Influence of Plasticizer Type and Storage Conditions on Properties of Poly(methyl vinyl ether-*co*-maleic anhydride) Bioadhesive Films

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ABSTRACT: Poly(methyl vinyl ether-*co*-maleic anhydride) formed films from aqueous formulations with characteristics that are ideal as a basis for producing a drug-containing bioadhesive delivery system when plasticized with a monohydroxyl functionalized plasticizer. Hence, films containing a novel plasticizer, tripropylene glycol methyl ether (TPME), maintained their adhesive strength and tensile properties when packaged in aluminized foil for extended periods of time. Films plasticized with commonly used polyhydric alcohols, such as the glycerol in this study, underwent an esterification reaction that led to polymer crosslinking, as shown in NMR studies. These revealed the presence of peaks in the ester/carbonyl region, suggesting that glyceride residue formation had been initiated. Given the polyfunctional nature of glycerol, progressive esterification would result in a polyester network and an accompanying profound alteration in the physical characteristics. Indeed, films became brittle over time with a loss of both the aqueous solubility and bioadhesion to porcine skin. In addition, a swelling index was measurable after 7 days, a property not seen with those films containing TPME. This change in bioadhesive strength and pliability was independent of the packaging conditions, rendering the films that contain glycerol as unsuitable as a basis for topical bioadhesive delivery of drug substances. Consequently, films containing TPME have potential as an alternative formulation strategy. © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 91: 1576–1589, 2004

Key words: adhesion; glass transition; poly(vinyl ethers); drug delivery systems; tripropylene glycol methyl ether

INTRODUCTION

Films cast from aqueous blends of poly(methyl vinyl ether-*co*-maleic anhydride) (PMVE/MAH) have diverse uses, such as a means of establishing an electrically conducting interface for bioelectrodes[1] and as an adhesive drug-delivery matrix.[2] Film formulations based on PMVE/MAH are known to possess moisture-activated bioadhesive properties.[3]

In structural terms, the five-membered anhydride ring of PMVE/MAH contributes two carbon atoms to the polymer backbone and therefore confers rigidity on the system. When hydrolyzing this anhydride moiety to the corresponding free acid form (PMVE/maleic acid), a reduction in the glass-transition temperature (T_g) of only 10°C from the relatively high T_g of the dry powder (151°C) is observed, because of the increased flexibility of the free acid structure.[4] Films cast from aqueous blends of the free acid are consequently very brittle and of little use in formulating films for drug-delivery purposes. Therefore, these systems require the inclusion of a suitable plasticizer in the film casting blend.

Plasticizers used for PMVE/MAH film formulations are typically water-miscible, polyhydric alcohols, such as glycerol.[5] These plasticizers are suspected of crosslinking PMVE/MAH on heating or on prolonged standing at room temperature.[5] There are several proposed mechanisms by which crosslinking of bioadhesive polymer chains may reduce bioadhesive performance.[6] In particular, crosslinking reduces chain flexibility and subsequent interpenetration into the mucin network. Crosslinking is also known to diminish the bioadhesive capacity of a polymer by reducing its ability to make intimate contact with the tissue substrate by elastic deformation and viscous flow.[7] Crosslinking that involves hydrogen bond formation between the plasticizer and suitable functional groups on the bioadhesive polymer may also diminish the

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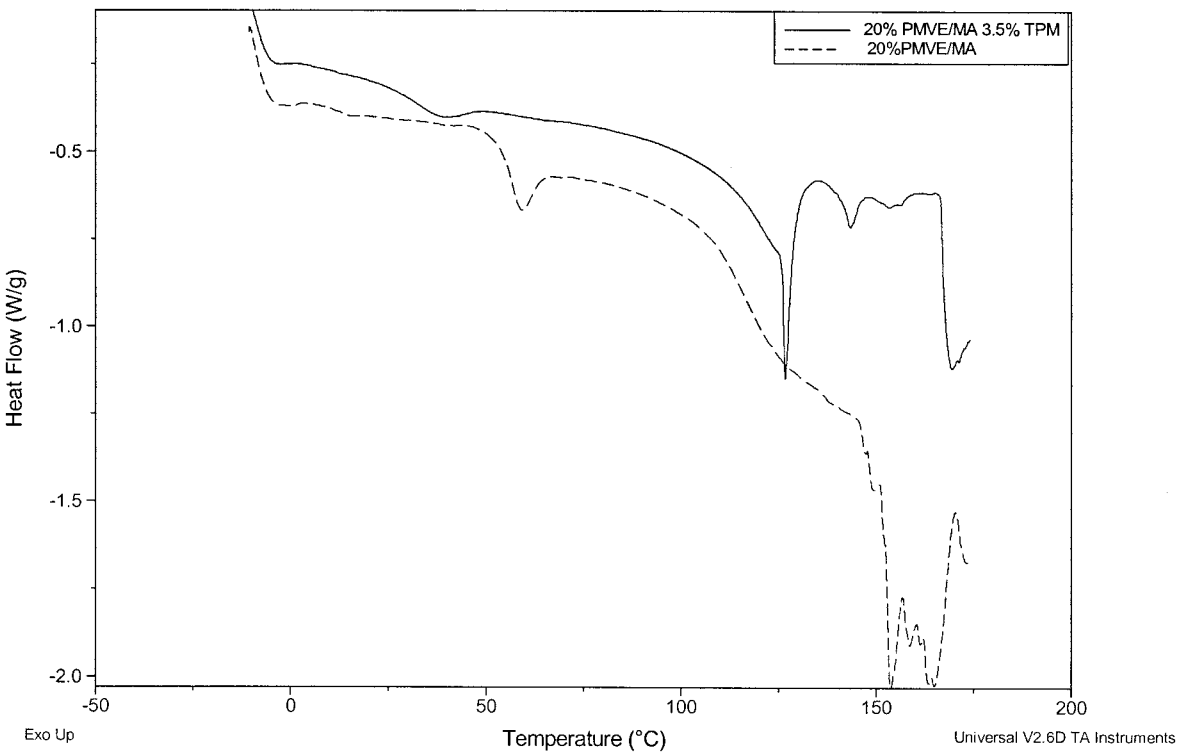

Figure 1 Differential scanning calorimetry of films cast from aqueous blends of poly(methyl vinyl ether-*co*-maleic anhydride), showing a lowering of the glass-transition temperature in the presence of tripropylene glycol methyl ether.

extent of hydrogen bond formation between the polymer and the substrate.[8]

Tripropylene glycol methyl ether (TPME) is a high boiling point (243°C) liquid, which is completely miscible with water.[9] It is used as a solvent but it has a toxicity profile[10] that makes it suitable for inclusion in externally applied pharmaceutical formulations. The chemical properties[9] of TPME suggest that it may be capable of plasticizing water-soluble polymers such as PMVE/MAH. More importantly, because TPME possesses only one hydroxyl group and no acid groups, it should be unable to act as a crosslinker of polymer chains. This is particularly relevant because bioadhesive films intended for drug delivery to mucosal surfaces must maintain their adhesive and surface conformability properties during storage. If latent crosslinking occurs after manufacture, then device failure can be expected, because of low adhesion and/or poor conformability to the tissue substrate. This study therefore investigates the influence of plasticizers on the properties of PMVE/MAH films and potential mechanisms by which the polymer may crosslink when in storage. The aim is to produce a stable film that maintains its adhesion and conformability properties with storage, rendering it suitable for use as a topical drug-delivery system.

EXPERIMENTAL

Materials

Gantrez® AN-139, a copolymer of MVE and MAH (PMVE/MAH), was obtained from ISP Co. Ltd. (Guildford, U.K.). TPME (Dowanol™ TPM) and Hydranal™ were obtained from Sigma Aldrich (Dorset, U.K.). All other chemicals were analytical reagent quality. Polyester film, in the form of a one-sided siliconized release liner (FL2000™ PET 75 μ 1S), was obtained from Rexam Release B.V. (Apeldoorn, The Netherlands). Moisture-impermeable, heat-sealable polyester foils were obtained from Transparent Film Products Ltd. (N. Ireland, U.K.).

