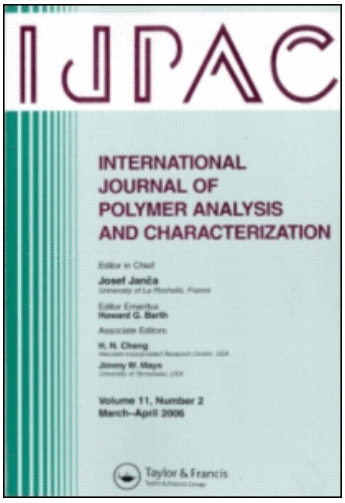

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Analysis of New Biodegradable Amphiphilic Water-soluble Copolymers with Various Hydrophobe Content by Multi-angle Light Scattering on Line with Flow Field Flow Fractionation*

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Flow field flow fractionation (F4) with an on-line multi-angle laser light scattering detector was used to characterize amphiphilic biodegradable water-soluble copolymers poly(methyl glyoxylate *-co-* potassium glyoxylate). These new products are prepared from hydrophobic poly(methyl glyoxylate) by partial and statistical saponification of methyl ester functions. Conformational shape and degradability of polymers in dilute aqueous solution were investigated as a function of saponification rate (y) ranged from 10 to 100%. Derivatives with high hydrophobe content ($y = 10\%$) forms compact intermolecular aggregates. In contrast, macromolecules of poly(potassium glyoxylate) ($y = 100\%$) are molecularly dispersed in solution because of the presence of numerous electrostatic repulsions. For intermediate compounds ($15 \leq y \leq 81\%$), the major part of the sample is represented by a population of single polymer molecules dispersed in solution. The kinetics of degradation of these different copolymers in aqueous solution was found to be a direct function of the macromolecular conformation and the percentage of methyl ester groups on the polymer chains.

Keywords: Flow field flow fractionation; Multi-angle light scattering; Amphiphilic copolymers; Degradation

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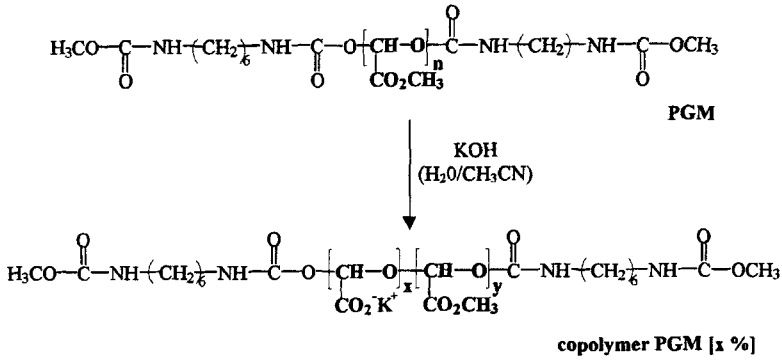
INTRODUCTION

Poly(methyl glyoxylate *-co-* potassium glyoxylate) are new products synthesized from hydrophobic poly(methyl glyoxylate) (PMG) by partial and statistical saponification of ester groups (Scheme 1). These amphiphilic copolymers are biodegradable and their ultimate degradation product is glyoxylic acid, a Krebs metabolite. Upon varying the hydrophilic/hydrophobic balance, we obtained a wide range of products differing in terms of solubility and degradability. Their applications in the field of drug delivery systems are expected.

The development of these new materials requires a study of their solution behavior. Therefore, measurements of changes in molecular conformation *versus* the macromolecular chemical composition are important in order to understand the solution properties of these copolymers.

Size exclusion chromatography (SEC) coupled on line with a multi-angle laser light scattering detector (MALLS) is the standard method providing the absolute determination of weight average (M_w) and number average (M_n) molecular weights, molecular weights distribution and radius of gyration (R_g). Nevertheless, amphiphilic polymers are difficult to characterize by this technique due to their complex solution behavior. In fact, SEC use is generally limited by specific interactions between the sample and the stationary phase, which disturb the separation process.[1,2] Moreover, amphiphilic polymers are known to form hydrophobic intermolecular associations in



SCHEME 1 Partial saponification of poly(methyl glyoxylate).

aqueous solution.[3] The latter generate aggregates with so large hydrodynamic volume that they are outside the separation range of SEC columns.

To overcome these difficulties, we used a novel analytical technique, flow field flow fractionation (F4) coupled on line with MALLS. By comparison with SEC, the F4 method, which is based on the diffusion behavior of the particles, offers many advantages: a greatly reduced surface area available for interactions with the sample and the possibility to separate the particles over a wide range of size with a good resolution.[4-6]

Finally, previous studies showed the power of the combination of F4 (symmetrical or asymmetrical)/MALLS for the characterization of various polymers such as hydroxypropylcellulose,[7] dextran and pullulan.[8,9] As a consequence, this technique seemed to be well suited for the characterization of amphiphilic copolymers.

In the present work, we report the characterization of partially saponified PMG derivatives using F4/MALLS on-line coupling. We particularly investigated conformation changes and chemical degradation of copolymers in aqueous solution as a function of saponification rate.

