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Synthesis of Degradable Materials Based on Caprolactone and Vinyl Acetate Units Using Radical Chemistry

By Seema AGARWAL,[1,] Rimpu KUMAR,[1] Thomas KISSEL,[2] and Regina REUL[2]*

Present studies are carried out with an aim to make degradable materials based on caprolactone and vinyl acetate units using radical chemistry. Radical ring-opening copolymerization of 2-methylene-1,3-dioxepane (MDO) with vinyl acetate in presence of AIBN initiator at 70 °C was carried out to achieve the aim. The copolymerization introduced degradable PCL repeat units onto the C-C backbone of poly(vinyl acetate). Microstructure analysis of the copolymers is done using different 1D and 2D NMR techniques. Complete ring-opening polymerization of MDO to give ester units was observed during copolymerizations. Reactivity ratios were found out by Kelen Tüdos method and were $r_{VAc} = 1.53$ and $r_{MDO} = 0.47$ leading to statistical introduction of ester linkages onto the polymer backbone. The materials showed varied glass transition temperatures (from 37 to −44 °C) depending upon the amount of ester linkages and very high elongations. The hydrolysis products were also tested for cytotoxicity studies in L929 cells and compared with that of known and accepted standard materials like poly(ethyleneimine). The hydrolysed products were non toxic and showed a cell viability > 95%. Keeping in view the combined properties like degradability, non-toxicity and low glass transition temperatures, the resulting materials could therefore be proposed for different applications like degradable gums, coatings etc.

KEY WORDS: Radical Ring-Opening Polymerization / Polymer Synthesis / Degradable Polymers / Characterization /

Ring-opening polymerization of ε-caprolactone using anionic or metal catalysts is conventionally used for the synthesis of polycaprolactone (PCL), a well studied and in-demand degradable aliphatic polyester.[1–7] A less known route to the formation of poly(caprolactone), first shown by Bailey *et al.*[8] and later followed by some others,[9,10] is by radical ring-opening polymerization of 2-methylene-1,3-dioxepane (MDO). 2-methylene-1,3-dioxepane is an interesting cyclic ketene acetal monomer giving poly(ε-caprolactone) (PCL), on the radical-ring-opening homopolymerization (RROP) and can introduce ester groups onto the vinyl polymer backbones during copolymerizations with vinyl monomers. The careful examination of 13C and ^{1}H NMR spectra by us[11] showed the occurrence of 100% ring-opening polymerization but the presence of about 9% branched structures in the resulting homopolymer obtained by RROP of MDO. This method of making ester linkages could be very well utilized for introducing degradability onto the nondegradable vinyl polymer backbones by copolymerizations. Also, the homopolymerization and copolymerization behaviour of different cyclic ketene acetals with some vinyl monomers like MMA, vinyl anisole, styrene etc. is reported by us[11–18] and others.[10,19–33] The main problem during the copolymerization is the huge reactivity difference between the CKA and the vinyl monomers leading to either low molecular weight homo vinyl polymers without ester linkages or copolymers incorporating only low amounts of the comonomers with block structure, incomplete ring-opening or no ring-opening at all.

Keeping in view our broad aim of making new degradable materials with new properties based on the conventional plastics, here an attempt has been made to study the copolymerization behaviour of vinyl acetate (VAc) and MDO under conventional radical polymerization conditions. The resulting materials depending upon the glass transition temperatures could be proposed for further studies as degradable gums, coating materials, adhesives etc. For example, poly(vinyl acetate) (PVAc) is used as base for chewing gums[34] but due to its stable C-C backbone, degradation under environmental conditions is very slow and is not counted in the category of degradable polymers. The degradation mechanism is by first hydrolysis to poly(vinyl alcohol) and then further degradation. On the other hand, poly(caprolactone) (PCL) is a very well known biodegradable polymer. Bringing hydrolysable and biodegradable PCL structure onto the PVAc backbone could lead to, in general, hydrolysable and biodegradable environmentally friendly gums and adhesives for short duration applications. Bringing PCL structure randomly onto PVAc backbone by conventional routes of either condensation polymerisation or ring-opening polymerisation of cyclic esters for the formation of esters is not possible. Therefore, here an attempt has been made to provide a CL and VAc based degradable material by radical ring-opening copolymerization of MDO with VAc. Before the materials could be utilized for any application, the basic studies in terms of copolymerizability and properties evaluation is required. Therefore, studies have been carried out to have the basic understanding of the copolymerization process between MDO and VAc. The microstructure of the resulting materials is a key factor in deciding the end-use properties as degradable material. A study for microstructural characterisation of the

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copolymers is also reported for the first time using 1D and 2D NMR techniques. Thermal characterization, hydrolytic stability data and their toxicity and mechanical properties of the copolymers is also provided.

EXPERIMENTAL

Materials

Vinyl acetate (Acros organics; 99%) was distilled before use. 2,2′-Azobisisobutyronitrile (AIBN) was recrystallized from methanol prior to use. *n*-Hexane (BASF) was distilled before use. Tetrahydrofuran (THF) was purified by distillation.

Instrumentation

^{1}H(400.13 MHz) and ^{13}C(100.21 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer using Tetramethylsilane (TMS) as an internal standard. ^{1}H-^{13}C correlation experiments were performed on a Bruker DRX-500 spectrometer, with a 5 mm multinuclear gradient probe and using gs-HMQC (heteronuclear multiple quantum correlation) and gs-HMBC (heteronuclear multiple bond correlation) pulse sequences. The HMQC experiment was optimized for coupling of 8 Hz, with decoupling during acquisition. 2D NMR data were acquired with 2048 points in t_2, and the number of increments for t_1 was 256. Four and Eight scans were used for HMQC and HMBC experiments respectively, and 4 dummy scans were used for both the experiments. A relaxation delay of 1s was used for all 1D experiments and 2s for all 2D experiments. Typical experiment time was about 1.5 and 3.0 h for HMQC and HMBC, respectively.

Mettler Thermal Analyser having 821 DSC module was used for thermal analysis of the polymers. DSC scans were recorded in nitrogen atmosphere (flow rate = 80 mL min^{-1}) at a heating rate of 10 °C min^{-1}. Thermal stability was determined by recording TGA traces in nitrogen atmosphere (flow rate = 50 mL min^{-1}). A heating rate of 10 °C min^{-1} and a sample size of 10 ± 1 mg were used in each experiment for both DSC and TGA.

Viscometric studies were done by dissolving the co-polymers in DMF. All the measurements were done at a constant temperature of 25 ± 1 °C using Ubbelohde viscometer.

Mechanical properties of the copolymer samples were measured by Zwick Roell tensile testing machine. Thin films were prepared by dissolving the samples in tetrahydrofuran. Films were cut out in the shape of a rectangle having width of 10 mm and the grip to grip separation was kept to be 10 mm.

