The Role of Synthetic Pharmaceutical Polymer Excipients in Oral Dosage Forms – Poly(ethylene oxide)-*graft*-poly(vinyl alcohol) Copolymers in Tablet Coatings

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Summary: A number of tablet coatings are available to provide a controlled release of pharmaceutically active compounds in the stomach or intestine using both instant or sustained released systems. The preferred properties of these tablet coatings are a low solution viscosity (preferable in water) combined with a phase separated morphology, showing good mechanical properties. PEO-*g*-PVAl copolymers have been developed as an instant-release tablet coating, and were obtained via a conventional radical polymerisation of VAc in the presence of PEO. No free PEO was observed in the PEO-*g*-PVAl copolymers **1f** and **1i** using 2D LCCC-SEC and MALDI-TOF analysis. Next to the requirement of being PEO free, the PEO-*g*-PVAl copolymers show 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, should provide the PEO-*g*-PVAl copolymers with relatively constant mechanical properties. A model reaction, using 2-methoxyethyl-ether and 1,4,7,10-tetraoxacyclododecane, has been developed to imitate the grafting reaction of VAc on PEO. Using this model reaction and using the same reaction conditions (temperature, initiator, concentration, VAc:"PEO" ratio, etc.) as applied in the PEO-*g*-PVAl polymerisation procedure, a degree of grafting for PEO of 13±3% was found. Comparing this figure with the results of LCCC-SEC and MALDI-TOF measurements, this figure seems a few percent too high, pointing to a slightly increased reactivity of the two model compounds compared to the PEO used.

Keywords: biological applications of polymers; synthesis

Introduction

The preferred and easiest intake of medicines is by oral ingestion in the form of tablets. Tablets today contain a combination of an active pharmaceutical ingredient and a (polymer) excipient – the "inactive" ingredient that delivers the pharmaceutical active compound.[1,2] Here, the use of polymer excipients in tablet coatings is described. The emphasis is on the synthesis and characterisation of a recently developed and introduced

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poly(ethylene oxide)-*graft*-poly(vinyl alcohol) (PEO-*g*-PVAl) copolymer that is used as a so-called instant release tablet coating.[3]

Polymer Excipients in Tablet Coatings[1,2]

A tablet coating has many functions and requirements. These are: 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, hydroxy propyl methyl cellulose (HPMC), 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. The release of the tablet content can be enhanced by using disintegrating agents like highly cross-linked poly(vinyl pyrrolidone) (PVP). This so-called popcorn PVP swells in contact with water and disintegrates the tablet.

An active pharmaceutical ingredient that is not stable in the stomach or gives rise to stomach injuries has to be delivered in the intestine, and hence has to pass through the stomach unhindered. This is obtained by using so-called enteric coatings that are insoluble in the stomach but soluble in the intestine. This characteristic is obtained by the use of carboxylic acid functionalities. The pK_a of these carboxylic acid functionalities is not low enough for deprotonation in the acidic environment of the stomach (pH $\approx$1). Deprotonation occurs in the intestine (pH $\approx$6.8), resulting in the dissolution of the coating. The enteric coatings can be optimised with regard to their dissolution behaviour by using a combination of different (meth)acrylates with various amounts of (meth)acrylic acid.

Sustained release systems have been developed to avoid the concentration peaks obtained with instant release systems. This is important for an active pharmaceutical ingredient that is consumed over a prolonged period of time, and hence should be present in an almost constant concentration in the blood. An additional advantage for the patient is that a sustained release system can reduce the intake of tablets to once daily. Sustained release

systems are based on diffusion and can be obtained using a water swellable but insoluble tablet coating or tablet matrix. Polymers used for a sustained release tablet matrix are for example ethyl cellulose or poly(vinyl acetate). A point of attention to be considered when using sustained release tablet coatings is the mechanical properties of the coating. In general, the drug load in a sustained release system is relatively high so that side effects will occur if the coating is damaged and the tablet content is released all at once. Multi-unit particle systems are used to prevent this. Smaller particles of about 0.5 mm are coated with, for example, ethyl cellulose or poly(vinyl acetate), and subsequently pressed with a tablet matrix in a conventional tablet. The tablet matrix dissolves in the stomach and the smaller particles possessing the sustained release coating enter the intestine. An alternative to the multi-unit particle systems is a coating obtained from a vinyl acetate dispersion polymerisation using poly(vinyl pyrrolidone) as a stabiliser. Due to the excellent mechanical properties of this material the risk of significant damage of the coating is minimised.