EXPERIMENTAL

Materials

Poly(methyl glyoxylate) (PMG) ($M_w = 35{,}000\,g \cdot mol^{-1}$, I = 3) measured by SEC in dichloromethane (polystyrene standards were used for calibration) and by static light scattering in acetonitrile, was obtained by anionic polymerization of methyl glyoxylate (MG) in dichloromethane at −20°C using triethylamine as initiator. End capping was performed using hexamethylene diisocyanate (HMDI) as terminating agent.[10]

MG was obtained by distillation of 2-hydroxy-2-methoxy-methylacetate (HMMA) (kindly supplied by Clariant) over P_2O_5 under the reduced pressure of 60 to 30 mm Hg.

Poly(methyl glyoxylate -*co*- potassium glyoxylate) partially saponified, was obtained by mixing a solution of PMG in acetonitrile, with

an aqueous phase containing the requisite KOH in distilled water (see Scheme 1). The proportion of acetonitrile in the aqueous phase is modulated according to the saponification rate. The reaction mixture is left at room temperature under stirring, until the complete consumption of KOH, and then partially evaporated. The concentrated aqueous phase is lyophilized and the copolymers are recovered as powder.[11]

Poly(potassium glyoxylate) is synthesized by the same process with an excess of KOH. The reaction mixture is then dialyzed against demonized water before lyophilization to remove excess of alkali.

PMG [x %] refers to a copolymer with a saponification rate of x %.

The carrier liquid was 0.1 M lithium nitrate containing 0.02% of sodium azide and filtered through a 0.10-μm Millex VC-type membrane. $LiNO_3$ and NaN_3 (analytical reagent grade) were purchased respectively from ACROS and Merck. Water came from a Milli-Q water reagent system (Millipore).

Polymer Solutions

Dried solid copolymer samples were directly dissolved in the appropriate solvent at a polymer concentration (Cp) of $10\,g \cdot L^{-1}$, at room temperature. The resulting solutions were clarified through a 0.45 μm Millex GS-type filter unit.

Chemical Degradation Study

50 mg of copolymer were directly dissolved in 5 mL of 0.1 M $LiNO_3$. The resulting solution was clarified through a 0.45-μm Millex GS-type filter unit, then placed in tight-shut test tube and maintained at 30°C in a thermostat-controlled water bath. Solution fractions were regularly taken and analyzed by F4/MALLS.

Instrumentation

After the separation by the F4 system, eluted components were successively detected by a multi-angle laser light scattering (MALLS) and a differential refractive index detector (RI) connected on-line.

F4 Description

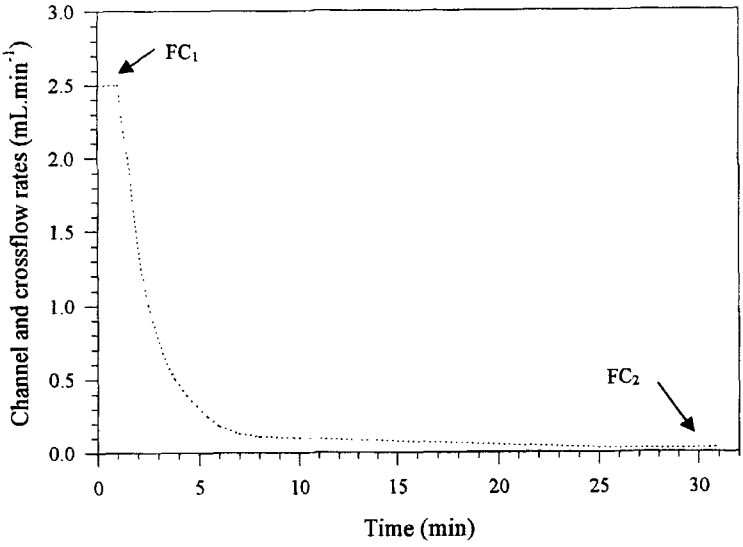
FFF separation is achieved in a flat channel by the application of a field perpendicular to the channel flow.[12, 13] In symmetrical flow field flow fractionation (F4), the transverse field consists of a secondary external cross flow (FC) of eluent. The fractionation procedure consists of three steps: sample is injected and transported by linear flow stream over a short distance. When it reaches the head of the channel, the linear flow (FL) is diverted while the cross flow is maintained to allow polymer to equilibrate in the channel. The relaxation time needed to reach the equilibrium is proportional to the applied cross flow rate. Then, the channel flow is resumed, the separation process begins and the components are eluted and detected.

After the elution of the sample, the channel is rinsed by the application of a high linear flow rate of $1\,mL \cdot min^{-1}$ during 10 min to remove any adsorbed material from the membrane surface. Moreover, the cross flow stream which is recycled by a loop pumping system during the elution, is diverted to waste and a flow rate of $3.5\,mL \cdot min^{-1}$ is applied during 20 min to remove all impurities passing the membrane.

