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Chemistry Modification of PMMA-g-PEG copolymer

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Summary: Copolymers are polymers consisting of different repeat units and their production is usually motivated by the changing of polymers properties. An important application are the transportation of drugs within the organism with the aim of controlling the release of the substance. The synthesis of these new copolymers is based on simple semi-synthesis and low cost. The synthetic routes are based on the interaction of the graft copolymer (PMMA-g-PEG) with a variety of reagents such as acetic anhydride, acetic acid, methyl iodide, sulfuric acid and hydrochloric acid. The products from these reactions of esterification, methylation, acetylation and halogenation will be characterized by Fourier-transforminfrared spectroscopy (FTIR). The use of this technique allowed us to detect the main absorption bands related to the C=O bonds, C-Cl, R-COOR and CO, thus confirming the efficiency of modification reactions of the graft copolymer chain.

Keywords: chemistry modification; Differential Scanning Calorimeter; graft copolymers; infrared spectroscopy; Scanning Electron Microscopy (SEM); thermogravimetric analysis; X-rays diffraction (XRD)

Introduction

Nowadays, some polymers are developed to operate as drug delivery at specific sites in the organism. Currently, modified polymeric compounds are being used as drug delivery systems, acting as carriers of drugs able to target tissues or tumor cells and protecting the premature inactivation of the active ingredient of the drug during transport.[1–5] Polymers used as a matrix in drug delivery system shall be chemically inert and free of impurities, have a proper physical structure and be easily processable by the organism. Due to the characteristics derived from their origin polymers such as transparency and strength of PMMA[6–8] and an appropriate structure and easy processing of PEG,[9] our research group has studied the modification of the copolymer PMMA-g-PEG from various organic reactions.[10] One of the most current forms for controlled release is the development of new polymeric materials, which allows the use of various techniques for encapsulation of many compounds in multiparticulate systems such as microspheres and microcapsules, in order to protect, stabilize, or mask undesirable flavors modify the release properties. Research in this area has become very important due to the ability of the microspheres to modify certain kinetic parameters and biodistribution of the molecules transported, allowing its application in the area of selective and controlled delivery of drugs.[11] The use of formulations that allow the optimization of the speed of transfer and dosage of drugs has been an area of intense research in recent decades. Polymeric microparticles as microcapsules and microspheres, have been proposed as modulators and drivers in drug release at specific sites in the organism, as a strategy for stabilizing against agents such as pH or light drugs, mask organoleptic characteristics[12] and decrease the side effects of certain drugs, highlighting the nonsteroidal anti-inflammatory drugs

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(diclofenac and indomethacin), which often cause irritation to the intestinal mucosa.[13]

Polymers are selected according to the formulation and the desired release mechanism, for example, parenteral enteral or the dosage form. Two criteria must be followed in the preparation of a polymer formulation. The chemical characteristics of the polymer should not compromise the action of the active ingredients, and the physical properties of the polymer must be consistent and reproducible from batch to batch.[5]

Because of its various applications and features, especially in therapies for controlled release of the drug, polymers excipients are the most used for obtaining pharmaceutical forms.[5] After modifying the polymer properties, a matrix system may be prepared for sustained or controlled release of drugs.[13] The initial objective of this work was to modify the copolymer chains of PMMA-g-PEG with the insertion of different chemical groups to enable, in the future, their biomolecular interactions (antigen-antibody, enzyme-substrate and drug-receptor) with various types of drug delivery systems.[14,15]

Experimental Part

Chemical Reagents

Sodium hydroxide (NaOH), dichloromethane (CH_2Cl_2), acetic anhydride ($CH_3COOCOCH_3$), acetic acid (CH_3 COOH), hydrochloric acid (HCl), sodium bicarbonate ($NaHCO_3$), sulfuric acid (H_2SO_4) were purchased from Vetec. Methyl iodide (CH_3I), chloride sodium (NaCl), benzoyl peroxide, methyl methacrylate (MMA), polyethylene glycol were purchased from Sigma Aldrich and distilled water.