The tablets are generally coated using a spraying process. The tablets are tumbled, the coating solution is added via a spraying device and, in the same procedure, the solvent is evaporated. The preferred solvent for this process is water. The use of water compared to an organic solvent has the advantage in that it presents no safety (explosion limits) or environmental problems. A disadvantage of using water as a solvent is the relatively high heat of evaporation that results in an increased energy consumption. However, the use of highly concentrated polymer solutions will minimise this effect.

An additional advantage of a tablet coating is the presence of a phase-separated morphology. This phase-separated morphology is important to cope with variations in the relative humidity. In contrast to non-phase-separated, completely amorphous polymers, no significant differences in the mechanical properties are observed at increased relative humidity. The co-continuous crystalline phase, which is responsible for the mechanical properties, is largely unaffected, since the additional amount of water is dissolved or stored in the amorphous phase.

In summary, numerous tablet coatings and systems are available to provide the controlled release of pharmaceutically active compounds in the stomach or intestine using both instant or sustained released systems. The main properties of these tablet coatings are a

low solution viscosity (preferably in water), combined with a phase-separated morphology showing good mechanical properties.

Synthesis and Characterisation of Poly(ethylene oxide)-*graft*-poly(vinyl alcohol) (PEO-*g*-PVAl) Copolymers

Instant-release tablet coatings are used to obtain a fast release of the active pharmaceutical ingredient. The main coating material currently used is hydroxy propyl methyl cellulose (HPMC).[2] A drawback of this material is the potential non-constant quality of a modified natural product and a relatively high solution viscosity in water. An alternative material used as an instant release tablet coating is poly(vinyl alcohol) (PVAl).[2] Despite its good film-forming properties and low solution viscosity, PVAl shows a relatively high brittleness and slow dissolution in water.[4] Both are caused by the crystalline nature of the polymer. The use of a copolymer or a plasticiser could prevent or reduce the crystallinity of the PVAl, and hence increase the coating properties. The use of a copolymer is preferred due to the non-favourable image of a plasticiser, combined with the fact that the use of a copolymer shows improved polymer properties.

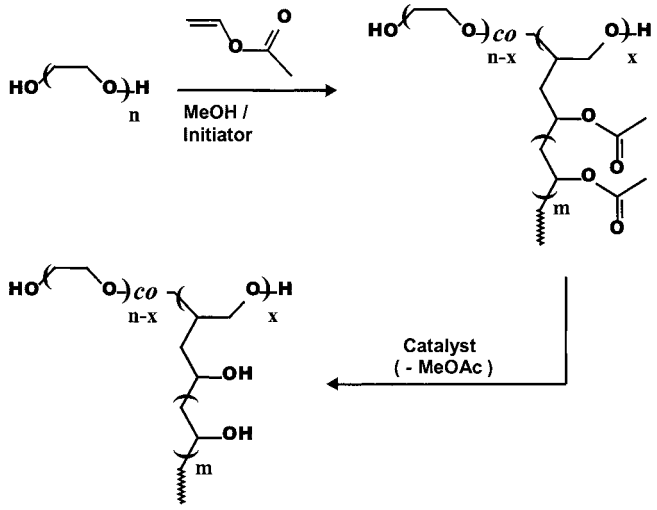


Figure 1. Synthetic route used for the preparation of the poly(ethylene oxide)-*graft*-poly(vinyl alcohol) (PEO-*g*-PVAl) copolymers.

Besides PVAl, another commonly used pharmaceutical polymer excipient is poly(ethylene oxide) (PEO).[1] Due to its good water solubility and its miscibility with PVAl, the combination of PVAl and PEO should result in an excellent instant-release tablet coating. One way to obtain a copolymer of PVAl and PEO is to make use of the high reactivity of the vinyl acetate radical (VAc), which leads to chain transfer and other side reactions,[5,6] and use the PEO as a chain transfer agent in the polymerisation of VAc. A resulting saponification or methanolysis results in the desired poly(ethylene oxide)-*graft*-poly(vinyl alcohol) (PEO-*g*-PVAl) copolymer (Figure 1).