The symmetrical F4 was an universal fractionator model F-1000, from Fractionation, LLC (Salt Lake City, USA). The channel dimensions were length = 27.7 cm, breath = 2 cm, and thickness = 254 μm. The accumulation wall consisted of an ultrafiltration membrane of regenerated cellulose (M_w cut off = $10{,}000\,g \cdot mol^{-1}$). An intelligent pump HPLC FLOM 301 was employed for delivering channel flow stream. The cross-flow stream was generated and regulated by a P-500 (Pharmacia Biotech) dual piston syringe pump. Samples were introduced through an injection valve with a 100 μL loop.

F4 Operating Conditions

In flow FFF, the cross flow can be held constant or varied with time during elution. The latter procedure is allowed for a better separation of broad molar mass distribution polymers. Running conditions used to analyze saponified PMG are shown in Scheme 2 and consisted of an exponential programmed decrease of the cross flow rate from FC_1



SCHEME 2 Profile of programmed cross flow in the F4 channel.

to FC_2 with time: FC_1 of $2.5\,mL \cdot min^{-1}$ was applied during 1 min then decreased during 30 min to reach a final rate value FC_2 of 0.03 $mL \cdot min^{-1}$. Injections were performed at room temperature.

MALLS/RI

MALLS photometer, a DAWN-F from Wyatt Technology Inc. (Santa Barbara, USA) used a wavelength $\lambda = 633\,nm$. Simultaneous concentration detection was performed by a refractive index detector DRI-ERC 7515A. MALLS and RI detectors were calibrated by filtered toluene and glycerol, respectively. The MALLS instrument was normalized with standard pullulan P-100.

The *dn/dc* parameter was determined by injection of four different concentrations (from 0.8 to $1.6\,g \cdot L^{-1}$) of copolymer sample directly into a Shimadzu RID-6A-type RI detector previously calibrated with sodium chloride solutions. For all copolymers studied, the *dn/dc* value obtained was 0.130 ± 0.002 in $LiNO_3$ 0.1 M solvent.

Data collection from the MALLS photometer and RI detector was carried out and analyzed using ASTRA V-4.5 software.

RESULTS AND DISCUSSION

Sample Recovery

The sample recovery obtained from the ratio of the mass eluted from the system (determined by integration of the RI signal) and total injected mass, was between 55 and 60% for all copolymers studied. Different assumptions can explain the polymer loss. First explanation could be the retention of the sample in the channel resulting from interactions between the polymer chains and the ultrafiltration membrane. This artefact could be ascribed to the high cross flow ($2.5\,mL \cdot min^{-1}$) applied during the relaxation step at the beginning of the analysis: at high cross field, the distance between the macromolecules and the ultrafilter decreases thus increasing the possibilities for sample/membrane interactions. Nevertheless, in our case, we did not observe the elution of further material from the RI or MALLS detectors during the rinsing step for which the cross flow was stopped and the channel flow was enhanced to $1\,mL \cdot min^{-1}$. Moreover, different experiments were realized using lower initial values of cross flow rate (from 1.5 to $2.5\,mL \cdot min^{-1}$): when the cross flow is decreased, the sample's compression against the accumulation wall is lower which should reduce adsorption. However, sample recovery was not improved under these conditions. Considering the mentioned observations, a hypothesis of polymer retention in the channel could be eliminated.

Another explanation can be based on the loss of low-molecular-weight macromolecules or components by penetration through the ultrafiltration membrane (M_w cut off $= 10{,}000\,g \cdot mol^{-1}$). This assumption seems particularly probable since the studied copolymers were prepared from PMG precursor sample with low M_w ($35{,}000\,g \cdot mol^{-1}$) and large polydispersity index ($I = 3$). As a consequence, the polymer part eluted from the system does not reflect the whole sample composition. Moreover, the penetration of the small molecules or oligomers through the ultrafilter resulted in contamination of the cross flow stream, which is pumped in a loop recycling system during the elution. For this reason, it was necessary to rinse the system before each injection (see experimental section) to avoid pumping back impurities into the channel which causes driftting RI baseline during elution.

Influence of Saponification Rate

The molecular characteristics of the saponified PMG's in aqueous solution were investigated as a function of saponification rate (from 10 to 100%) by F4/MALLS. Figure 1 displays the semi-logarithmic plot of molecular weight *versus* elution volume for PMG [10%]. The filled line depicts refractive index whereas the dotted line shows the laser light scattering profile. It can be noticed that the distribution of molecular weight increases with elution volume, as expected, and in agreement with the FFF theory. The refractive index detector showed a curve with a bimodal shape denoting the presence of two distinct populations. The shoulder at the beginning of the RI peak represents a small part of the sample, which scatters light with very low intensity. Therefore, this fraction can be clearly attributed to the presence of low-molecular-weight molecules. In contrary, the major peak centered