Methods

Preparation of bioadhesive films

Aqueous polymer blends were prepared using the required weight of PMVE/MAH, which was added to ice-cooled water (reagent grade 1) and stirred vigorously to ensure complete wetting and prevention of aggregation. The mixture was then heated and maintained between 95 and 100°C until a clear solution was formed. Upon cooling, the required amount of plasticizer was added, the pH was adjusted to 4.5 using 10*M* NaOH, and the casting blend was adjusted to a final weight with water.

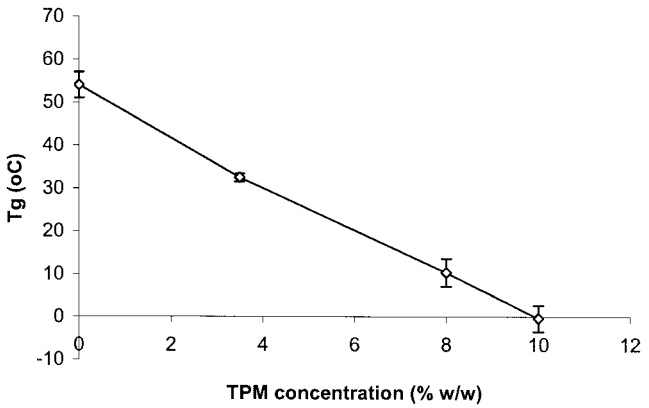

Figure 2 The influence of tripropylene glycol methyl ether on the glass-transition temperature of films cast from aqueous blends of poly(methyl vinyl ether-*co*-maleic anhydride).

Bioadhesive films were prepared by slowly pouring the aqueous blend (30 g) into a mold consisting of the release liner (with the siliconized side up) secured to a Perspex base plate using a stainless steel clamp. Once assembled, the internal dimensions available for casting were 100 × 100 mm. The mold was placed on a leveled surface to allow the blend to spread evenly across the area of the mold. The cast blend was dried under a constant air flow at 25°C.

Determination of glass-transition temperature

The ability of TPME to plasticize films cast from aqueous blends of PMVE/MAH was determined by differential scanning calorimetry. Films cast from blends containing 20% (w/w) PMVE/MAH and 0, 3.5, 8, and 10% (w/w) TPME were used. The determination of the T_g was performed using a DSC 2920 differential scanning calorimeter with a refrigerated cooling system (TA Instruments, Surrey, U.K.) and a heating rate of 10°C min^{-1} in nitrogen. The midspan temperature of the step change in the heat capacity curve was chosen as T_g. The DSC 2920 calorimeter was calibrated with the melting temperature of indium. The results were reported as the mean (±SD) of three replicates.

Storage conditions for bioadhesive films

Films cast from blends containing PMVE/MAH alone, PMVE/MAH with glycerol, and PMVE/MAH with TPME were divided into two test groups. One group was stored at 25°C in a sealed vessel with a relative humidity of 65%, which was maintained by the presence of a saturated solution of sodium nitrite. Films in a second group were placed in moisture-impermeable polyester foils, which were heat sealed and stored in the same vessel. The seal integrity of the foil pockets was checked by prior immersion in concentrated potassium permanganate solution and inspection for internal discoloration after opening. Films were removed from storage at 7-day intervals and their bioadhesive, tensile, and swelling characteristics investigated. The water contents of the films was also determined.

Bioadhesion measurements

The bioadhesion properties of all films were evaluated quantitatively using a TA-XT2 texture analyzer (Stable Microsystems, Haslemere, U.K.) in tensile mode. Full thickness, shaved, neonate porcine skin was attached with cyanoacrylate adhesive to a lower platform. Film segments (1 cm^2) were attached to the probe of the texture analyzer using double-sided adhesive tape. Adhesion was initiated by adding a defined amount of water (10 μL) over an exposed skin sample (1 cm^2) and immediately lowering the probe with the attached film. Upon contact, a force of 5 N was applied for 30 s before the probe was moved upward at a speed of 0.1 mm s^{-1}. The adhesion was recorded as the force required to detach the sample from the surface of the excised skin. The distance to separation of a test film from the skin substrate, which is the vertical displacement from the skin surface that the probe had traveled at the instant the film and substrate lost contact with each other, was also recorded to provide some measure of the cohesion within the film sample. The results were reported as the mean (±SD) of five replicates.

TABLE I
Influence of Plasticizers on Tensile Properties and Water Content of Freshly Prepared Films Cast from Aqueous Blends of PMVE/MA

PMVE/MA (w/w %)	Plasticizer (w/w %)	Tensile strength N m^{-2} ($\times 10^{-6}$)	Elongation at break (%)	Water content (w/w %)
10	0	18.96 ± 1.18	0	3.78 ± 0.21
10	5% glycerol	0.31 ± 0.08	919.6 ± 62.1	8.46 ± 0.15
10	10% glycerol	0.04 ± 0.01	1005 ± 11.2	14.27 ± 0.38
10	5% TPM	1.61 ± 0.30	592.2 ± 104.2	8.71 ± 0.05
10	10% TPM	0.39 ± 0.06	940.9 ± 119.1	9.57 ± 0.36

TABLE II
Influence of Plasticizers on Adhesion and Distance to Removal of Freshly Prepared Films Cast from Aqueous Blends of PMVE/MA

PMVE/MA (w/w %)	Plasticizer (w/w %)	Adhesion (N)	Distance to removal (mm)
10	0	0.92 ± 0.33	5.03 ± 4.60
10	5% glycerol	1.20 ± 0.28	13.48 ± 6.20
10	10% glycerol	1.38 ± 0.55	54.35 ± 2.77
10	5% TPM	1.04 ± 0.38	4.63 ± 4.45
10	10% TPM	1.43 ± 0.16	7.89 ± 2.567

Determination of tensile properties

The tensile strength and percent elongation at break of the films were determined using the texture analyzer. Film strips (5-mm width) were grasped using an upper and lower flat-faced metal grip laminated with a smooth rubber grip. The distance between the grips was set at 20 mm, and this distance therefore represented the length of the film under stress. A crosshead speed of 6 mm s^{-1} was used for all measurements. The resulting force–time profiles were analyzed using proprietary software (Dimension 3.7E). The only results that were used were from films that were broke in the middle region of the test strip during testing. The results were reported as the mean (±SD) of five replicates.

Swelling studies

The swelling behavior of the films was investigated by immersing dry, preweighed film segments (1 cm^2) in distilled water (30 mL) at 25°C. The segments were allowed to swell to equilibrium and then reweighed following careful blotting with absorbant paper to remove surface water. The equilibrium weight swelling index (SI) of the films was defined as the ratio of the weight of the swollen film (W_s) to that of the dry film (W_d), as shown in eq. (1).[11] The results were reported as the mean (±SD) of three replicates.

$$SI = \frac{W_s}{W_d} \quad (1)$$

Determination of water content

The percentage (w/w) of the water content of the films was determined by Karl Fischer titration. The water