The grafting reaction of VAc from PEO is hardly known and very little details are given in literature.[7,8] The most similar reaction described is the grafting of acrylic acid from a poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide) copolymer.[9-11] Assuming an analogous reaction sequence,[10] the following mechanism is proposed for the formation of the PEO-*g*-PVAl copolymers. The thermally decomposed radical initiator initiates the VAc polymerisation. A chain transfer reaction occurs between the growing PVAc chain and a PEO chain, resulting in a PEO radical and a terminated homo-PVAc chain. Subsequently, the PEO radical initiates the VAc polymerisation, which results in the PEO-*g*-PVAc copolymer. One PEO chain can probably be involved more than once in this chain transfer reaction, leading to multiple grafts. It is known that VAc shows chain transfer reactions to its acetate functionality, introducing branched PVAc polymers.[5,6] In the subsequent saponification or methanolysis step these side chains are cleaved, leading to the formation of homo-PVAl polymers. Since the chain transfer constant of VAc to PEO is not accurately known, it is not possible to predict the amount of homo-PVAl together with the desired PEO-*g*-PVAl copolymers.

A variety of PEO-*g*-PVAl copolymers have been prepared, differing in the VAc to PEO ratio and the molecular weight of PEO (Table 1). The use of, amongst others, 2-methoxyethyl-ether as a model compound (see below) resulted in the optimised polymerisation parameters. Analysis of the copolymers by IR and ^{1}H- and ^{13}C-NMR showed the presence of both PEO and PVAl. A small C=O absorption or resonance was still present, and is explained by a non-quantitative saponification. Titration experiments of **1a-i** showed a degree of saponification exceeding 95%. The SEC curve of the PEO-*g*-PVAl copolymers showed a molecular weight distribution (M_w/M_n) of around 5, with a

small tailing to the low molecular weight side. The latter was probably caused by the relatively low molecular weight homo-PVAl formed by the chain transfer reaction of VAc, both to the PEO and its acetate functionality. UV detection of the C=O functionality in the SEC measurement demonstrated the presence of PVAc over the entire molecular weight distribution of the non-saponified PEO-*g*-PVAc copolymers.

Table 1. The poly(ethylene oxide)-*graft*-poly(vinyl alcohol) (PEO-*g*-PVAl) copolymers prepared and the analytical results with regard to the presence of non-reacted free PEO, as determined by LCCC-SEC and MALDI-TOF.

Polymer	VAc content (%(w/w))	M_n PEO ($g.mol^{-1}$)	Presence free PEO[a]	
			LCCC-SEC	MALDI-TOF
1a	15	1500	y	y
1b	50	1500	y	y
1c	85	1500	[b]	y
1d	15	6000	y	y
1e	50	6000	y	y
1f	85	6000	n	n
1g	15	12000	y	y
1h	50	12000	y	y
1i	85	12000	n	n

a. y = yes, n = no free PEO found
b. could not be determined due to solubility issues

One of the main requirements of the PEO-*g*-PVAl copolymers is that no free PEO is present. Three methods have been used to determine this, *i.e.* extraction, liquid chromatography and mass spectrometry. Due to PVAl, PEO and the slightly grafted PEO-*g*-PVAl copolymers having similar solubility properties having extraction experiments were relatively difficult and results not very reliable.[12] Gradient HPLC measurements were performed, using a H_2O/THF eluent mixture. No complete separation of a reference PEO and the investigated PEO-*g*-PVAl copolymers could be obtained.[13] However, liquid chromatography under critical conditions (LCCC) resulted in the desired separation.[13] The critical point for PEO was obtained at a 82.5/17.5 water/MeOH mixture. To obtain an even better separation a SEC measurement was performed in a second dimension following the LCCC analysis. Two-dimensional LCCC-SEC measurements showed that polymers **1a-e**, **1g**, and **1h** do all contain non-reacted free PEO. Only polymers **1f** and **1i**, possessing a low 15:85 PEO:VAc ratio together with the higher molecular weight PEO 6000 and 12000, showed complete conversion of the PEO and did not contain free PEO. This is depicted in Figure 2 for polymer **1f**. Infrared (IR) analysis showed the presence of both PEO and PVAl

over the entire molecular weight distribution, with a higher concentration of PVAc in the low molecular weight region.[13]