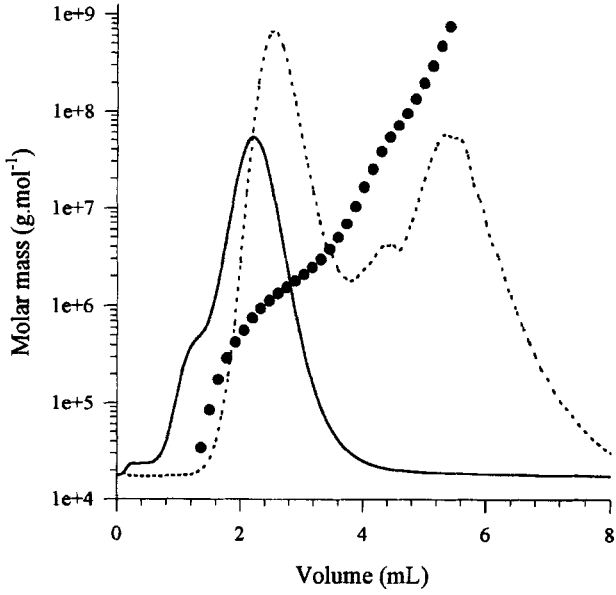


FIGURE 1 Molar mass (•) *versus* retention volume for copolymer PMG [10%]. Fractograms from RI (filled line) and light scattering (90° signal, dotted line) detectors are superposed. Mobile phase $LiNO_3$ 0.1 M, $Cp = 10\,g \cdot L^{-1}$. F4 conditions: $FL = 0.3\,mL \cdot min^{-1}$, $FC_1 = 2.5\,mL \cdot min^{-1}$ (1 min) followed by an exponential decrease (30 min) down to FC_2 $0.03\,mL \cdot min^{-1}$.

around 2.2 mL reflects the major portion of the sample as suggested by the high refractive index. This second fraction scattered light with high intensity indicating that it is composed of large-molecular-weight species. Finally, a third population eluted at high retention volumes (from 4 to 8 mL) is also shown by MALLS but not by RI detector. The high intensity of light scattering signal also indicates that this fraction represents large-molecular-weight species. Nevertheless, with regard to the very low refractive index value, this latter fraction does not represent a significant amount of the sample.

The second fraction, which represents 85% of the sample, has a weight – average molecular weight of about $1 \cdot 10^6\,g \cdot mol^{-1}$ while the whole sample M_w is about $5 \cdot 10^6\,g \cdot mol^{-1}$. These results show that the apparent molecular weight of PMG [10%] is much higher than that of the PMG precursor determined by static light scattering ($M_w = 35{,}000\,g \cdot mol^{-1}$). This clearly indicates that aggregates resulting from the strong intermolecular associations exist even in dilute solution. Similar results were obtained in the case of charged amphiphilic copolymer prepared from poly(styrene-*co*-methyl methacrylate-*co*-maleic anhydride) and poly(ethylene oxide).[14] This behavior was attributed to the poor solvatation of macromolecules with high hydrophobe content. The hydrophobic parts could be assumed to form a dense core surrounded by hydrophilic moieties (carboxylate groups) in various polymolecular structures. Moreover, PMG [10%] did not exhibit an angular dependency of the scattered light. This indicates that the intermolecular associations form compact self-aggregates with a low apparent hydrodynamic volume.

Fractograms for PMG saponified from 10 to 100% are reported in Figure 2. PMG [15%] and [31%] exhibit the same behavior: RI and MALLS detectors showed only one population eluted at a lower retention volume (1.4 mL) compared with the major part of PGM [10%]. The noise of the light scattering intensity was not important to perturb the calculation of the molecular weight. This result denotes the presence of low-molecular-weight macromolecules. It seems probable that this peak represents a population of single polymer molecules dispersed in solution. When the saponification rate increases to 50 and 61%, the scattered light profiles show a second large peak eluted at high retention volumes (from 3 to 7 mL). The Figure 3 shows an enlargement of the elution profiles for samples PMG [50%] and [61%];