Hydrolyzed sample was analyzed with a 125/2 Nucleodur C18ec column (Macherey-Nagel, Germany) utilizing a Agilent 1100 series HPLC-system (Hewlett Packard, Germany), which was directly coupled with a LTQ-FT mass spectrometer (Thermo, Germany) through an ESI interface and with a linear gradient from 0–30% acetonitrile in water within 30 min. Masses were measured in negative ion mode and parent ion peaks were detected. The capillary temperature was 280 °C and the injection volume was 25 µL.

Table I. Copolymerization of 2-methylene-1,3-dioxepane (MDO) and Vinyl acetate (VAc) by bulk polymerization method, at 70 °C, using AIBN initiator and varying monomer feeds (reaction time = 4 h)

Run	Feed composition (Molar ratio) MDO:VAc	Yield %	Copolymer composition (molar ratio) MDO:VAc	T_g (°C)[a]	$[\eta]$[b]
1[c]	8:92	80	5:95	38	1.5575
2	19:81	77	18:82	17	1.2041
3	29:71	73	25:75	5	0.9831
4	52:48	48	47:53	−22	0.5618
5	76:24	64	73:27	−44	0.3360

[a] T_g is the glass transition temperature, [b] $[\eta]$ is the intrinsic viscosity calculated at 25 °C using Viscosimetry method using DMF as the solvent, [c] Reaction time = 4 h.

Table II. Copolymerization of 2-methylene-1,3-dioxepane (MDO) and vinyl acetate (VAc) [MDO:VAc 50:50 (molar ratio)] at 70 °C, using AIBN initiator for different time intervals by bulk polymerization [monomer:initiator = 100:1 (molar ratio)]

Run	Time	Yield %	Copolymer composition (molar ratio) MDO:VAc
1	30 min	33	37:63
2	1 h	42	50:50
3	2 h	48	43:57
4	4 h	52	47:53
5	70 h	74	47:53

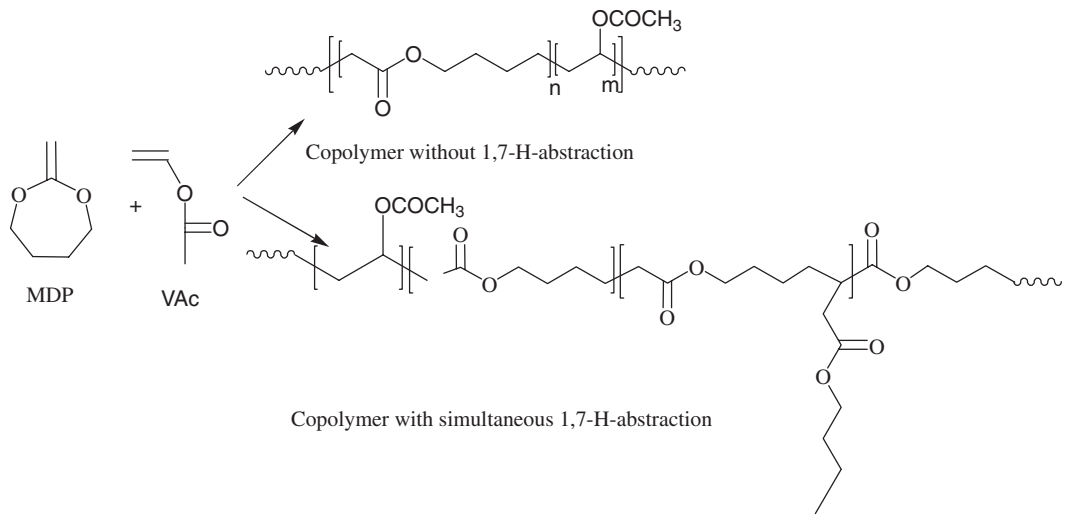
Homo- and Copolymerization of MDO and VAc

Co-polymerizations were carried out under Argon in pre-dried, Schlenk tubes using free radical initiator, AIBN, at 70 °C. In a typical bulk co-polymerization reaction (entry 3 Table I), 0.5750 g (6.6 mmol) of VAc and 0.3028 g (2.6 mmol) of MDO, followed by 1 mol-% (0.01 mg) of initiator (AIBN) were added and kept for polymerization in an preheated oil bath at 70 °C for 4 h. Post-polymerization, THF was used as the dissolving medium, while *n*-hexane was the precipitating medium. The reaction mixture was dissolved in 15 mL THF and precipitated in 250 mL of *n*-hexane. The polymer was obtained as white powder and was dried in vacuum at 40 °C for 15 h. For purification, the sample was re-dissolved in THF and re-precipitated in *n*-hexane. The reaction conversion was estimated by Gravimetry, *i.e.*, by taking the mass of the polymer as compared to the mass of the initial monomers used and was found to be 73%. Co-polymers with varying composition were made by changing the molar ratio of two monomers MDO and VAc in the initial feed and the details are given in the Table I.

By using the similar copolymerization procedure, the kinetics of copolymerization was studied by keeping the feed of the co-monomers (MDO and VAc) to be constant and by varying the time of reaction. The experimental details are given in Table II.

Hydrolytic Degradability

200 mg of the copolymer samples were stirred in 20 mL of KOH in Methanol (5 wt %) for 20 h. The extra base was



Scheme 1. Copolymerization of 2-methylene-1,3-dioxepane (MDO) and vinylacetate (VAc) using azobisisobutyronitrile (AIBN) as radical initiator at 70 °C.

neutralized by 10 mL of 10% HCl. The solution was extracted with chloroform, dried over sodiumsulfate, and the material left after evaporation of the solvent was further characterised by NMR and LC-MS. Cell viability studies of hydrolysed products were also carried out using the MTT assay as described previously.[35] Briefly, L929 cells were seeded into 96-well microtiter plates (NunclonTM, Nunc, Germany) at a density of 8000 cells/well. After 24 h, the culture medium was replaced with serial dilutions of polymer or hydrolyzed polymer stock solutions in antibiotic-free DMEM with FCS (n = 11, concentrations 0.001–4 mg/mL). After an incubation period of 24 h, 200 µL of DMEM and 20 µL MTT (Sigma, Deisenhofen, Germany) (2 mg/mL in PBS) were added. After an incubation time of 4 h, unreacted dye was removed by aspiration and the purple formazan product was dissolved in 200 mL/well dimethylsulfoxide (Merck, Darmstadt, Germany) and quantified by a plate reader (Titertek Plus MS 212, ICN, Germany) at wavelengths of 570 and 690 nm.

The relative cell viability [%] related to control wells containing cell culture medium without polymer was calculated by absorbance test/absorbance control × 100. Poly(ethylene imine) 25 kDa (BASF, Germany), a water-soluble polycationic polymer used in gene delivery and known to induce a cytotoxic response in cells, was used as a positive control. The IC50 was calculated as polymer concentration which inhibits growth of 50% of cells relative to non treated control cells. Data are presented as a mean of four measurements. IC50 was calculated using the Boltzman sigmoidal function from Microcal Origin® v 7.0 (OriginLab, Northampton, USA).

RESULTS AND DISCUSSION

The detailed studies regarding the copolymerization behavior and properties evaluation of MDO and VAc are required in order to recommend the new materials for different applications including degradable gums. In the present study, copolymerization of MDO and VAc was carried out under conventional free radical polymerization reaction conditions (Scheme 1). AIBN was used as an initiator at 70 °C.