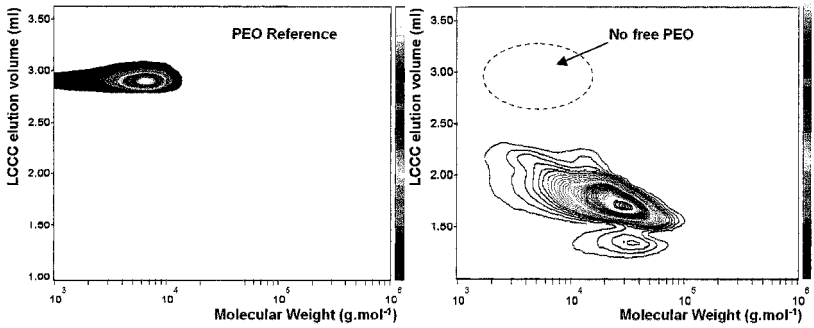
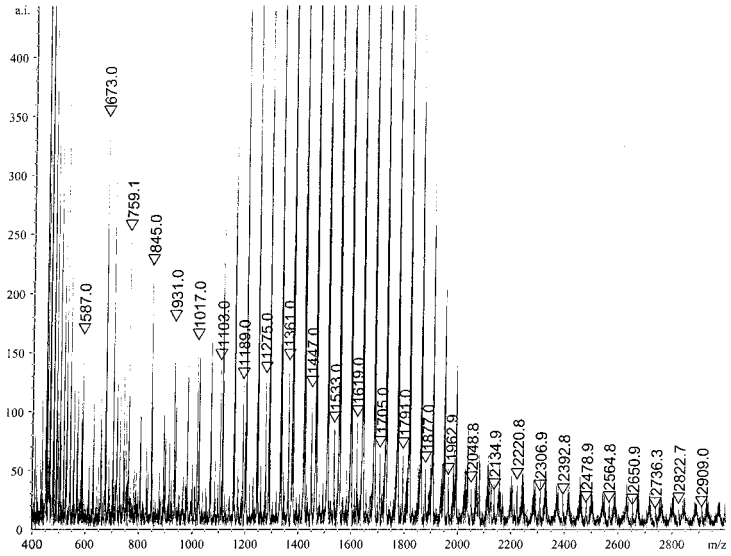


Figure 2. 2D LCCC-SEC measurements showing no free PEO in the PEO-*g*-PVAl copolymer **1f**.[13]

To confirm the LCCC method and additionally demonstrate the presence of free PVAl, mass spectrometry was performed. Due to the identical molecular weight of "vinyl alcohol" and ethylene oxide, these measurements were performed with the non-saponified PEO-*g*-PVAc instead of the PEO-*g*-PVAl copolymers. MALDI-TOF measurements using 1,8,9-trihydroyanthracene as the matrix and THF as solvent confirmed the above described LCCC-SEC measurements and showed the presence of PEO in copolymers **1a-e**, **1g**, and **1h**. No free PEO was found in copolymers **1f** and **1i**. Representative MALDI-TOF spectra of **1c** and **1f** are depicted in the Figures 3 and 4, respectively. A PEO distribution at molecular weights around 1500 $g.mol^{-1}$ can be seen for **1c** in Figure 3a. A more careful look shows that three different PEO signals can be distinguished, *i.e.* PEO possessing two-OH end groups, and PEO possessing one and two acylated end groups. The latter are explained by a transesterification of the PEO with VAc. Besides these PEO signals, smaller signals can be observed possessing a difference of 86 amu, indicating the presence of homo-PVAc. As depicted in Figure 4a, pure PEO is not observed for **1f**. A closer look demonstrates the presence of various signals possessing a difference of 86 amu, showing the existence of homo-PVAc with various end groups (Figure 4b). Homo-PVAc with molecular weights of up to 11.10^3 $g.mol^{-1}$ were detected after a SEC fractionation of copolymer **1f** (not shown here).