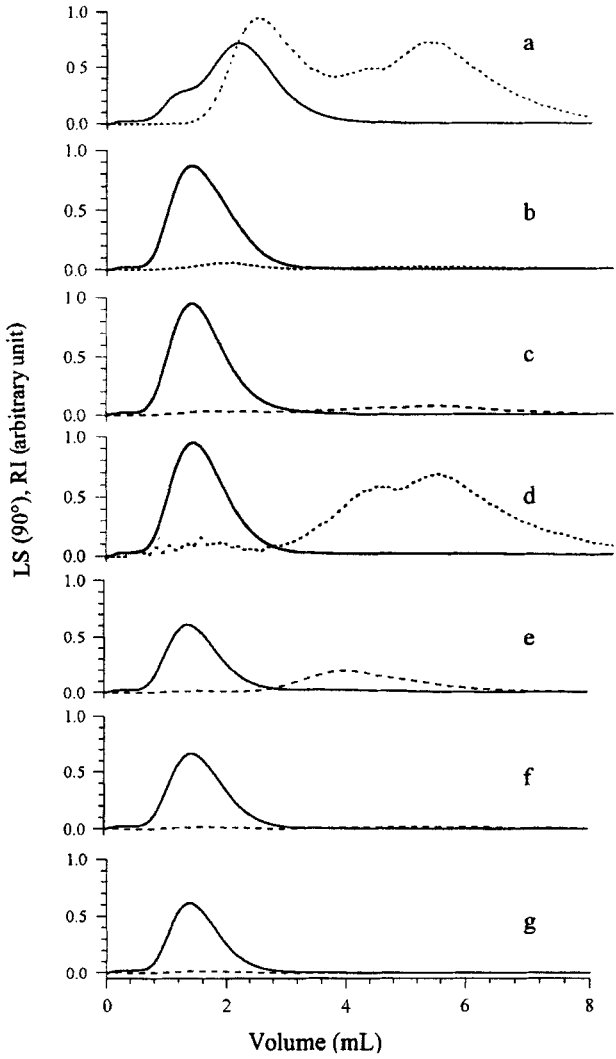


FIGURE 2 Fractograms *versus* retention volume from RI (filled line) and light scattering (90° signal, dotted line) detectors for copolymers PMG [10%] (a), [15%] (b), [31%] (c), [50%] (d), [61%] (e), [90%] (f) and [100%] (g). Mobile phase $LiNO_3$ 0.1 M, $Cp = 10\,g \cdot L^{-1}$. F4 conditions: $FL = 0.3\,mL \cdot min^{-1}$, $FC_1 = 2.5\,mL \cdot min^{-1}$ (1 min) followed by an exponential decrease (30 min) down to FC_2 $0.03\,mL \cdot min^{-1}$.

a shoulder also appears at the end of the refractive index peak. This second fraction, which scatters the light with high intensity and represents about 10% of the sample analyzed, can be attributed to

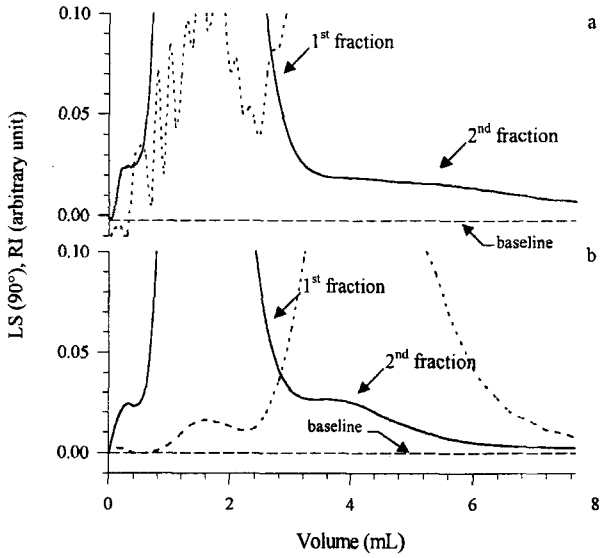


FIGURE 3 Broadening of the fractograms for copolymers PMG [50%] (a) and [61%] (b).

very high molecular weight aggregates. In contrary, the fractograms of PMG [90%] and [100%] do not exhibit this second population. These samples showed the same RI and MALLS profiles as PMG [15%] and [31%].

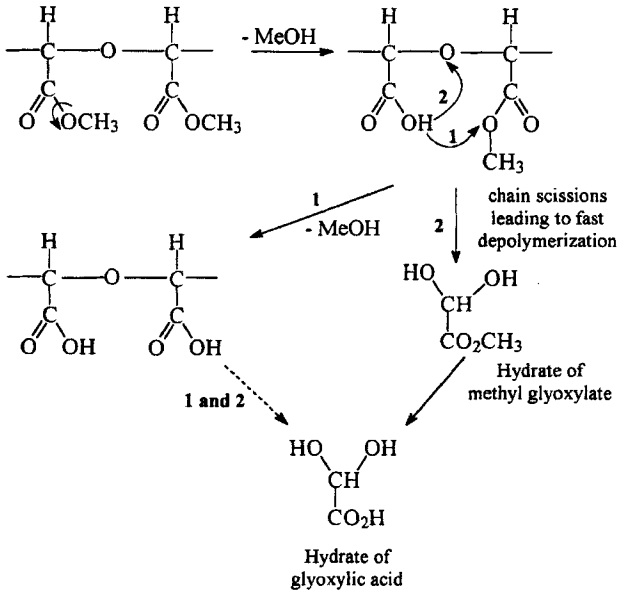
The variation of the fractogram shapes with saponification rate can be explained by changes in copolymer conformation. Hydrolysis of ester functions generates the carboxylate groups on the polymer backbone and improves the aqueous solvatation of macromolecules. Thus, when the saponification rate is enhanced from 10 to 15%, the hydrophobic polymolecular structures are disrupted and copolymer molecules are probably present in some intramolecular micellar conformation, resulting from hydrophobic intramolecular association. However, as the saponification rate reaches 50%, the high charge density of macromolecular chains causes electrostatic repulsion which prevents intramolecular association and leads to expanded chain conformation. Therefore, the intermolecular associations by hydrophobic groups, most notably by urethane groups, become facilitated and the polymolecular structures with a large size can occur. This associating behavior is typically described in the literature for neutral water-soluble telechelic polymers like HEUR's.[15,16] Nevertheless,

when the charge density becomes very high (*i.e.*, when the saponification rate reaches 90%), electrostatic repulsion is so important that intermolecular associations are not possible: only the monomolecular conformation is present.