The various copolymers of MDO with VAc were made by changing the molar ratio of the two monomers in the initial feed (Table I).

The structural characterization of the homopolymers and copolymers was done in $CDCl_3$ using various NMR spectroscopic techniques. The representative ^1H NMR of copolymers is shown in Figure 1 (entry 3 Table I).

The characteristic signals of both VAc and MDO were seen in the copolymers. The $–CH_2C(O)OC\underline{H}_2$- protons of MDO were seen between 4.0–4.1 ppm. Other aliphatic protons of MDO (-$C\underline{H}_2C(O)OCH_2CH_2CH_2CH_2$-, -$CH_2C(O)OCH_2C\underline{H}_2$-$CH_2C\underline{H}_2$- and -$CH_2C$ (O)$OCH_2CH_2C\underline{H}_2CH_2$- were obtained at 2.2, 1.5 and 1.3 ppm, respectively, by comparison with our previous reference.[11] ^1H NMR also showed a small peak at 0.85 ppm (marked X). The origin of this extra peak during homopolymerization of MDO[11] was proved by us to be mainly from the 1,7-H abstraction reactions (Scheme 1) leading to some branches having -CH_3 groups as branch ends. In the present work, although 1,7-H abstraction reactions are also seen during copolymerization leading to branched structures in very small amounts but the quantitative estimation of branches could not be estimated with any accuracy because of very low intensity.

$–C\underline{H}OC(O)CH_3$ protons from VAc units were observed as two peaks centered on 4.8 and 5.1 ppm. Methyl protons of VAc were obtained around 2.0 ppm and other aliphatic protons (-$C\underline{H}_2CHOC(O)CH_3$)-) were observed between 1.7–1.8 ppm. The splitting of $–C\underline{H}OC(O)CH_3$ peak of VAc units between 4.8 and 5.1 ppm and the presence of an additional peak at 2.6 ppm showed the presence of different configurational and conformational sequencing of the two comonomeric units (MDO and VAc) onto the polymer backbone. The copolymer composition (Table I) was determined by using the peak intensities at 4.8–5.1 ppm of VAc (I_{VAc} ($–C\underline{H}OC(O)CH_3$)) and 4.0–4.1 ppm of MDO I_{MDO} ($–CH_2C(O)OC\underline{H}_2$-) in ^1H NMR. The molar ratio of

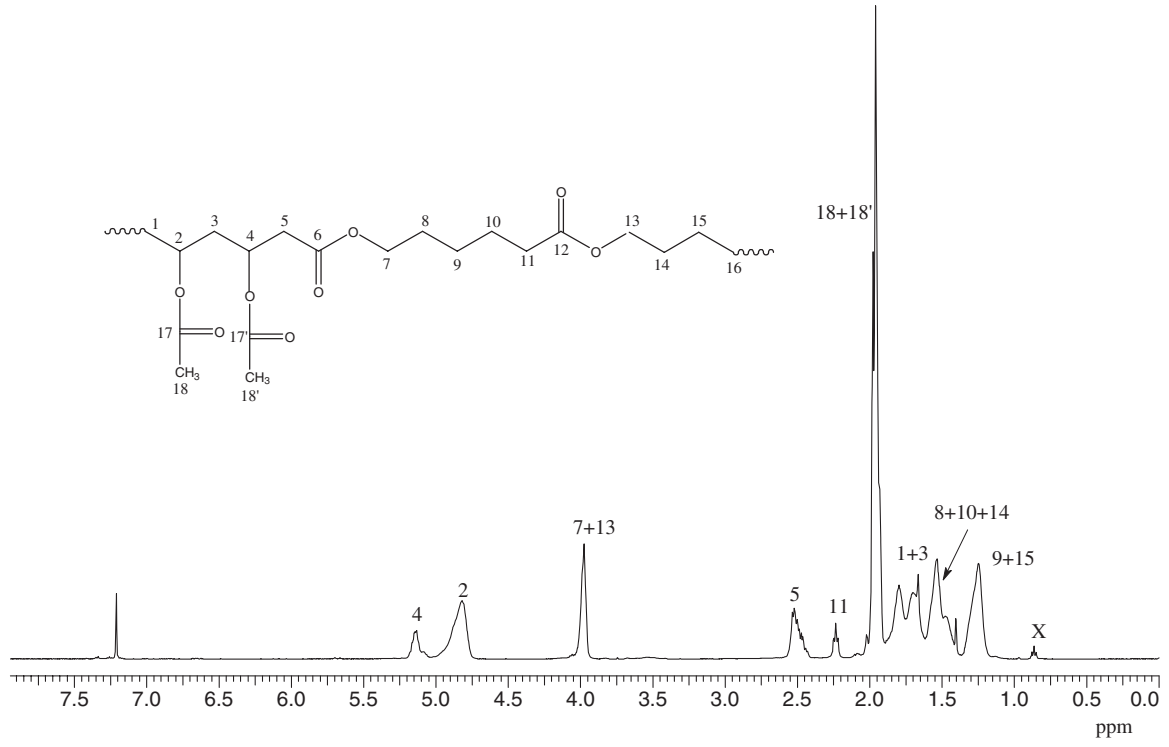


Figure 1. ^{1}H NMR spectrum of poly(VAc-*co*-MDO) (entry 3, Table I) in $CDCl_3$ as solvent.

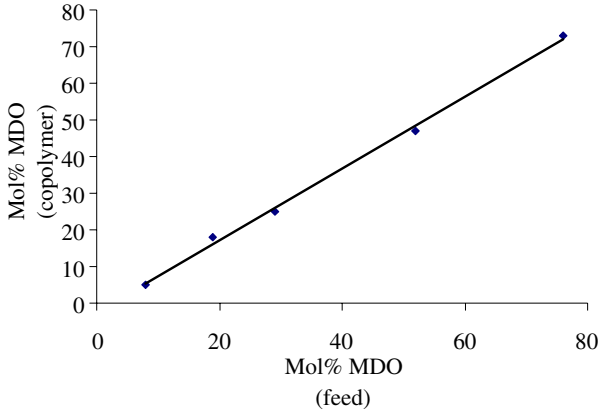


Figure 2. Mol-% of MDO in the feed versus mol-% of MDO in the copolymer (details of reactions given in Table I).

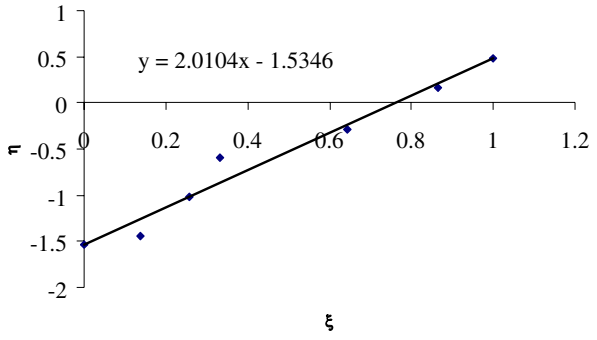


Figure 3. Kelen-Tüdos plot for VAc-MDO copolymers; copolymer composition was determined from ^{1}H NMR for low conversions (15–20%).