A.



B.

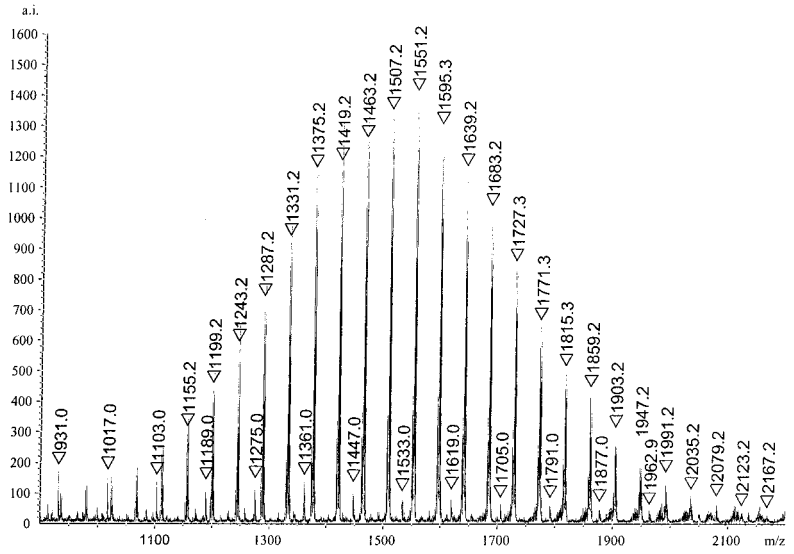
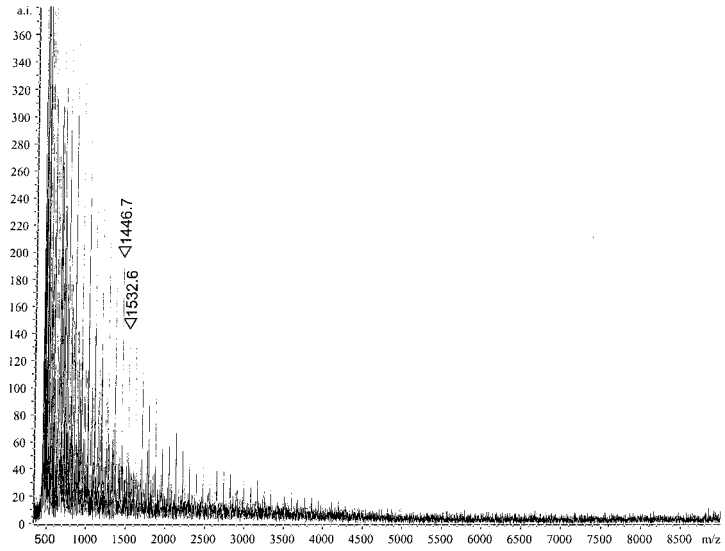


Figure 3. MALDI-TOF spectrum of **1c**; a) spectrum as obtained; b) detail.

A.



B.

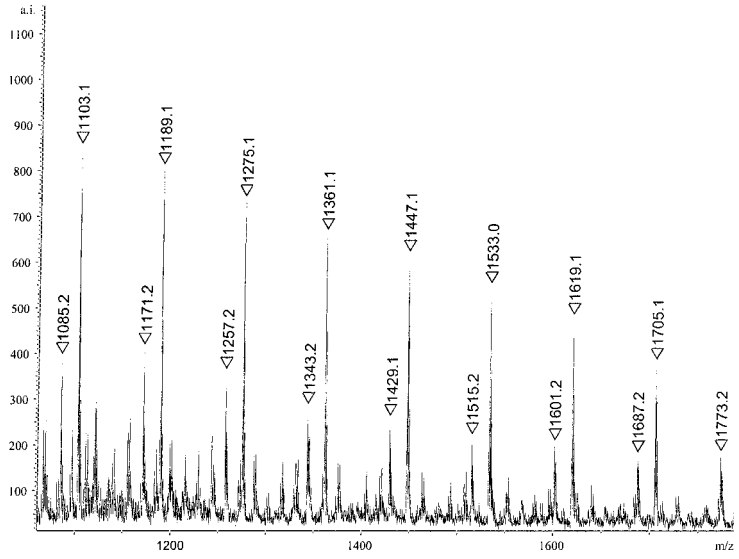


Figure 4. MALDI-TOF spectrum of **1f**; a) spectrum as obtained; b) detail.