These experiments showed that the modification of the hydrophilic/hydrophobic balance greatly influences the conformation of copolymers in solution. In particular, the aggregation phenomena could be exploited to solubilize hydrophobic active compounds and to increase the solubility limit of such products. It is clear that only PMG [10%] really shows aggregates in proportion and size.

Kinetic of Chemical Degradation

PMG is a bioresorbable polymer, rapidly depolymerizing in aqueous solution. The mechanism of degradation was investigated and described in previous papers;[17, 18] it is summarized in Scheme 3. Briefly, the hydrolysis of methyl ester functional groups generates



SCHEME 3 Mechanism of PMG degradation.

carboxylic acid involving chain scissions and immediate depolymerization. The small residual molecule released from the degradation is glyoxylic acid.

In contrast to PMG, the chemical degradation of saponified copolymers had never been studied. In this part, we describe the kinetics of the depolymerisation of copolymers as a function of saponification rate (from 10 to 100%). The F4 technique seemed to be a suitable method to follow the polymer degradation because small molecules are eliminated by penetration through the ultrafiltration membrane and, therefore, the residual molecules resulting from macromolecular degradation do not affect the RI signal and only the polymer present in solution is detected. As a consequence, it is possible to measure the elimination of the depolymerized sample with the time.

The polymer concentration decrease as a function of time for PMG [10%], [31%], [50%] and [100%] as shown in Figure 4. The mass

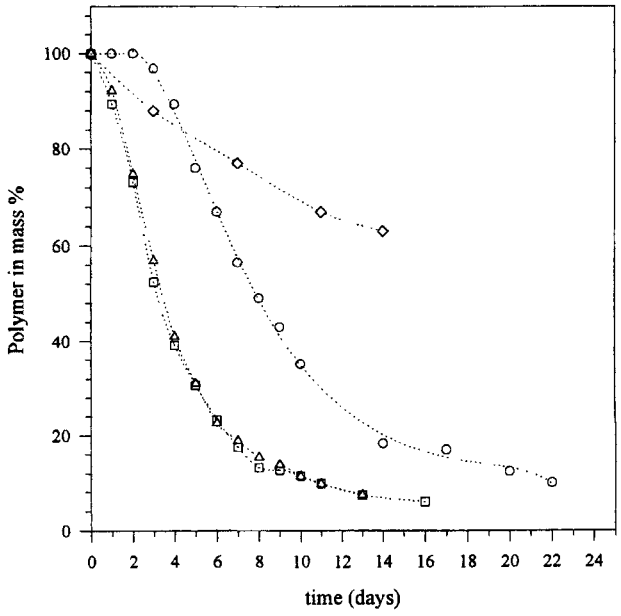


FIGURE 4 Mass percentage of polymer *versus* time for copolymers PMG [10%] (○), [31%] (△), [50%] (□) and [100%] (◇). $Cp_{initial} = 10\,g \cdot L^{-1}$.

percentage of polymer (*cf.* *Y*-axis) was determined by using the equation:

$$Y = 100 \cdot S_t/S_0$$

where S_0 and S_t are integrations of the RI signal obtained respectively at 0 and t days. Different behaviors were observed concerning the saponification rate. For PMG [31%] and [50%], an important decrease of the mass percentage of polymer occurred from the first day till the 10th day, followed by a slow decline with time. In contrast, the behavior of PMG [100%] strongly differs from other samples. The polymer concentration slowly but continuously decreased with the time and after 14 days, the polymer loss was about 35%.

The results obtained for PMG [31%] and [50%] are not surprising considering the mechanism of PMG degradation (Scheme 3). The presence of methyl ester functional groups on the macromolecular backbone involves chain scissions in the resulting acidic medium, followed by fast depolymerization. In contrast, the presence of carboxylate groups on the macromolecules of PMG [100%] should prevent this rection. Nevertheless, PMG [100%] entirely saponified was never obtained, whatever the temperature and reaction time used. Residual esters (about 2%) have been detected by ^{1}H NMR and FTIR. These esters are responsible for the degradation initiation, according to the same Scheme 3, but polymer degradation is considerably slower.

The behavior of PMG [10%] is more complex. The shape of the degradation curve clearly shows three different stages. During the first three days, the concentration of the polymer remained unchanged. Then, a dramatic drop appeared upto 14th day followed by a slow decline with the time. The fractogram evolution during time plotted in Figure 5 could explain this result. As described in the previous paragraph, two distinct populations initially occur, as suggested by the bimodal shape of RI curve. During the first three days, the concentration of the first fraction is enhanced whereas the concentration of the second one dramatically decreases to zero. In the same time, the intensity of the scattered light signal continuously decreases with time. Beyond three days, only one population scattering light with very low intensity occurs in the refractive index profile; the concentration decreases with time, reflecting polymer loss.