VAc:MDO in the copolymer for high conversions (till about 80%) was always found to be almost same as that of the feed (Table I). A negligibly small variation of copolymer composition from feed composition could be due to the inherent experimental error in integrations of NMR spectra which could not be avoided. The different copolymers could be made in high yields having increasing amount of MDO units just by changing the molar ratio of the two comonomers in the initial feed (Figure 2).

The intrinsic viscosity as measured in DMF which is an indirect measure of molecular weight decreased with increasing amount of the MDO units in the polymer chain under similar reaction conditions. But, in general very high intrinsic viscosity polymers could be made (Table I). Efforts to determine molecular weights by gel permeation chromatography (GPC) were not successful because of interaction of materials with GPC columns. Therefore, intrinsic viscosities are reported in the Table I. There was a decrease in the intrinsic viscosity on increasing the amount of MDO in the copolymers. The values were between 0.33–1.55 dL/g depending upon the ratio of VAc and MDO in the copolymers. For homo polycaprolactone (PCL), the intrinsic viscosity of 0.33 dL/g corresponds to M_n (number average molecular weight) of about 14000[36] and for homo poly(vinyl acetate) the intrinsic viscosity of 0.33 dL/g corresponds to molecular weight of about 75000 according to the literature.[37] This gives an hint of having relatively high molecular weight copolymers in this study. Reactivity ratios for MDO and VAc are determined using Kelen-Tüdos method[38] and was determined to be $r_{VAc} = 1.56$ and $r_{MDO} = 0.47$ (Figure 3).

For reactivity ratio determinations a separate batch of copolymerizations were carried out and the reactions were stopped at low conversions (15–20%) and copolymer composition which is required for the calculation of reactivity ratios was determined by using the peak intensities at 4.8–5.1 ppm of VAc (I_{VAc} (–C<u>H</u>OC(O)CH_3)) and 4.0–4.1 ppm of MDO I_{MDO} (–CH_2C(O)OC<u>H_2</u>-) in ^{1}H NMR. The reactivity parameters give a hint about the copolymer microstructure as statistical comonomer sequences along the polymer chains. The copolymer composition is decided by the amount of the monomers in the feed. The reactivity ratio data available in the literature for MDO during its copolymerization with other vinyl monomers showed very high reactivity of the vinyl monomers as compared to the cyclic ketene acetals, for example, Bailey *et al.* showed MDO = 0.021; $r_{St} = 22.6$.[8] On contrary to it, Davis *et al.* have reported a complete absence of copolymerization and their experimental data indicated the homopolymerization of styrene, with the MDO merely acting as a diluent.[9] Davis *et al.* have reported copolymerization parameters for copolymerization of MDO with MMA at 40 °C as $r_{MDO} = 0.057$ and $r_{MMA} = 34.12$ thereby showing the low tendency of cyclic ketene acetals to copolymerize with vinyl monomers.[10] In this work we show very good copolymerizability of MDO with VAc which is due to the similarity in monomer structures in terms of nucleophilic double bond and stability of growing radicals. We calculated Q (monomer reactivity) and e (monomer polarity) values for MDO using a well known Alfrey-Price equation.[39] The Q (0.026) and e (−0.88) values for vinyl acetate were taken from the literature. The Q and e values for MDO were calculated to be 0.010 and −0.3363, respectively. Very similar Q values of VAc and MDO explains good copolymerizability of the two monomers.

Further careful examination of the ^{1}H NMR spectrum helped in analysing the microstructure of the copolymers. With increase in the amount of MDO in the copolymers the peaks at 5.2 and 2.6 ppm increased and also a new peak at 2.2 ppm appeared (Figure 4).

The new peak appearing at 2.2 ppm is assigned to the (-C<u>H_2</u>C(O)O$CH_2CH_2CH_2CH_2$- protons of MDO-MDO diad with reference to our previous work on homopolymerization of MDO.[11] The other two prominent peaks that increased with an increase in the amount of MDO in the copoylmers could be due to the C<u>H</u>OC(O)CH_3 VAc protons linked to MDO (<u>VAc</u>-MDO) (5.2 ppm) and -C<u>H_2</u>C (O)O$CH_2CH_2CH_2CH_2$- protons of MDO linked to VAc (VAc-<u>MDO</u> diads sequences) (2.6 ppm) in the copolymers. This shows with increase in the amount of MDO in the copolymers the diads of the types both VAc-MDO and MDO-MDO increases showing more randomisation of the copolymer structure. In fact, at very low concentrations of MDO in the copolymers, *i.e.*, 5:95 molar ratio, hardly any diads of the type MDO-MDO were seen. The MDO units were present in this particular copolymer as isolated units mainly in the form of VAc-MDO diads. Since microstructure of the polymers could influence the final properties of materials, efforts were made to further confirm it using 2D NMR techniques like HMQC and HMBC.

2D HMQC was used to provide unambiguous ^{13}C NMR peak assignments and 2D HMBC was used to prove chemical links between VAc and MDO units. Also, HMBC helped in confirming the correct peak assignments to the ^{1}H NMR. The representative 2D HMQC NMR spectrum is shown in Figure 5 with the cross peaks used for assigning the ^{13}C NMR spectrum.

In ^{13}C NMR spectra of all the copolymers made in this work no peak between 100–110 ppm is seen thereby showing the complete ring-opening reaction forming ester linkages. The representative 2D HMBC NMR spectrum is shown in Figure 6.

The proposed peak from MDO-MDO diad at 2.2 ppm in ^{1}H NMR (Figure 1) from the protons (-C<u>H_2</u>C(O)OCH_2CH_2-CH_2CH_2-) showed only one correlation in the ester carbonyl carbon region with ^{13}C peak at 173.4 ppm (cross peak A). This shows the peak in ^{1}H NMR spectrum at 2.2 ppm is correctly assigned as it should show only one ^{1}H-^{13}C cross-correlation through one bond in HMBC with carbonyl carbon 12. The protons 5 of MDO at 2.6 ppm (-C<u>H_2</u>C(O)O$CH_2CH_2CH_2CH_2$-) from linking MDO unit (VAc-MDO diad) did not show any correlation with carbonyl carbon 12, instead it showed strong correlations in the peak region 170–171 ppm (cross peaks D) (carbonyl carbon 6 and carbonyl carbons of neighbouring VAc). Also, protons 5 showed broad and strong 1 and 3 bond correlations (cross peak E) with the carbons 2 and 4 of VAc units and therefore, is correctly assigned. The increased amount of MDO-MDO diads on increasing the amount of MDO in the feed, *i.e.*, from going from entry 1 to entry 5 of Table I could also be clearly seen from the carbonyl carbon region of ^{13}C NMR spectra. The ^{13}C NMR spectra of copolymers having low mole % of MDO in the copolymers (5–18 mol %) hardly show any carbonyl peak at 173.4 ppm arising from homo MDO-MDO diads (Figure 7).