Synthesis of the Graft Copolymer (PMMA- g-PEG)[10,16]

General Reactions

Synthesis: The copolymer was prepared in a beaker by dissolving 40.00 g of PEG in 100.00 mL of dichloromethane. The contents of the beaker were transferred to a round bottom flask along with 2.80 mL of MMA and 0.05 g of benzoyl peroxide initiator. Then the reaction mixture was left under magnetic stirring at 80 °C for 6 hours. At the end of the reaction were added 50.00 mL of dichloromethane and 50.00 mL of distilled water, producing a colorless homogeneous solution. The contents of the flask were transferred to a separatory funnel and the organic layer separated from the aqueous phase with dichloromethane. The copolymer (COP GRAFT) obtained in the reaction was transferred to a beaker and left at room temperature to evaporate the solvent and solidify.

Synthesis of the Copolymers[17]

General Scheme

Synthesis 1: Methylation of Graft Copolymer PMMA-g- PEG- (1)

In a beaker were solubilized 2 g of graft copolymer in 10 mL of CH_2Cl_2. Then were added 10 mL of 10% NaOH solution. The

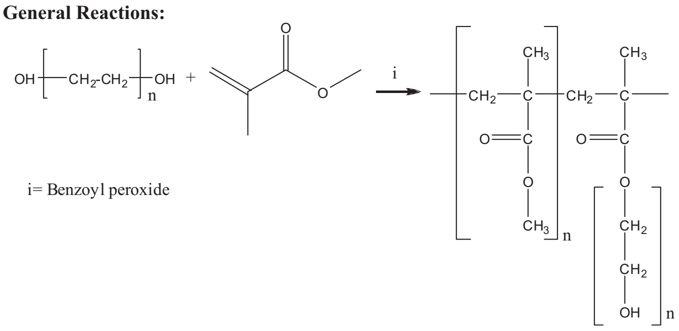
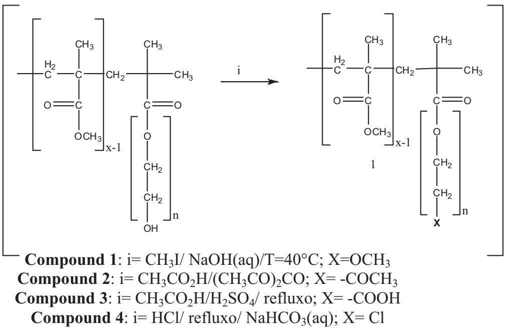


Figure 1.
General reaction to the synthesis of Graft Copolymer (PMMA- g-PEG).

General Scheme:



Compound 1: i= CH_3I/ NaOH(aq)/T=40°C; X=OCH_3
Compound 2: i= $CH_3CO_2H/(CH_3CO)_2CO$; X= -$COCH_3$
Compound 3: i= CH_3CO_2H/H_2SO_4/ refluxo; X= -COOH
Compound 4: i= HCl/ refluxo/ $NaHCO_3$(aq); X= Cl

Figure 2.
General reaction to the synthesis of Graft Copolymer (PMMA- g-PEG) derivatives.

reaction mixture was transferred to a round bottom flask and heated in an oil bath with magnetic stirring for 45 minutes. Was added 2.4 mL of CH_3I and the reaction mixture was maintained at the temperature of 40 °C for 4 hours. After reaction, the mixture was transferred to a separatory funnel and was added 10 mL of water, 20 mL of CH_2Cl_2 and a saturated NaCl solution for phase separation. The organic phase was collected. FT-IR characterization was made after complete solvent evaporation was taken.

Synthesis 2: Acetylation of Graft Copolymer PMMA-g-PEG (2)

In a round bottom flask were added 2 g of graft copolymer and it was solubilized in 10 mL of CH_2Cl_2. In another beaker was prepared a solution of 5 ml of acetic anhydride with 5 ml of acetic acid. This solution was added to the flask containing the copolymer. The reaction mixture was maintained at the temperature of 40 °C for 30 minutes. Upon completion of the reaction, the mixture was poured into a beaker with 100 mL of ice water. The modified copolymer solidified and was separated by simple filtration. FT-IR characterization was made after complete solvent evaporation was taken.