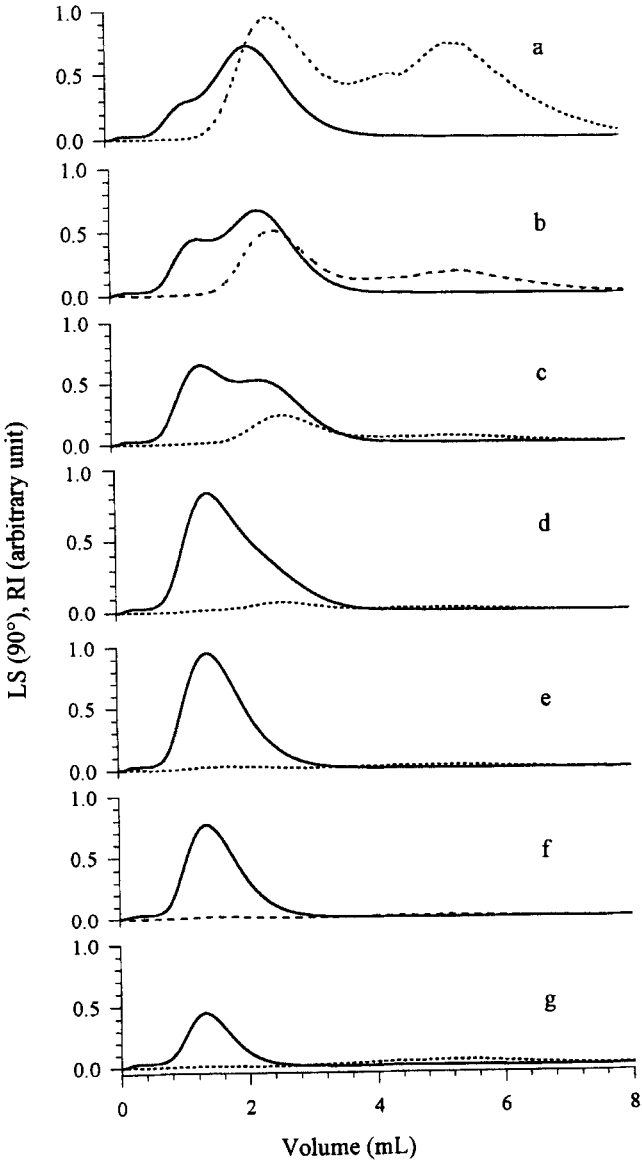


FIGURE 5 Fractograms from RI (filled line) and light scattering (90° signal, dotted line) detectors for copolymers PMG [10%] for different times: 0 day (a), 1 day (b), 2 days (c), 3 days (d), 4 days (e), 6 days (f) and 10 days (g). Mobile phase $LiNO_3$ 0.1 M, $Cp = 10\,g \cdot L^{-1}$. F4 conditions: $FL = 0.3\,mL \cdot min^{-1}$, $FC_1 = 2.5\,mL \cdot min^{-1}$ (1 min) followed by an exponential decrease (30 min) down to FC_2 $0.03\,mL \cdot min^{-1}$.

Moreover, the semi-logarithmic plots of molecular weight of PMG [10%] *versus* retention volume for 0, 1, 2 and 3 days given in Figure 6 shows an important decrease of molecular weight with the time. The weight – average molecular weight as a function of time represented in Figure 7 exhibits a continuous decrease from 5.5×10^6 to 150,000 $g \cdot mol^{-1}$ during the first three days and remained unchanged beyond day three.

As described previously, the macromolecules of PMG [10%] are initially self-associated by hydrophobic groups to minimize their contact with the solvent. This compact conformation should notably reduce the accessibility of the methyl ester functional groups towards the molecules of water, so that the mechanism represented on Scheme 3 was not effective and no polymer degradation occurred at the beginning of the study (Fig. 4). However, while the polymer