Also, copolymerization reaction was followed at different intervals of time and change in microstructure of the copolymers is studied with time. For a sample with initial feed molar ratio of MDO:VAc 1:1, copolymer composition was determined at different time intervals using ^{1}H NMR technique and is given in Table II.

It can be seen from the data (Table II) that rate of consumption of VAc was more at the start. This also gives a hint that at the start there were more VAc-VAc type of sequences followed by the more randomisation and more VAc-MDO diads. After about 1 h of polymerization, the yield increased but the copolymer composition remained almost same.

Effect of the incorporation of MDO ester units onto the PVAc hydrocarbon chain is also investigated on the thermal stability and glass transition temperature. The degradation of PVAc prepared by the radical polymerization generally takes place in two steps.[37] The acetate group elimination takes place at lower temperature between 300 and 330 °C followed by breakdown of polymeric backbone at higher temperature (between 360–450 °C). Addition of MDO units on the PVAc backbone did not affect the thermal stability of PVAc and the copolymers also showed two step degradations with T_i in the range of 314 °C–282 °C.

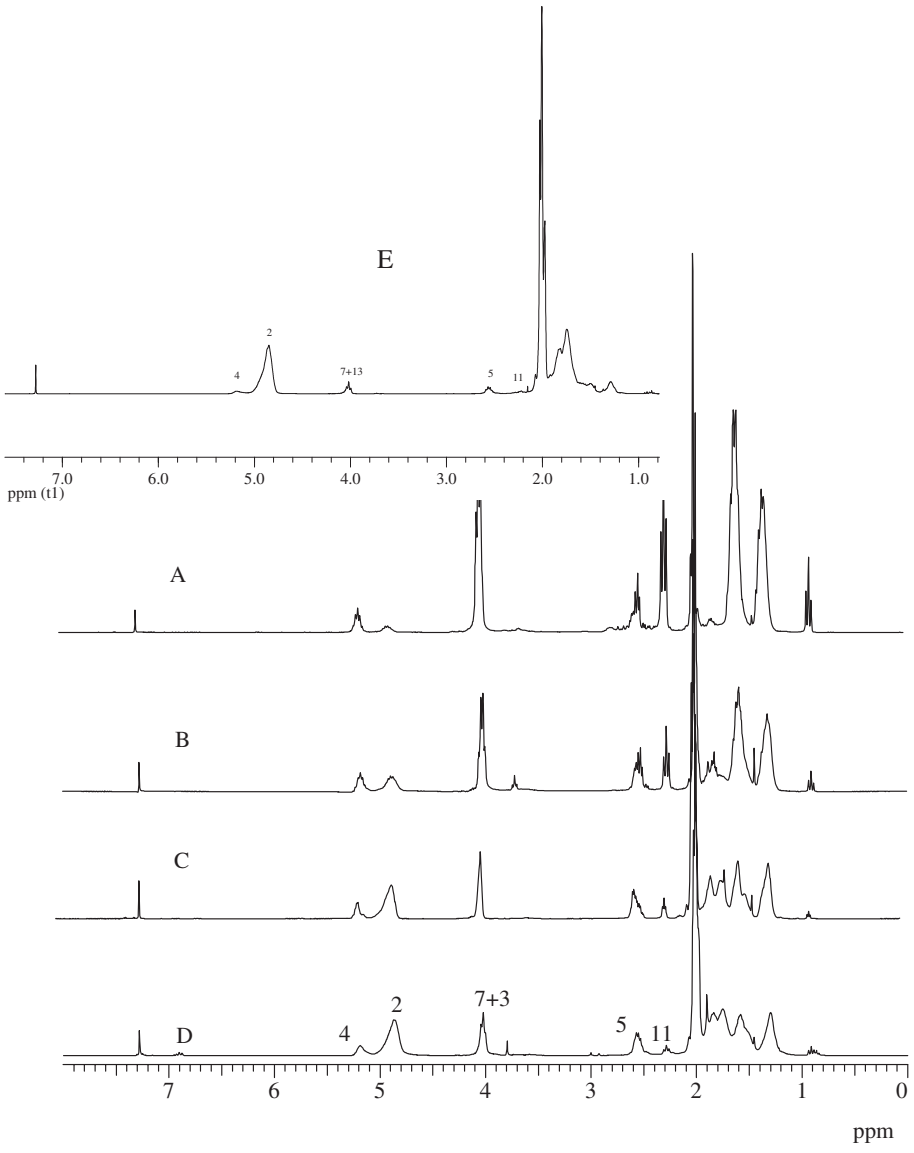


Figure 4. ^{1}H NMR spectra of copolymers with different amounts of MDO in the copolymers in $CDCl_3$ as solvent; A) entry 5 Table I; B) entry 4 Table I; C) entry 3 Table I; D) entry 2 Table I E) entry 1 Table I: hardly any peak 11 is visible.

For DSC measurements the samples were heated in the first heating cycle from $-60\,^{\circ}C$ till $200\,^{\circ}C$ at a heating rate of $10\,^{\circ}C$/min. The samples were cooled again to $-60\,^{\circ}C$ with a cooling rate of $10\,^{\circ}C$/min and again heated in the second heating cycle till $200\,^{\circ}C$. The glass transition temperatures are noted in the Table I from the second heating cycle. Single glass transition temperature was observed for the copolymers (poly(VAc-*co*-ester)s. There is a decrease in the glass transition temperature on increasing the amount of MDO onto the PVAc backbone (Table I). Different copolymers with a wide range of glass transition temperatures from $38\,^{\circ}C$ to $-44\,^{\circ}C$ were obtained.

Since the incorporation of ester linkages are expected to introduce degradability and was one of the aims of this work, the studies on hydrolytic degradation of the MDO-PVAc copolymer samples were carried out in KOH (5 wt% in Methanol). After 20 h of hydrolysis, the polymer was completely soluble in the hydrolysis medium. The degraded material was extracted with chloroform, dried over sodium sulphate and after evaporation and drying the left over waxy/oily material was subjected to NMR analysis (Figure 8; entry 3 Table I).

Since the polymer degradation would be by hydrolysis of the ester linkages of PCL units, all degradation products, *i.e.*, oligomers/small organic molecules with hydroxyl and acid functional groups would be formed. The probable hydrolysis products from the linear copolymer structure are shown in Scheme 2.