In summary, no free PEO was observed in the PEO-*g*-PVAl copolymers **1f** and **1i** using 2D LCCC-SEC and MALDI-TOF analyses. Next to the requirement of being PEO-free,

both polymers showed a good combination of fast dissolution and low solution viscosity in water, with good mechanical and film forming properties.

The morphology of the PEO-*g*-PVAl copolymers was investigated by transmission electron microscopy (TEM), differential scanning calorimetry (DSC), dynamic mechanical measurements (DMTA), and wide angle X-ray spectrometry (WAXS). TEM measurements showed a phase separated morphology, possessing non-stained (crystalline PVAl) domains of less than 10 nm. DSC analysis demonstrated glass transition temperatures (T_g) of PEO and PVAl at about –45°C and 50°C, and melting points of PEO and PVAl at about 40°C and 205°C, respectively. A broad T_g transition from about –50°C to 60°C, showing two regions as indicated by two tangents, was observed in a DMTA measurement. The broad tan δ, indicating many thermal transitions, showed two small maxima at about 0 and 50°C. WAXS measurements also demonstrated the presence of crystalline PVAl. From these measurements it is concluded that a phase separated morphology is obtained consisting of pure crystalline PVAl and PEO phases, together with a mixed amorphous PEO-PVAl phase. Based on these measurements, the presence of a pure amorphous PVAl or PEO phase cannot be confirmed or excluded. Despite the presence of a crystalline PVAl phase, the PEO-*g*-PVAl copolymers showed a faster dissolution in water compared to PVAl. This is explained by the presence of smaller, less extended crystalline PVAl regions in the PEO-*g*-PVAl copolymers.

The molecular structure of the PEO-*g*-PVAl copolymers, including the average degree of grafting, is difficult to determine. The chain transfer constant of VAc to PEO is not accurately known and a careful ^{13}C-NMR analysis to quantify the amount of tertiary carbons in the PEO chain was unsuccessful. Although the latter could be improved using ^{13}C-labeled PEO, it was decided to use model compounds to look at the average degree of grafting in more detail, and hence into the molecular structure of the PEO-*g*-PVAl copolymers. Model compounds possessing similar reactivity towards VAc as PEO were selected. In addition, these model compounds should contain an ethylene oxide structural unit and should easily be detected by gas chromatography (GC). In the model reaction, the model compound replaces the PEO during the polymerisation of VAc, is partly grafted, and the amount of non-reacted model compound is determined by GC. From this result the amount of grafted model compound, and hence the degree of grafting of the PEO, can be

determined. PEO 2-methoxyethyl-ether, **2a**, and 1,4,7,10-tetraoxacyclododecane (12-crown-4), **2b**, were chosen as a model compound.

Based on the MALDI-TOF results, diethylene glycol is not preferred here due to the acylation of the hydroxy functionalities. The GC signal of diethylene glycol should therefore be combined with the signals of the mono- and di-acylated diethylene glycol to prevent making an estimation of the degree of grafting that is too high. To determine the different amounts of **2a** and **2b** before and after the reaction, an internal standard is needed. The relatively low boiling solvent MeOH that is used as the solvent in the grafting reaction is not suitable due to the fact that some of the MeOH will evaporate and escape from the reaction equipment during the experiment. Therefore methoxybenzene, **3**, possessing a boiling point in the same region as **2a**, was used. To increase the accuracy of the experiment, the **2a**:**3** ratio was determined using GC both before and after the VAc reaction. SEC and NMR measurements demonstrated the inertness of **3** in the grafting reaction. No UV absorption and no ^{1}H-, ^{13}C-NMR resonances of **3** were observed in the polymeric fraction of the reaction product, and no difference in the aromatic and CH_3 ^{1}H and ^{13}C ratio of **3** was detected. To eliminate the influence of **3** on the grafting process various reactions using a constant VAc:**2a** ratio of 85:15, and different amounts (10, 20, 25, 32.5 and 50%) of **3** compared to **2a,** were carried out.[14] A linear extrapolation to 0% **3**, assuming 1 PVAc graft per molecule **2a**, results in a conversion of 13±3% for **2a**. Assuming the same reactivity for **2a** and the PEO used, this results in 18±4 and 35±8 grafts per molecule, respectively, for the PEO-*g*-PVAl copolymers **1f** and **1i.**