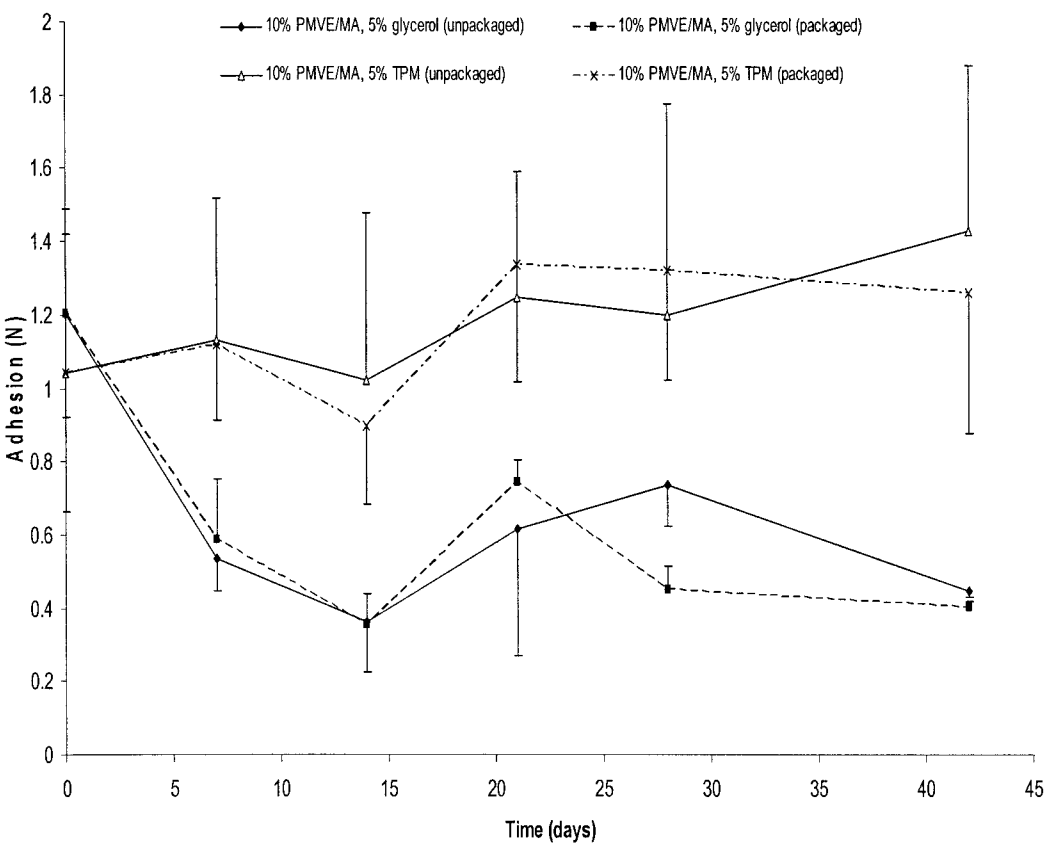

Figure 3 The influence of storage time on the bioadhesion of packaged and unpackaged films cast from aqueous blends of poly(methyl vinyl ether-*co*-maleic anhydride) and either 5% (w/w) glycerol or tripropylene glycol methyl ether (mean ± SD, $n = 5$).

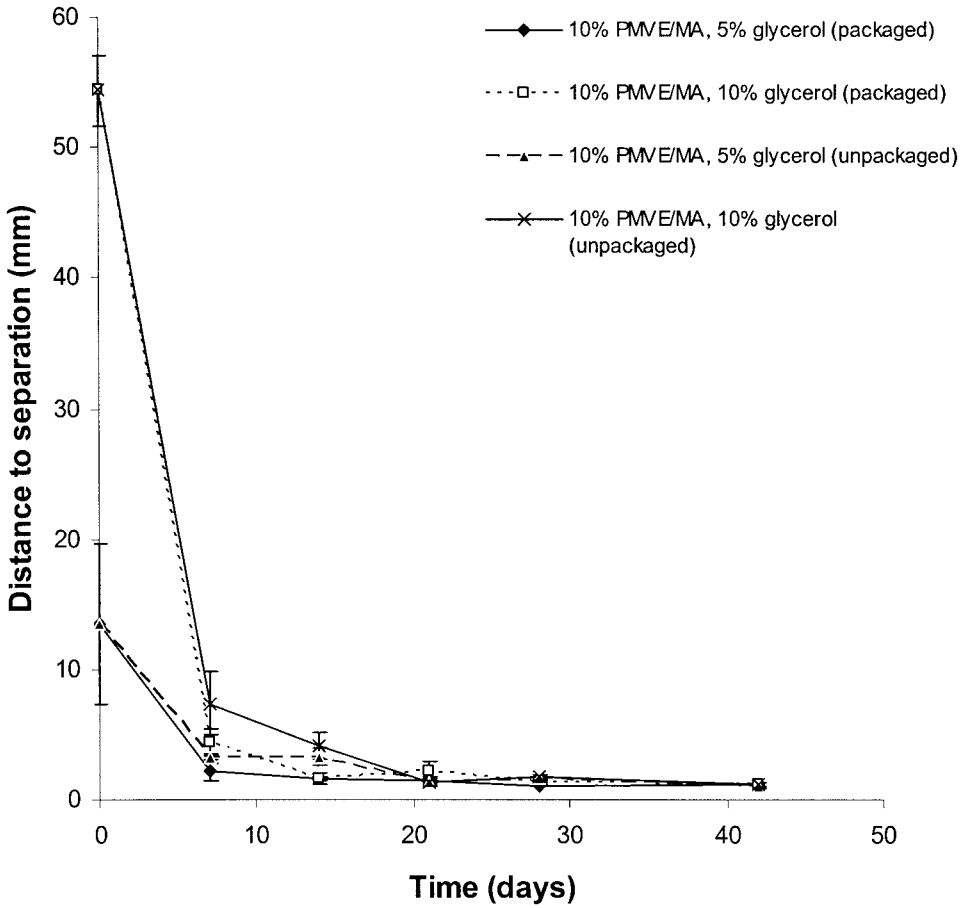

Figure 4 The influence of storage time on the distance to skin–film segment separation for poly(methyl vinyl ether-*co*-maleic anhydride) films plasticized with glycerol (mean ± SD, $n = 5$).

contained in the 1 cm^2 film segments was titrated against pyridine-free Karl Fischer reagent using an automated 701 KF Titrino titrator (Metrohm Instruments, Herisau, Switzerland) previously calibrated using Hydranal proprietary standards. Sufficient time was added to each analysis procedure to ensure that all available water was titrated. The results were reported as the mean (±SD) of five replicates.

NMR spectroscopy

The NMR spectra for glycerol and TPME were recorded at 25°C (General Electric QC500 spectrometer) using a 5-mm probe and operating at 126 MHz for carbon with $CDCl_3$ as a solvent. Solid-state ^{13}C-NMR spectra were obtained under cross-polarization/magic-angle spinning (CP/MAS) and direct polarization/MAS (DP/MAS) conditions on a Varian UNITY Inova spectrometer with a 7.05 T Oxford Instruments magnet and a 7-mm standard MAS probe (Doty Scientific Instruments) operating at 300 MHz. A film sample (200–250 mg) was placed in a double-bearing rotor made of zirconia. The spinning speed was set in the 4800–5000 Hz range.

Statistical analysis

Where appropriate, the results were analyzed using a single factor analysis of variance, where $p < 0.05$ was taken to represent a statistically significant difference.

RESULTS

Films cast from aqueous blends of PMVE/MAH with no plasticizer were brittle and unsuitable for use as the basis of a conformable, bioadhesive delivery system. As can be seen from Figures 1 and 2, the addition of TPME caused a significant ($p < 0.0001$) reduction in the T_g of cast films. The tensile strengths decreased significantly ($p < 0.0001$), whereas the percent elongations at break showed significant ($p < 0.0001$) increases (Table I). Table I shows that, as the glycerol ($p < 0.0001$) or TPME ($p < 0.0001$) content in films cast from aqueous blends of PMVE/MAH was increased, their water contents also increased significantly. Thus, films cast from blends containing 10% (w/w) glycerol had a mean water content of 14.27% compared to 3.78% for unplasticized films. The water contents of films packaged in heat-sealed foils remained constant