As mentioned above, the branches due to 1,7-H abstractions reactions were negligibly small, the hydrolysis products formed from such structures are not considered. Besides oligomeric hydroxyl and acid functionalised poly(vinyl alcohol) units due

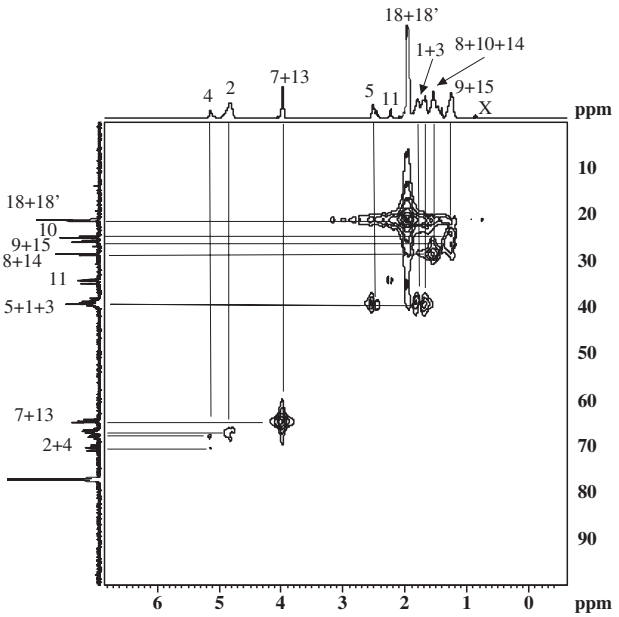


Figure 5. A part of 2D HMQC (heteronuclear multiple quantum correlation) NMR spectrum (entry 3 Table I) (^{1}H 0–7 ppm; ^{13}C 0–100 ppm) in $CDCl_3$ as solvent.

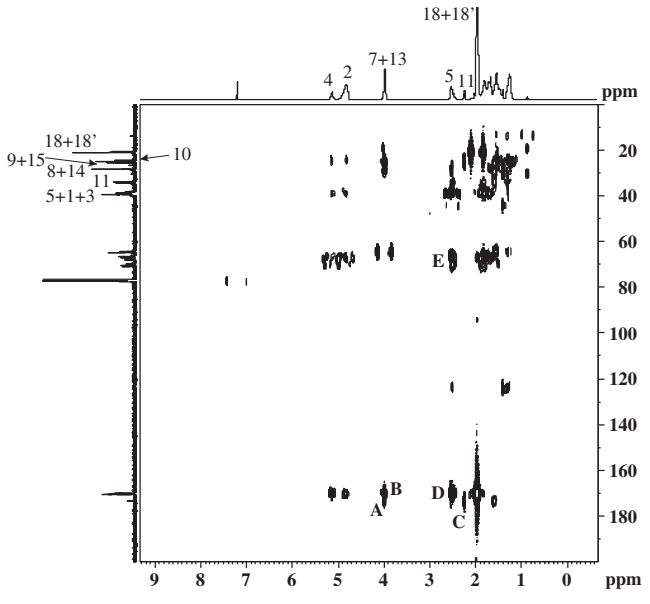


Figure 6. 2D HMBC (heteronuclear multiple bond correlation) NMR spectrum (entry 3 Table I) (^{1}H 0–10 ppm; ^{13}C 0–200 ppm) in $CDCl_3$ as solvent.

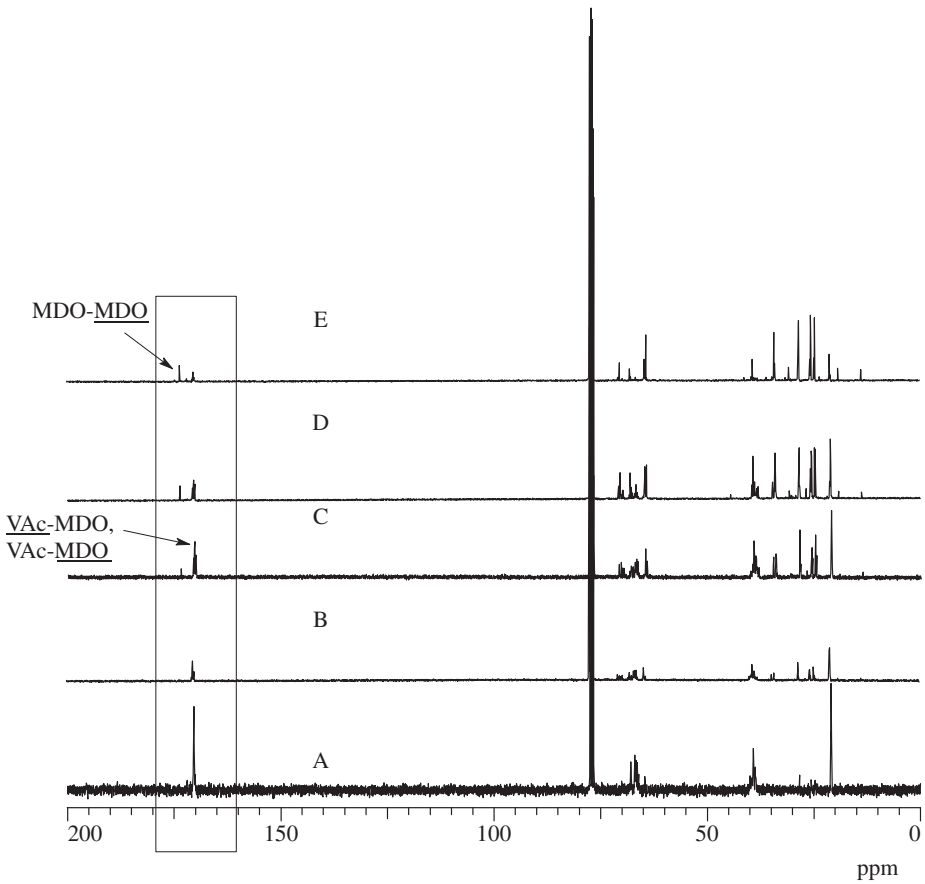


Figure 7. ^{13}C NMR spectra of different copolymers in $CDCl_3$ A) entry 1 Table I; B) entry 2 Table I; C) entry 3 Table I; D) entry 4 Table I E) entry 5 Table I; Clearly shows the appearance of MDO-MDO diads with increasing amount of MDO in feed.