The reaction product of VAc with **2a** using 25% **3** was also analysed by ^{13}C-NMR. Based on the CH_2:CH_3 ratio, again assuming one PVAc graft per **2a** molecule, a degree of grafting of 17±6% was found. This value is in good agreement with the results obtained using GC, and additionally point to the fact that the methoxy unit of **2a** is not involved in the grafting reaction. Similar results as for **2a** were obtained for **2b**. As mentioned above, diethylene glycol is not a good model compound for this reaction due to the potential acylation of its hydroxy units. However, for curiosity, an experiment using a 1:1:1:1 mixture of **2a**, **2b**, diethylene glycol and **3** was performed. Similar results were obtained for **2a** and **2b**, but surprisingly, diethylene glycol showed (also in reproductions) about half the conversion. No explanation for this effect can be given at the moment.

In summary, a model reaction has been developed to imitate the grafting reaction of VAc on various polyalkoxides. Using this model reaction, 13±3% grafting of PEO was found, and using the same reaction conditions (temperature, initiator, concentration, VAc:"PEO" ratio, etc.) as applied in the PEO-*g*-PVAl polymerisation procedure. Applying this number to the PEO-*g*-PVAl copolymers **1c**, **1f**, and **1i**, an average degrees of grafting of 4±1, 18±4 and 35±8 grafts per molecule are expected. For the polymers **1c**, **1f**, and **1i**, only **1c** showed non-converted free PEO using LCCC-SEC and MALDI-TOF analysis. The presence of non-reacted free PEO in **1c** could be explained by statistics or reactivity. An average degree of grafting of 4±1 could statistically result in some non-grafted PEO molecules. Alternately, the reactivity of model compound **2a** is slightly higher than that of the higher molecular weight PEO compounds used. Additional studies focussing on the grafting of various polyalkoxides using a variation of monomers and reaction conditions (temperature, concentration, type of solvent and initiator, etc.) are in progress, and the results will be described elsewhere.

Conclusions

A number of tablet coatings are available to provide the controlled release of pharmaceutically active compounds in the stomach or intestine, using both instant or sustained released systems. PEO-*g*-PVAl copolymers have been developed as an instant release tablet coating. They were obtained via a conventional radical polymerisation of VAc in the presence of PEO. No free PEO was observed in the PEO-*g*-PVAl copolymers **1f** and **1i,** using 2D LCCC-SEC and MALDI-TOF analysis. Next to the requirement of being PEO free, the PEO-*g*-PVAl copolymers show 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, should provide the PEO-*g*-PVAl copolymers with relatively constant mechanical properties. A model reaction was developed to imitate the grafting reaction of VAc on various polyalkoxides. Using this model reaction a degree of grafting 13±3% for PEO of was found, using the same reaction conditions (temperature, initiator, concentration, VAc:"PEO" ratio, etc.) as applied in the PEO-*g*-PVAl polymerisation procedure. Applying this number to the PEO-*g*-PVAl copolymers **1c**, **1f**, and **1i**, an average degree of grafting of 4±1, 18±4 and 35±8 grafts per molecule is expected, respectively. Comparing these

figures with the LCCC-SEC and MALDI-TOF measurements, these figures seem a few percent too high, pointing to a slightly increased reactivity of **2a** and **2b** compared to the PEO used.

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13. M. Adler, *PhD Thesis, University of Technology Darmstadt, Germany*, 2004
14. These experiments demonstrated that the experimental error in the GC analysis becomes too high using a **3** to **2a** ratio <20% (w/w)