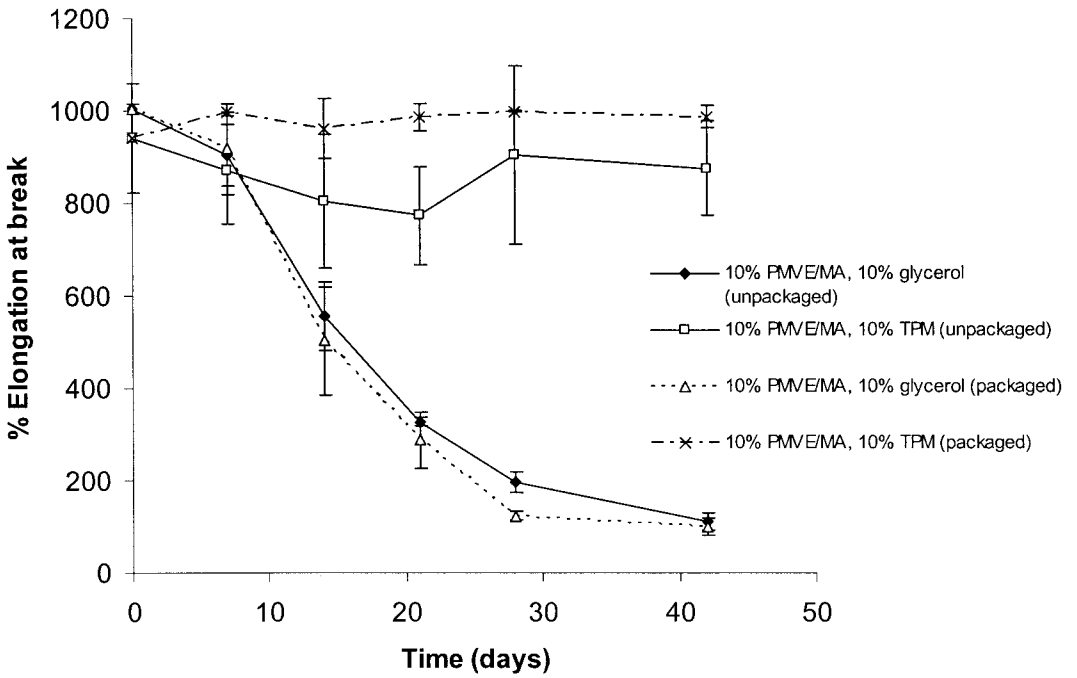

Figure 5 The influence of storage time on the elongation at break percentage of films cast from aqueous blends of poly(methyl vinyl ether-*co*-maleic anhydride) and containing either 10% (w/w) glycerol or tripropylene glycol methyl ether (mean ± SD, $n = 5$).

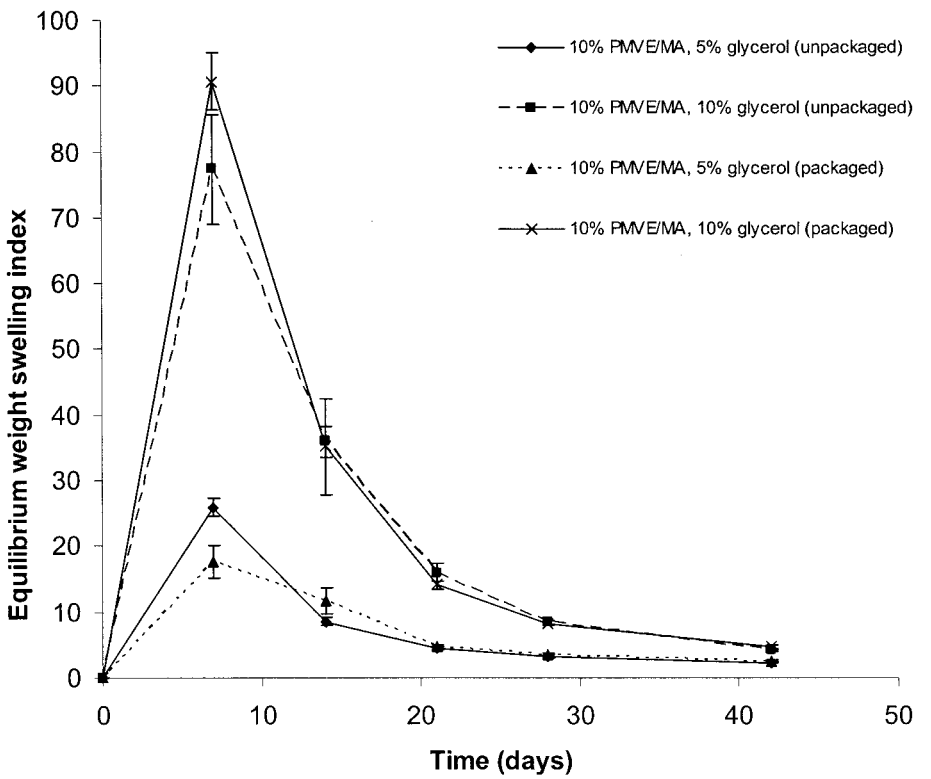

Figure 6 The influence of storage time on the equilibrium weight swelling index of films containing glycerol (mean ± SD, $n = 5$).

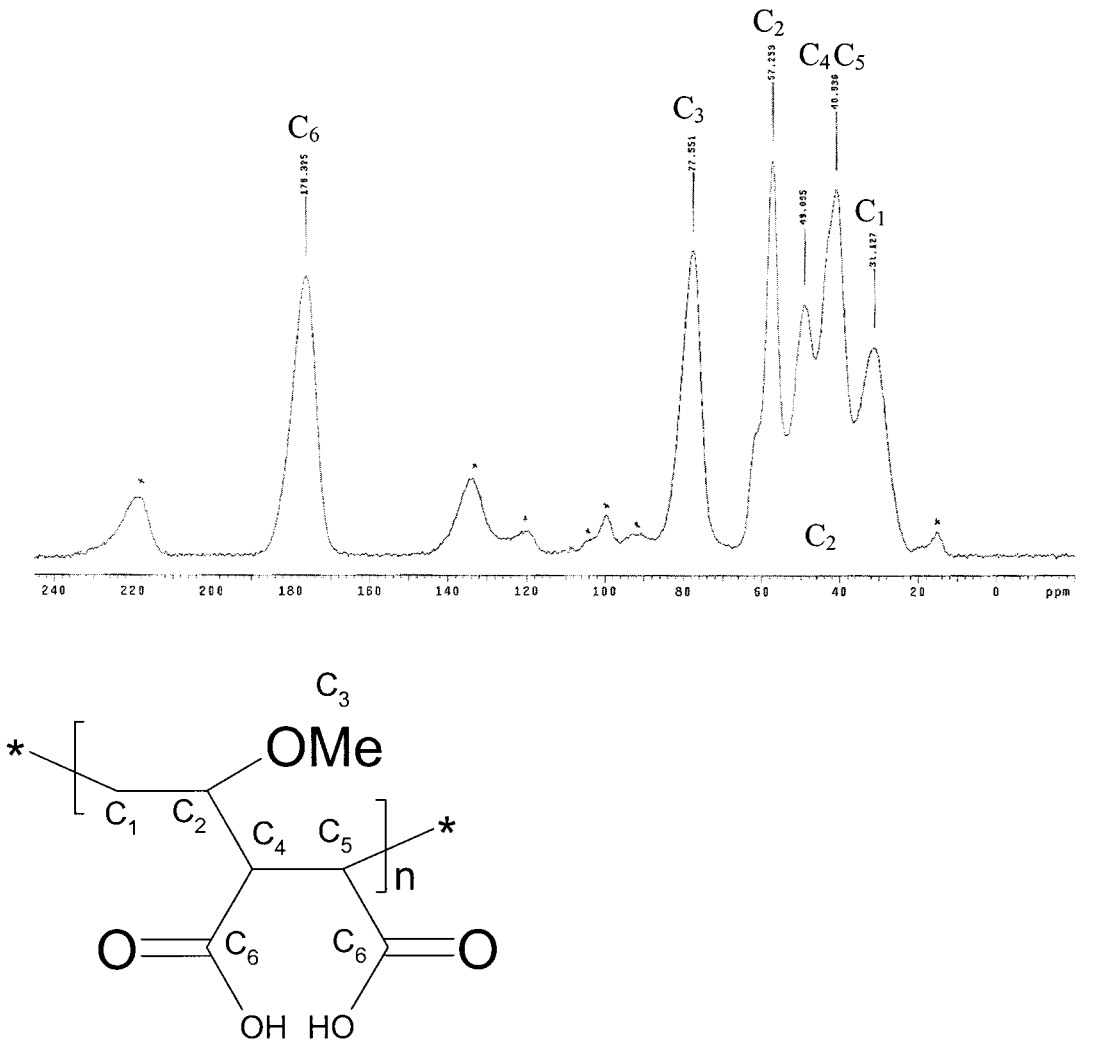

Figure 7 The ^{13}C-NMR cross-polarized solid-state spectrum of an unplasticized poly(methyl vinyl ether-*co*-maleic anhydride) film with associated assignments of carbon atoms.

over time, but the unpackaged ones lost significant amounts of water during storage. For example, a glycerol plasticized film with an initial mean water content of 14.27% had a water content of <4% after 42 days of storage in an unpackaged state at 25°C.