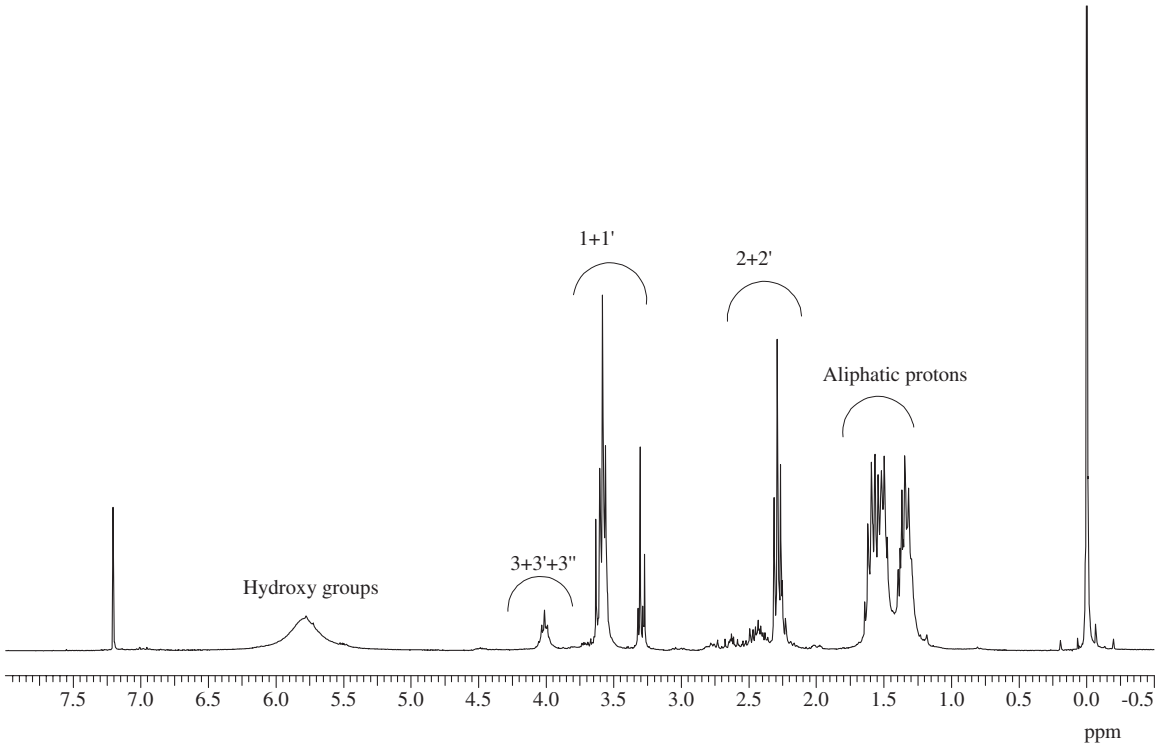


Figure 8. ^{1}H NMR spectrum in $CDCl_3$ of hydrolysis product of poly(VAC-*co*-ester) (entry 5 Table I).

to VAc-VAc-VAc-VAc-VAc type of units and 6-hydroxy pentanoic acid (structure A) from MDO-MDO-MDO-MDO-MDO units, other structures as shown in Scheme 2 are also possible from hetero structures. From all these degradation products mainly overlapping signals in the region for protons 1(HO-C$\underline{H}_2$-), 2(-C$\underline{H}_2$-COOH), 3(-C$\underline{H}$(OH)-), 4(-CH(OH)C$\underline{H}_2$-COOH) and aliphatic protons are expected (Scheme 2) in ^{1}H NMR. There was a clear change in the NMR peak positions (Figure 8) of the hydrolysed product as compared to the original NMR of the copolymer (please compare it with Figure 1). The very strong and characteristic peaks of VAc units, *i.e.*, –OC$\underline{H}_3$ protons and –C$\underline{H}$(OCOCH$_3$)- in the unhydrolysed copolymer at 1.96 ppm and between 4.8–5.2 ppm respectively (Figure 1) disappeared after hydrolysis and a new and very broad peak appeared between 5.3–6.2 ppm from chain end –OH and –CH(OH) groups appeared. The –COOH protons could not be seen in ^{1}H NMR which could be due to the fast relaxation but ^{13}C NMR showed the presence of this group, as a peak at 177 ppm was observed. Also, the hydrolysis of ester linkages led to the formation of small moieties as shown in the Scheme 2 with –OH and –COOH functional groups. This changed the peak position of –CH$_2$C(O)OCH$_2$CH$_2$CH$_2$- and –CH$_2$C(O)OCH$_2$CH$_2$CH$_2$- protons of PCL units in the unhydrolysed copolymer from 4 ppm to the new characteristic peaks of 1, 2, 3, 4 and aliphatic protons (Scheme 2) at 3.3–3.6 ppm, 2.3 ppm, 4.1 ppm and between 1.2–1.7 ppm (Figure 8). Although, in this study it was not possible to identify each degradation product quantitatively but the NMR clearly showed the hydrolytic degradability tendency of the new materials.

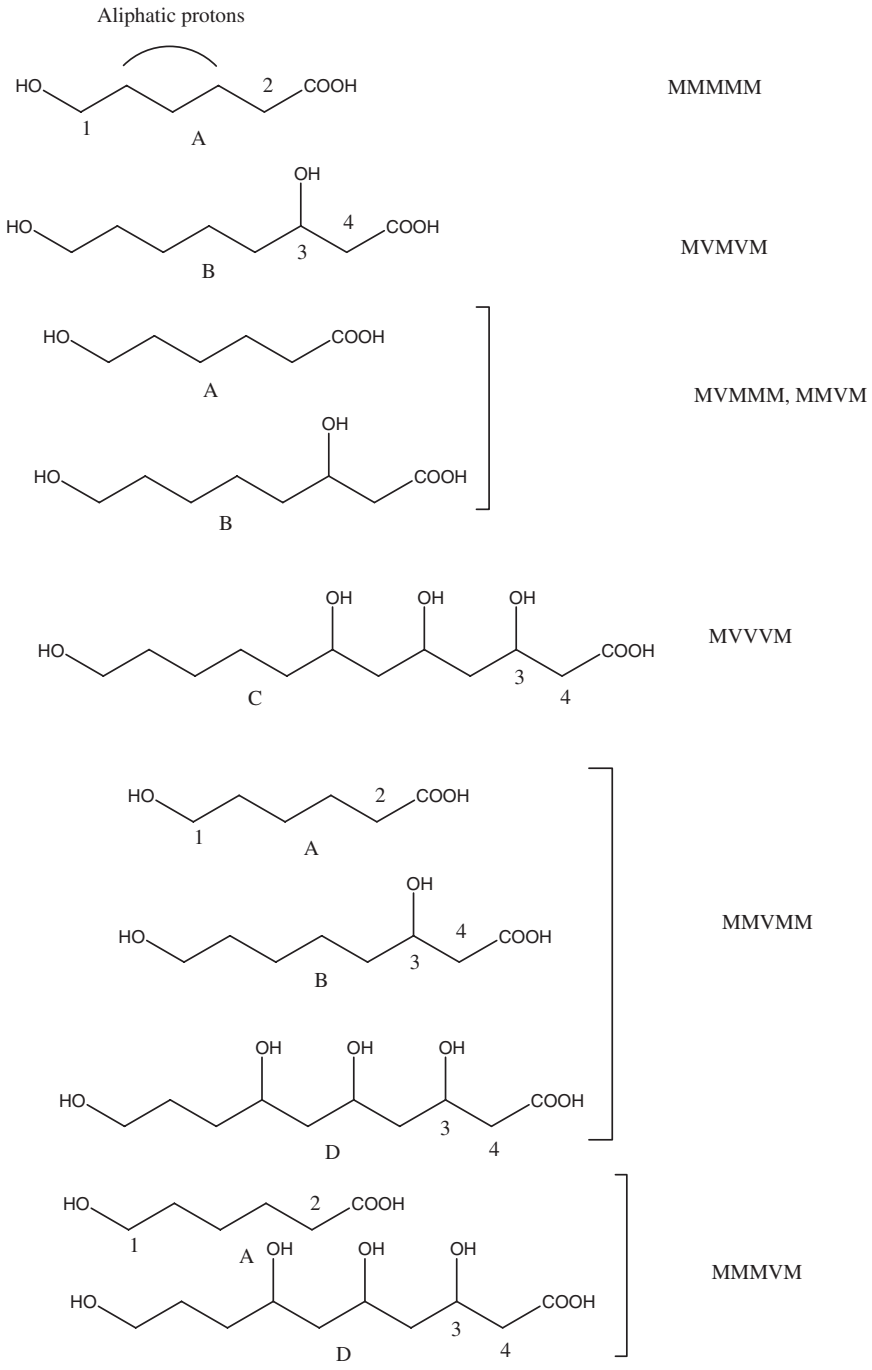
Hydrolysed sample (poly(VAC-*co*-ester) (entry 5 Table I)) was analysed by LCMS in negative ion mode to get further insight into the hydrolysis products (Figure 9).

