for PEO was obtained at an eluent of MeOH-water of 82.5:17.5% by volume.

The LC-CC elugrams in Fig. 9 show the chromatographic behaviour of PEO and two graft copolymer samples. PEO is well separated from the copolymer fractions that elute at elution volumes between 1.5 and 2.8 mL. As can be seen, there are significant differences between copolymers 1 and 2. Copolymer 1 having a high PEO-to-PVA ratio exhibits a quite broad distribution with regard to chemical composition and a significant amount of non-grafted PEO. In contrast, copolymer 2 having a low

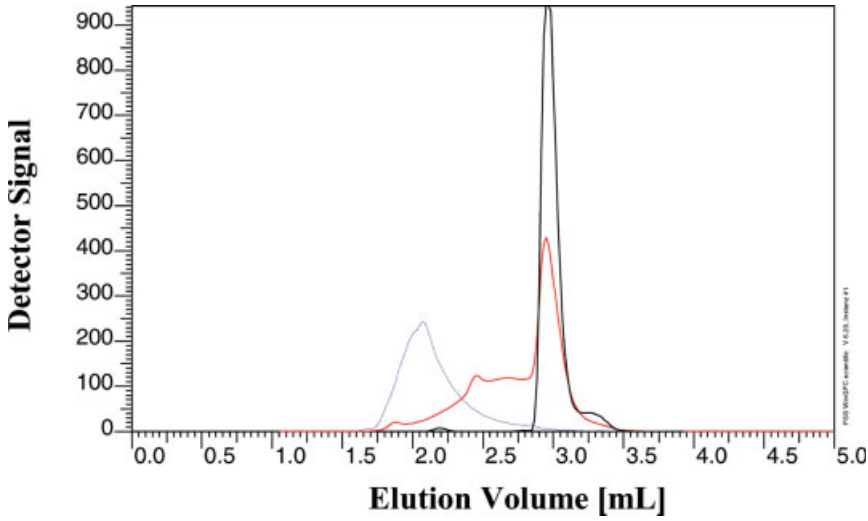

Figure 9.
LC-CC analysis of PEO and PEO-g-PVA, stationary phase: Nucleosil C_{18}, mobile phase: MeOH:H_2O 82.5:17.5% by volume, samples: PEO (black), copolymer 1 (red) and 2 (blue)

PEO-to-PVA ratio does not contain free PEO.

To obtain an even better separation SEC was performed in a 2nd dimension following the LC-CC analysis. As has been described previously, the resolution of a 2D experiment may be significantly higher as compared to the single chromatographic separations. A typical experimental result is shown in Fig. 10[35].

The comparison of the 2D plot of a graft copolymer with the 2D plot of the precursor PEO shows clearly that the graft copolymer sample does not contain any free PEO. This result was also confirmed by MALDI-TOF mass spectrometry.

Next to the requirement of being PEO free, the PEO-*g*-PVA copolymers showed a good combination of film forming properties, a fast dissolution and a low solution viscosity in water. The phase separated morphology, as demonstrated by TEM, DSC, DMTA, and WAXS experiments, provided the PEO-*g*-PVA copolymers with relatively constant mechanical properties.

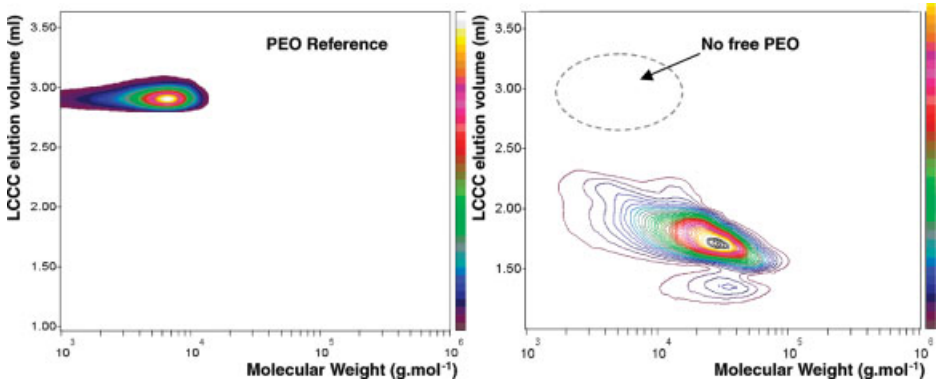

Figure 10.
2D-LC separation of PEO-*g*-PVA copolymer 2, 1st dimension: LC-CC, 2nd dimension: SEC, calibration: PEO

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