Neither the addition of glycerol ($p = 0.5964$) nor the addition of TPME ($p = 0.0516$) had a significant effect on the bioadhesion of freshly prepared films to shaved neonate porcine skin (Table II). Initially, freshly prepared films plasticized with glycerol showed significant ($p < 0.0001$) increases in distance to separation relative to unplasticized films, whereas similar changes were not observed in films plasticized with TPME.

Films cast from blends containing 5% (w/w) glycerol lost their bioadhesive strength over time, as shown in Figure 3. There were significant decreases in adhesion after only 7 days of storage, whether packaged ($p < 0.0001$) or unpackaged ($p < 0.0001$). By contrast, the bioadhesive properties of films cast from blends containing 5% (w/w) TPME remained unaltered over a similar time frame. Films cast from blends containing 10% (w/w) glycerol also showed significant reductions in adhesion after 6 weeks of storage ($p < 0.0001$) for both packaged and unpackaged films, an effect not seen for films cast from blends containing 10% TPME or for unplasticized films.

All films containing glycerol showed pronounced decreases in distance to separation over time, as shown in Figure 4, with significant decreases being noted in each case after 7 days of storage. Unplasticized films did not display this effect, whereas only slight decreases were noted for films containing TPME. Packaging these films in heat-sealed, moisture-impermeable polyester foils had no influence on maintaining bioadhesion or the distance to separation. An examination of the elongation at break for films cast from blends containing 10% (w/w) glycerol showed

significant decreases when stored, whether packaged or unpackaged (Fig. 5). By contrast, packaged films cast from blends containing 10% (w/w) TPME showed no significant decreases in the elongation at break percentage after 6-week storage.

Films cast from aqueous blends of PMVE/MAH, with and without plasticizer, dissolved in water initially. Films cast from blends containing 5% (w/w) glycerol became insoluble in water after 7-day storage, showing significant increases in the equilibrium weight swelling indices that were independent of the packaging status ($p < 0.0001$). The swelling indices (Fig. 6) then decreased progressively, and a similar pattern was displayed by films cast from blends containing 10% (w/w) glycerol. However, the initial rise in the swelling index was much more pronounced in the latter case.

The ^{13}C-NMR cross-polarized spectrum of an unplasticized film cast from PMVE/MAH is shown in Figure 7, along with associated assignments of carbon atoms. A DP spectrum could not be obtained for the rigid film. The solid-state ^{13}C-NMR spectra obtained for PMVE/MAH films plasticized with glycerol and TPME are shown in Figures 8 and 9, respectively. Films plasticized with TPME displayed a poorly resolved CP spectrum at 5% (w/w) plasticizer and the formation of a carbonyl band at 177 ppm within the DP spectra. A well-resolved CP spectrum was obtained at a 10% (w/w) TPME concentration.

DISCUSSION

Plasticized bioadhesive films based on PMVE/MAH are potentially useful drug-delivery platforms for a range of topical applications, including local delivery to moist mucosal epithelial tissue. Such films have excellent initial adhesion and conformability (flexibility) properties.[1–3] However, this article is the first to demonstrate the loss of adhesion and concomitant changes in the mechanical properties that occur during storage. Consequently, a detailed investigation has been made of the fundamental behavior of the plasticized PMVE/MAH film system in order to facilitate the formulation of drug-delivery films with stable adhesion and mechanical properties.

Polyhydric alcohols, such as propylene glycol, glycerol, and poly(ethylene glycol) 400, were previously shown to act as plasticizers of PMVE/MAH films.[1] Glycerol is the most typically used plasticizer for PMVE/MAH. However, films cast from blends plasticized with glycerol progressively lose their adhesion on storage (Fig. 3). The elongation at break during tensile mode adhesion testing also decreases. The flexibility of glycerol plasticized films was reduced concomitantly over time, with films becoming insoluble and showing a marked reduction in the water swelling indices (Fig. 6) after only 7 days of storage. These observations are all consistent with a progressive increase in the film crosslinking density during storage

TPME was shown to be an effective plasticizer (Figs. 1, 2) for PMVE/MAHH based films intended for drug administration purposes. It progressively lowered the glass-transition temperature of the bioadhesive polymer in direct proportion to the plasticizer concentration in the casting blend. Films cast from PMVE/MAH blends containing 5% (w/w) TPME maintained their bioadhesive properties (Fig. 3) and remained water soluble after 6 weeks of storage. The elongation at break was also maintained in stored films plasticized with TPME (Fig. 5).

In contrast to previously reported plasticizers of PMVE/MAH, TPME is monohydric, possessing only a terminal hydroxyl group. It was chosen as an alternative plasticizer in this study because it could not crosslink PMVE/MAH chains by means of an interaction with the carboxylic acid groups on the bioadhesive polymer, for example, by forming ester linkages. Although films plasticized with 5% (w/w) TPME displayed a slight loss of flexibility on storage, this effect was more prominent in unpackaged films, which became less flexible in comparison to those packaged in foils, suggesting the importance of water as a synergistic plasticizer of PMVE/MAH. Notwithstanding this slight loss in flexibility, packaged films remained sufficiently pliant for topical application. It was not determined whether this reduction in flexibility was due to enhanced hydrogen bonding, a progressive increase in physical entanglements, or limited ester formation leading to increased interchain cohesion. However, films cast with higher levels of TPME (10%, w/w) displayed mechanical properties similar to those found immediately after drying (packaged or unpackaged), the increased plasticizer content presumably aiding retention of water within the film structure.

The time-dependent decreases in the adhesion and distance to separation (Figs. 3, 4) seen with glycerol plasticized films are indicative of a polymer system that is becoming more restricted in movement by the formation of a tighter network of crosslinks. Hence, film cohesion rises and distance to separation falls. In addition, the loss of functional groups, such as —COOH, which are capable of hydrogen bonding to a biological substrate, may contribute to the observed reduction in bioadhesion. In contrast, films containing TPME showed decreased distances to separation but maintained their bioadhesive strength, suggesting an increased interchain cohesive attraction with preservation of chemical residues capable of hydrogen bonding.

The swelling indices (Fig. 6) of 5% (w/w) glycerol plasticized films progressively decreased, suggesting a system that is becoming increasingly organized and of tighter disposition and that can therefore accommo-