The compounds showed no retention in the column and all relevant masses were detected directly in the breakthrough. Three hydrolysed components could be confirmed, *viz.*,a.,*viz.*, $C_6H_{11}O_3$, $C_8H_{14}O_4$, $C_{12}H_{22}O_6$, having molecular weights 131, 175, 263, respectively (Structures **A**, **B**, **C** in Scheme 2). However, by ESI-MS, it is not possible to assign the positions of the OH groups. Absence of the fourth expected component, *i.e.*, $C_{10}H_{18}O_5$, (Scheme 2; Structure **D**) could not be seen and proved that (M-M-V-V-M) or (M-V-V-M-M) type of pentad were less probable. This result is again in accordance to our NMR results for microstructure analysis, which states that MDO prefers VAc as its comonomer rather than MDO.

Hydrolyzed materials (entry 3 Table I) were also tested for cytotoxicity studies in L929 cells and compared with that of known and accepted standard materials like poly(ethyleneimine) (Figure 10).

The hydrolysed products were non toxic and showed a cell viability $> 95\%$. Therefore, no IC 50 value could be calculated. PVA was also used as a comparison as PVA is also one of the hydrolysis products. PVA also displayed no cytotoxicity and no IC 50 value could be calculated. PEI 25 K was used as positive control and showed the typical sigmoidal curve and an IC 50 value of 0.0091 mg/mL.

An attempt has also been made to evaluate the mechanical properties of resulting materials. The new materials having higher ratios of ester linkages, *i.e.*, $\geq$ 29 mole % of MDO units



Scheme 2. Probable hydrolysis products of poly(VAc-*co*-MDO) with random distribution of ester linkages with pentads of the type: (M-M-M-M-M), (M-V-M-V-M), (M-V-M-M-M), (M-V-V-V-M), (M-M-V-M-M), (M-M-V-V-M), (M-V-V-M-M), (M-M-M-V-M); where M: MDO and V: VAc, respectively; **A**, **B**, **C**, **D**: Distinguished hydrolysis products from all pentads given above having molecular weights 132, 176, 264, 220, respectively.

in the copolymer had very low glass transition temperatures and, therefore, could not be obtained in the film forms for mechanical testing. Mechanical properties of copoylmers having low molar ratios of MDO, *i.e.*, 5 and 18 mole % have been compared with the homo PVAc (Table III).

The introduction of low mole % of MDO led to significant decrease in modulus and increase in elongation of the polymers which are required for a gum material.

CONCLUSIONS

The ester units having PCL structure were successfully introduced onto PVAc backbone by ring-opening polymerization of MDO and VAc to make PCL based degradable materials. 1D and 2D NMR studies gave an insight into the polymer microstructure and shown to have random distribution

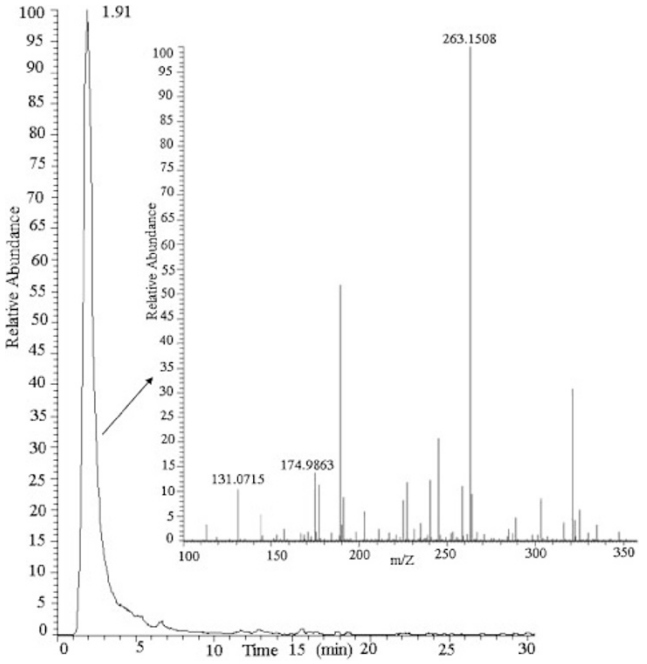


Figure 9. LCMS data for hydrolysed product of poly(VAc-*co*-ester) (entry 5 Table I) when measured in negative ion mode; **A**, **B**, **C** in Scheme 2 are confirmed at molecular ion peaks 131.0715, 174.9863, and 263.1508, respectively.

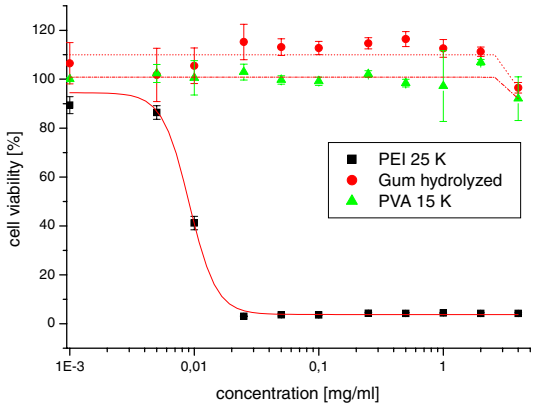


Figure 10. Cell viability studies for poly(VAc-*co*-ester) (entry 3 Table I).

Table III. Mechanical properties of poly(MDO-*co*-ester)s

Run	Copolymer composition MDO:VAc	$E_{modulus}$ (stress/strain)	Maximum stress σ_M (MPa)	Stress at break σ_B	Elongation or Strain at break %
1	0:100	0.0065	1.15	0.77	1007
2	5:95	0.0051	0.91	0.52	1093
3	18:82	0.0029	0.82	0.67	1285

of ester linkages onto the PVAc backbone. It was possible to control the properties of new materials such as glass transition temperature, viscosity, mechanical properties etc. by controlling the amount of MDO in the copolymers. The polymers were shown to be hydrolytically degradable due to the presence of ester linkage in the backbone and showed large elongations as compared to pure PVAc. The PCL based new materials poly(VAc-*co*-PCL) showing a combination of hydrolytic degradability and low glass transition temperatures, could be suggested as degradable substitute for chewing gums or other gum applications. The detailed (bio)degradation studies including the effect of composition, molecular weight etc. of the materials will be carried out before they can be used for any application.

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