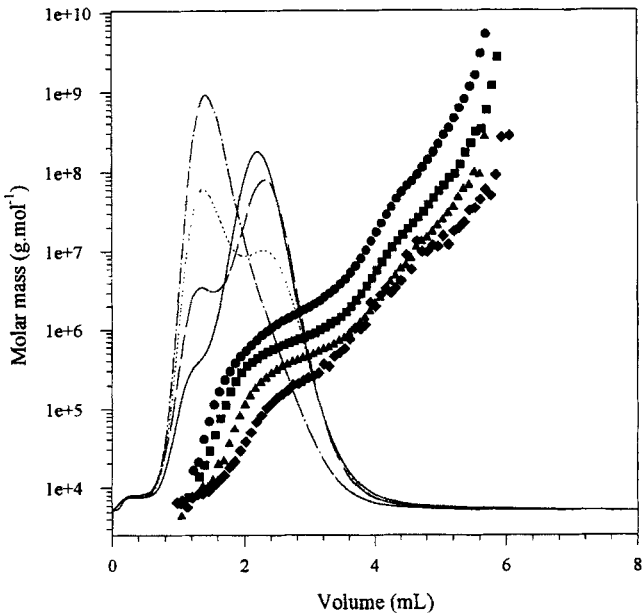


FIGURE 6 Molecular weight *versus* retention volume for copolymer PMG [10%] for different times. Fractograms from RI detector are superposed: 0 day (● and –), 1 day (■ and – –), 2 days (▲ and · · ·) and 3 days (◆ and – · –). Mobile phase $LiNO_3$ 0.1 M, $Cp = 10\,g \cdot L^{-1}$. F4 conditions: $FL = 0.3\,mL \cdot min^{-1}$, $FC_1 = 2.5\,mL \cdot min^{-1}$ (1 min) followed by an exponential decrease (30 min) down to FC_2 $0.03\,mL \cdot min^{-1}$.

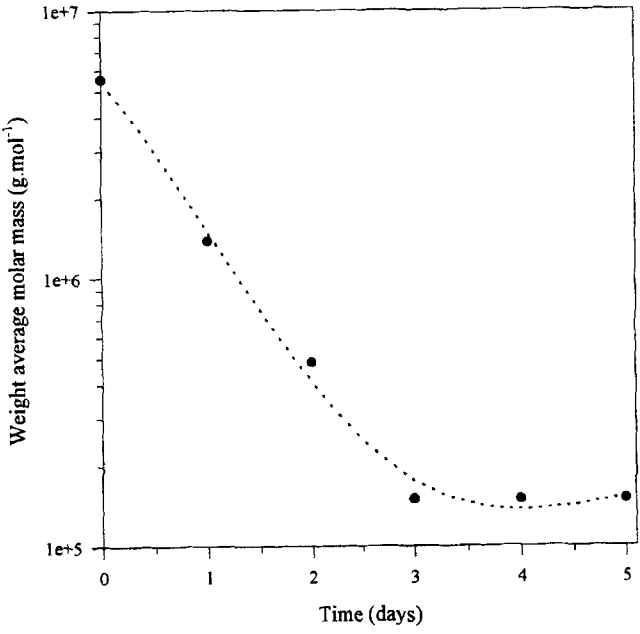


FIGURE 7 Weight average molecular weight *versus* time for copolymer PMG [10%]. Mobile phase $LiNO_3$ 0.1 M, $Cp = 10\,g \cdot L^{-1}$. F4 conditions: $FL \approx 0.3\,mL \cdot min^{-1}$, $FC_1 = 2.5\,mL \cdot min^{-1}$ (1 min) followed by an exponential decrease (30 min) down to FC_2 $0.03\,mL \cdot min^{-1}$.

concentration remained unchanged, a continuous decrease of the apparent weight–average molecular weight was observed during the first three days (Fig. 7). This result reflects a partial disruption of the aggregates in solution with time resulting from a slow diffusion of the molecules of water inside the compact macromolecular structures. Beyond 3 days, the hydration of the macromolecular chains should be sufficiently important to lead to the hydrolysis of ester groups and, consequently to polymer degradation (Fig. 4). It is also interesting to note that the disruption of the aggregates of PMG [10%] with time was not complete since the M_w reached a constant value of 150,000 $g \cdot mol^{-1}$, which is more important than the molecular weight of PMG precursor (35,000 $g \cdot mol^{-1}$).

This study showed that the kinetics of depolymerization of PMG derivatives strongly depends on the saponification rate and macromolecular conformation of copolymer in solution. In the case of

PMG's [31%] and [50%], which are mainly molecularly dispersed in solution, the degradation is very fast and occurs immediately. In contrast, the degradation of PMG [10%] is delayed by the presence of compact aggregates in solution. Finally, the presence of numerous carboxylate groups on the macromolecules of poly(potassium glyoxylate) considerably reduces the number of chain scissions and polymer degradation is slower.

CONCLUSION

The study of the amphiphilic polymers in aqueous solution is generally complex due to associations. In this paper, the recent analytical method F4/MALLS has been shown to be efficient for characterizing the amphiphilic water-soluble derivatives obtained by partial saponification of PGM. Different samples with various saponification rates were examined. The copolymer with a high hydrophobe content ($y = 10\%$) forms compact aggregates in solution. This behavior was ascribed to the intermolecular associations between the hydrophobic parts. In contrast, when the saponification rate increases ($y > 10\%$), the major part of the sample is molecularly dispersed in solution. This result could be explained by the presence of carboxylate groups, which enhances the hydrophilic character and the expansion of the backbone. Moreover, the investigation of the kinetics of polymer degradation in aqueous solution pointed out that the disappearance of macromolecules with time is clearly dependent on the saponification rate and the conformational shape of the chains. As a consequence, it is possible to easily adjust the degradability and the conformation of the copolymers with saponification rate. These results promote the potential use of the saponified PMGs in biomedical applications. It will be interesting to study the influence of external parameters like pH on the aqueous properties of these new charged compounds.

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