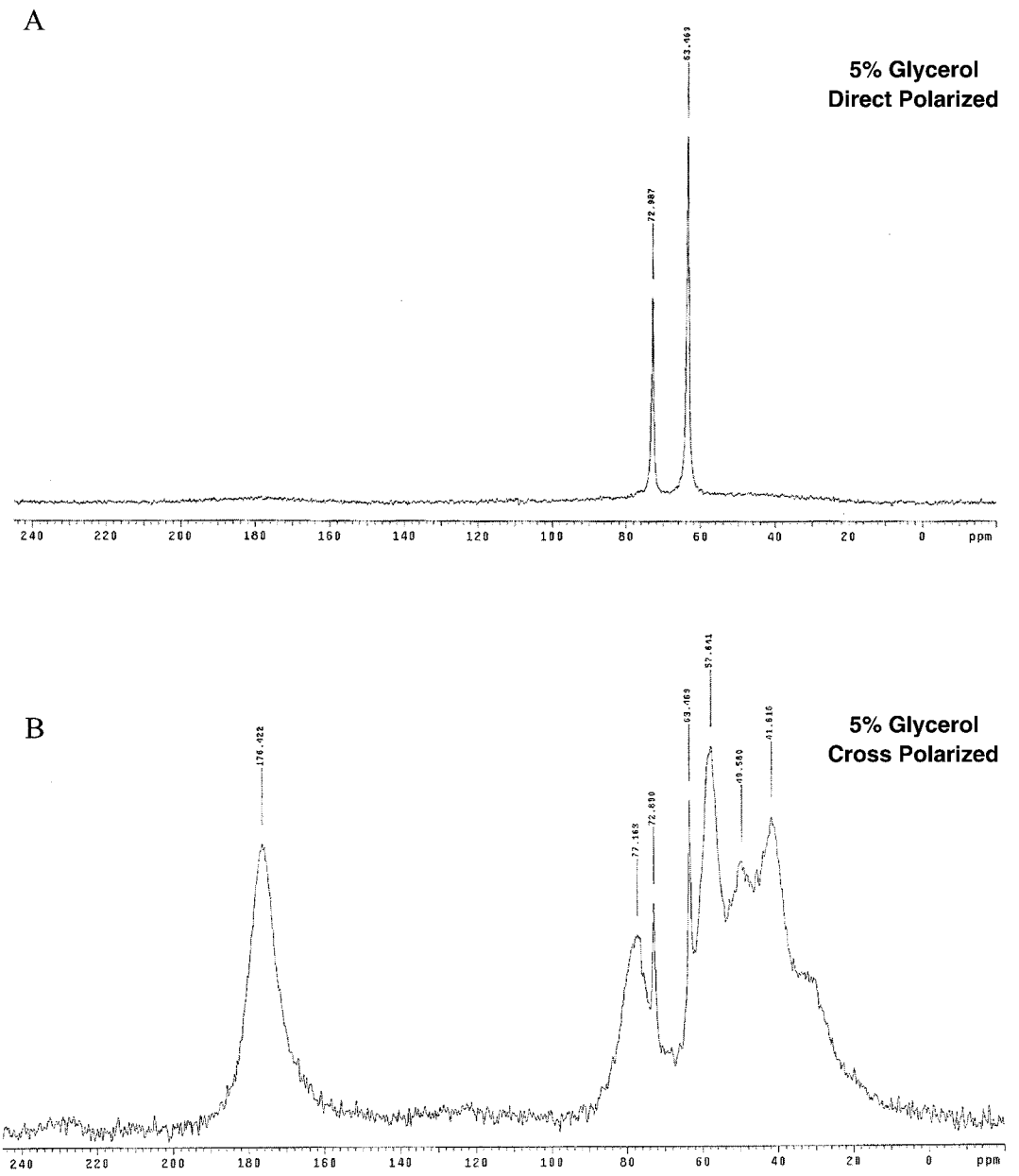

Figure 8 (A,C) Directly polarized solid-state NMR spectra of films cast from aqueous blends containing 10% (w/w) poly(methyl vinyl ether-*co*-maleic anhydride) with (A) 5 and (C) 10% (w/w) glycerol. (B,D) Cross-polarization solid-state NMR spectra of films cast from aqueous blends containing 10% poly(methyl vinyl ether-*co*-maleic anhydride) and (B) 5 and (D) 10% (w/w) glycerol.

date less water within its network. A similar pattern was found in films cast from blends containing 10% (w/w) glycerol, but the initial rise in the swelling index was much more pronounced. This may arise from the high glycerol content, leading to greater interchain separation and the formation of a looser network. All unplasticized films and those containing 5 and 10% (w/w) TPME remained water soluble throughout the study period. The swelling characteristics observed in films cast from blends containing glycerol, however, together with their gradual insolubilization in water, clearly suggest that there is a slow chemical alteration, typically occurring over about 7 days, in the glycerol plasticized PMVE/MAH film system. It is possible that glycerol is participating in a crosslinking reaction that is attributable to ester formation with the free carboxylic acid moieties formed on hydrolysis of PMVE/MAH. Because glycerol is polyhydric, attachment could occur at more than one point on the bioadhesive polymer chain, thereby contributing to formation of a three-dimensional PMVE/MAH network. Hydrogen bonding to the hydroxyl groups on the free acid form of PMVE/MAH is unlikely to be the predominant crosslinking mechanism,

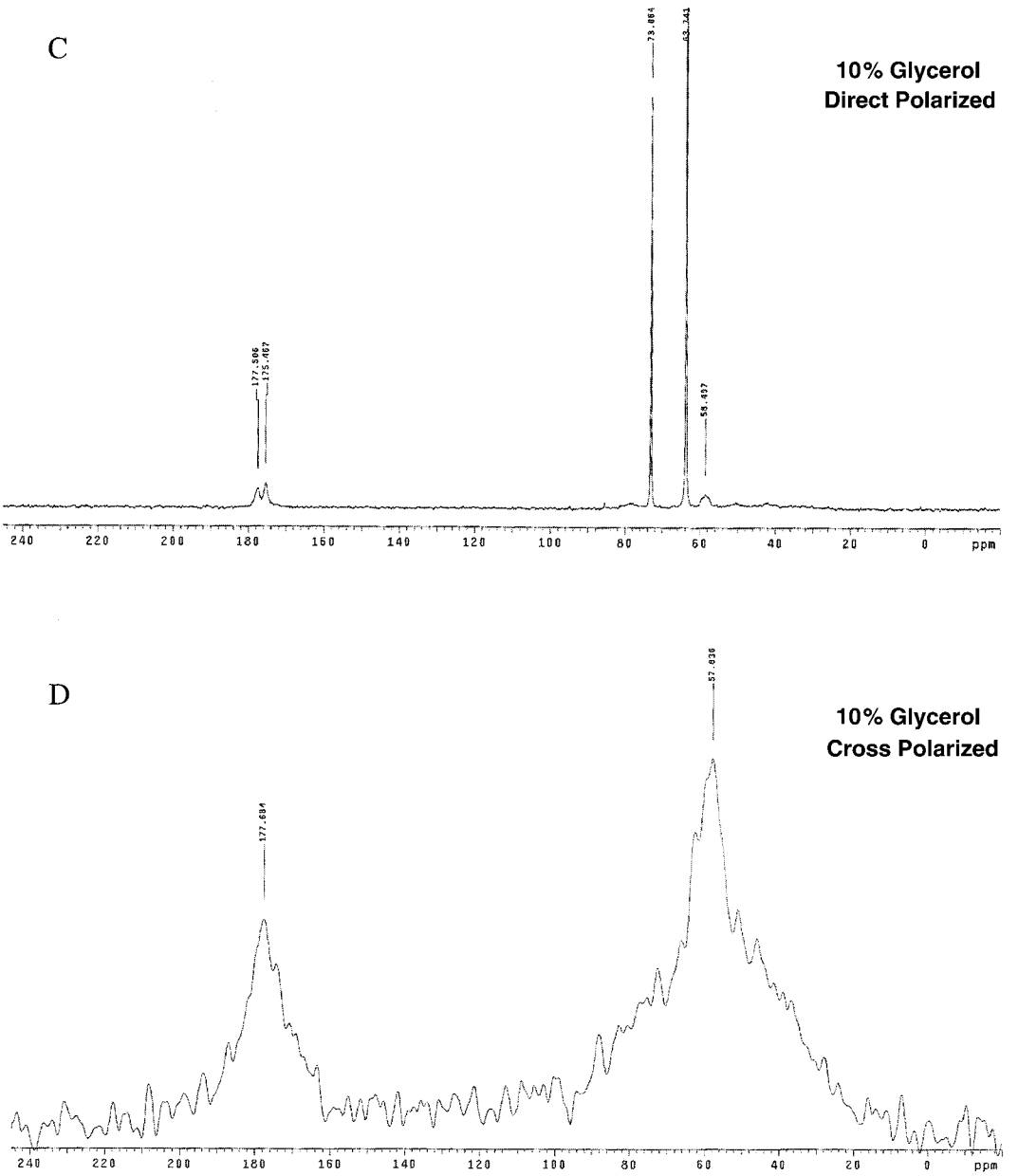

Figure 8 (*Continued from the previous page*)

however, because TPME has four equivalent oxygen atoms capable of hydrogen bonding in a similar way to those found in glycerol. The formation of a physically crosslinked system due to entanglements between neighboring chains is again unlikely, because this would be more feasible in unplasticized systems because of the reduced interchain separation.

A DP/MAS ^{13}C-NMR spectrum could not be obtained for the rigid film resulting when PMVE/MAH was cast in the absence of a plasticizer. However, an examination of the CP spectrum (Fig. 7) showed the carbonyl carbon (C_6) at 177 ppm and it is the most downfield of all the carbons because of the electronegativity of the oxygen group. The methyl carbon (C_3) is assigned to the peak at 77 ppm, which has been significantly shifted downfield in relation to a standard methyl group because of the attached oxygen group. The bands at 57, 49, and 40 ppm are assigned to methane carbons (C_2, C_4, and C_5), the exact order of which is uncertain. Finally, the methylene carbon (C_1) has the lowest frequency signal at a position of approximately 31 ppm.

The reaction between glycerol and difunctional acids has been well documented[12] and it is generally accepted that esterification can proceed at various sites along the glycerol molecule, thus producing several different glyceride residues. These mono-, di-, and triglyceride residues will subsequently react to form network structures by esterification at the second hydroxyl site of a difunctional acid, if prepared in the correct stoichiometric ratio.

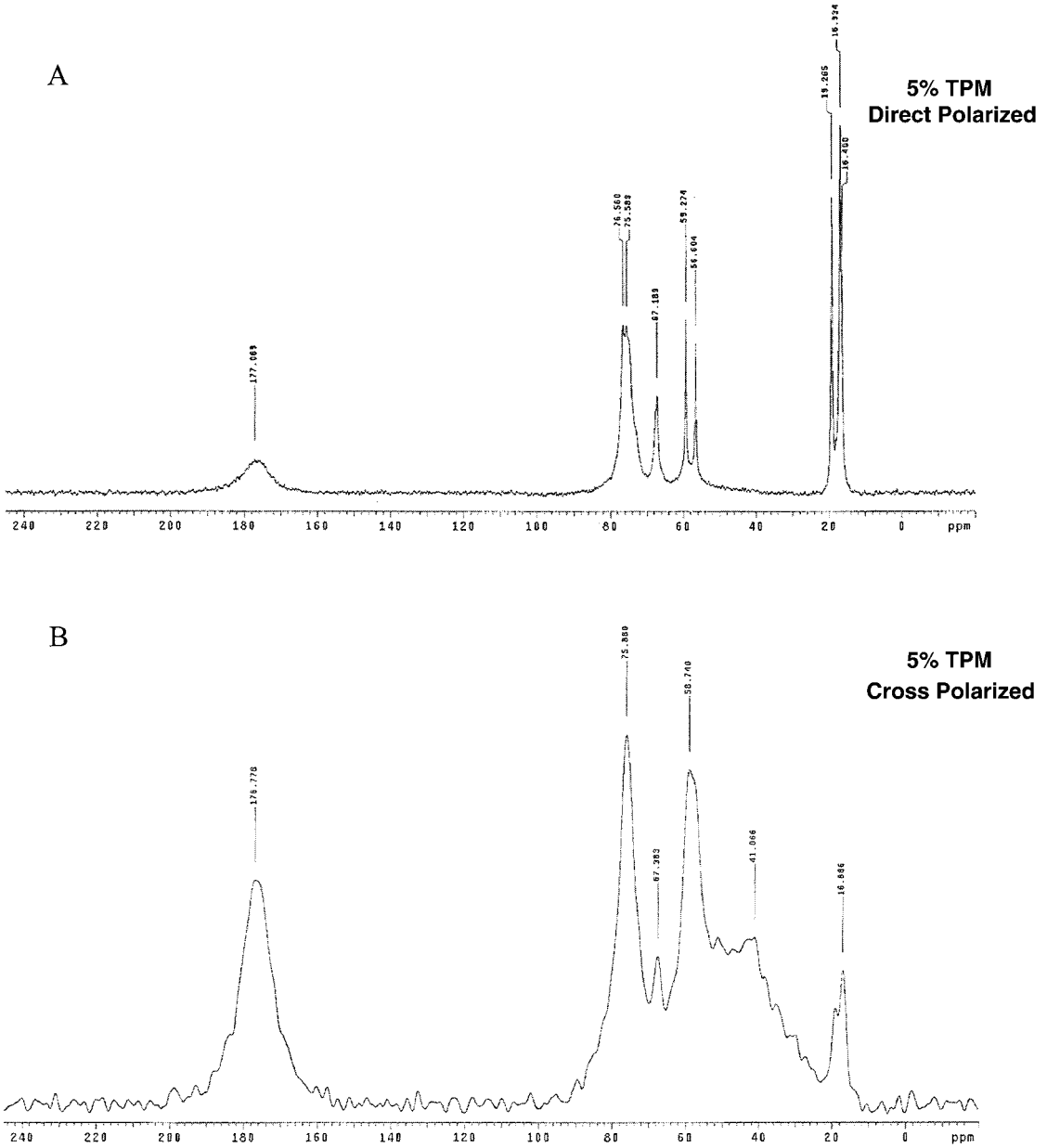

Figure 9 (A,C) Directly polarized solid-state NMR spectra of films cast from aqueous blends containing 10% (w/w) poly(methyl vinyl ether-*co*-maleic anhydride) with (A) 5 and (C) 10% (w/w) tripropylene glycol methyl ether. (B,D) Cross-polarized solid-state NMR spectra of films cast from aqueous blends containing 10% poly(methyl vinyl ether-*co*-maleic anhydride) and (B) 5 and (D) 10% (w/w) tripropylene glycol methyl ether.

The solid-state ^{13}C MAS spectra obtained for PMVE/MAH plasticized with glycerol and TPME are shown in Figures 8 and 9. Films plasticized with TPME displayed a poorly resolved CP spectrum at 5% (w/w) and the formation of a carbonyl band at 177 ppm within the DP spectra. A DP spectrum of the unplasticized film could not be obtained experimentally, which is strong evidence for the plasticizing ability of TPME. In addition, at a 10% (w/w) TPME concentration, there is a well-resolved CP spectrum, suggesting increasing rigidity of TPME and the PVME/maleic acid. This may be ascribed to the formation of a ester linkage between the TPME and PMVE/maleic acid. This is supported by the small shift upfield of the carbonyl carbon, which may have been induced by the formation of an ester species. This may also explain the increasing rigidity of the TPME plasticized polymer films, which are now becoming internally, rather than externally, plasticized, because internal plasticization is known to be less efficient than external plasticization.[13]

The CP spectra obtained for films plasticized with 5 and 10% (w/w) glycerol lose resolution as the concentration of glycerol increases, suggesting that the poly-

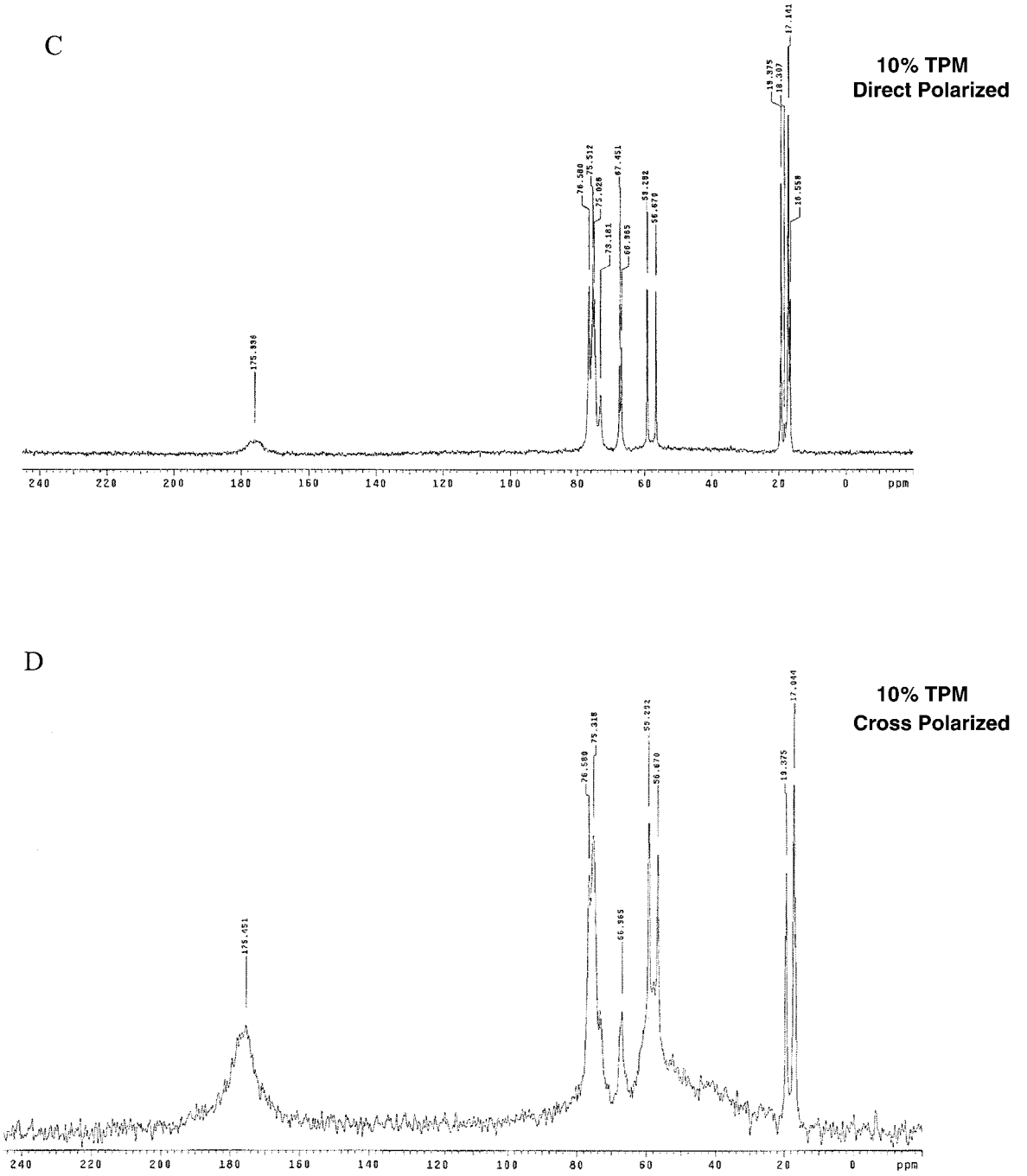

Figure 9 (*Continued from the previous page*)

mer is becoming more mobile as the resolution is decreased. Of particular interest is the small shoulder present on the carbonyl band at a 5% (w/w) glycerol plasticizer content, which is also slightly upfield, similar to TPME. Upon increasing the concentration of glycerol to 10%, the presence of the low frequency shoulder is clear. However, the mobility of the polymer at this stage hinders the resolution of the spectra.

The presence of two distinct peaks in the ester/carbonyl region in the DP spectra at the 10% (w/w) level is important. The peaks are not observed at the 5% level, which can be attributed to the decreased mobility of the polymer chain in comparison to films plasticized with 10% (w/w) glycerol. Although the formation of this new ester peak is not definite evidence for the formation of a polyester network, it suggests that the two molecules have the capability to form ester bonds. Therefore, there is strong evidence to support the presence of a glyceride residue, which at this preliminary stage may be acting as a plasticiz-

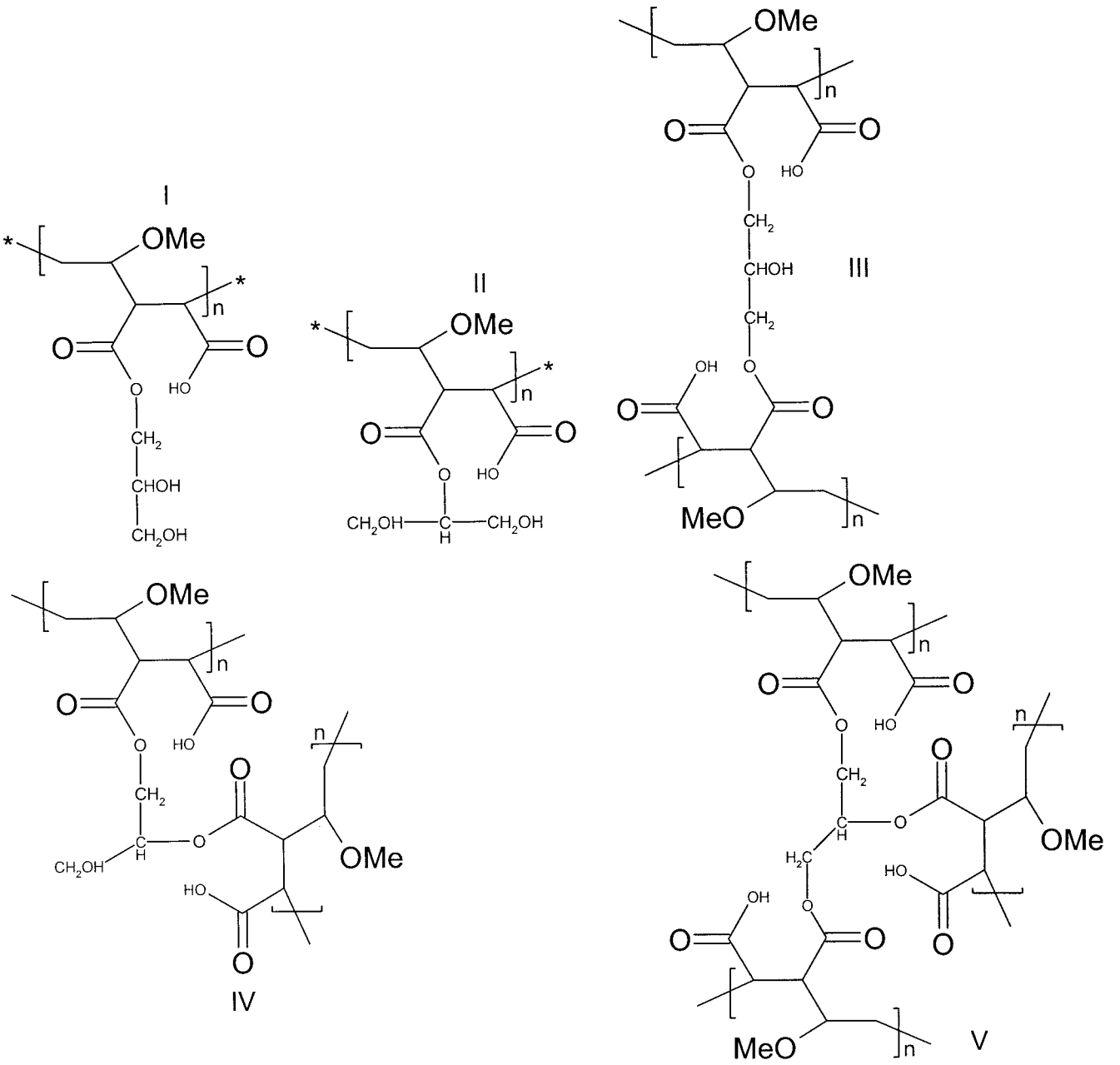

Figure 10 A depiction of several possible oligomers that may form as a result of the condensation reaction between poly(methyl vinyl ether maleic acid) and glycerol.

ing agent in conjunction with unreacted glycerol. The presence of a new ester species suggests that, given suitable reaction conditions, further condensation reactions may be possible, resulting in a three-dimensional polyester network. This, in addition to the gradual insolubility of films plasticized with glycerol, is strong evidence that polyester networks are indeed present with the glycerol/PMVE/maleic acid system. It has previously been shown[14] that maleic acid, which is structurally related to PMVE/MAH, and glycerol may be reacted together to form polyesters. It is therefore expected that PMVE/MAH will form simple ester linkages in the first instance, followed by super three-dimensional network structures, under appropriate conditions. The initial five oligomers that might be expected to form as a result of the reaction between the bioadhesive polymer and glycerol plasticizer are suggested in Figure 10.

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