Synthesis 3: Esterification Followed by Hydrolysis of Graft Copolymer PMMA-g-PEG (3)

2 g of the graft copolymer were dissolved in 10 mL of CH_2Cl_2. A mixture was prepared with 0.1 mL of concentrated H_2SO_4 and 7 mL of CH_3COOH. This mixture was added to the solubilized copolymer and was maintained at the temperature of 40 °C for 65 minutes. After cooling it were added 10 mL of water. FT-IR characterization was made after drying of the modified copolymer.

Synthesis 4: Halogenation of Graft Copolymer PMMA-g-PEG (4)

1 g of graft copolymer was dissolved in 10 mL of CH_2Cl_2 and. then was added 0.5 ml of HCl. The reaction mixture was maintained at the temperature of 30 °C and after the reaction was completed the mixture was placed in a separatory funnel. When the phase separation was finalized. It was added 5mL of 5% $NaHCO_3$. The organic phase was collected and after solvent evaporation the sample was characterized by FT-IR.

Solubility Test

About 200 mg of each copolymer (Graft, methylated, hydrolyzate and halogenated) were placed in tests tubes and were immersed in 2 ml of: water, ethanol, acetone, diethyl ether, chloroform and hexane. The tubes were agitated to solubilize the copolymers. Samples that do not solubilized at room temperature were heated in a water bath for complete solubilization.

Characterization

The modifications of the graft copolymer chains PMMA-g-PEG (COP GRAFT) were based on basic organic reactions such as methylation, acetylation, hydrolysis and esterification, halogenation in the presence of a variety of chemical reagents, generating new copolymers structures with methylated (COP MET), acetylated (COP ACET), esterified/hydrolyzed (HIDROLYZADE) and halogenated (COP HAL). Upon completion of the reaction the products were isolated and purified by the technique of liquid-liquid extraction using organic solvents such as dichloromethane and chloroform to separate the organic phase from the aqueous phase. After the extraction the aqueous phase was discarded and then the organic phase was left at room temperature to evaporate the solvent and solidify. Then the modified copolymers were characterized by the techniques of infrared (IR), differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

Infrared Analysis (IR)

Infrared analyzes were carried out using graft copolymer and the modified copolymers that were synthesized in an Infrared Spectrometer Varian 640 FTIR. IR spectra were reproduced by Resolutions Pro software.

Thermogravimetric Analysis (TGA)

The graft copolymer and its derivatives were evaluated by thermogravimetric analysis equipment on a TA Instruments Model SDT 2960 Simultaneous DTA-TGA using a heating rate of 20 °C/min, temperature range of 20–700 °C and under air atmosphere.

Differential Scanning Calorimeter (DSC)

The DSC analysis of the graft copolymer and its derivatives were conducted in an equipment of TA Instruments, model DSC 2010 operating at a heating rate of 20 °C/min, temperature range of 20–350 °C under air atmosphere.

X-rays Diffraction (XRD)

The X-ray diffraction was performed at room temperature and the samples were analyzed in the region of 5–70 °C (2θ) and 2 °C/mim^{-1}. The apparatus used was a diffractometer Shimadzu model XRD-6000, equipped with the monochromator and iron pipe graphite. Samples were prepared in the form of 2cm diameter disk. Use of this method enables knowledge of the content of crystallinity of the sample.

Scanning Electron Microscopy (SEM)

The SEM analyzes were performed on an Tescam equipment, Vega 3, and sample preparation was done in a Quorun evaporator.

Results and Discussions

In the reactions with the graft copolymer PMMA-g-PEG (COP24H), was necessary to test the condition of the reaction for more efficient syntheses in order to avoid losses of reactants and formation of undesirable products. The obtained compounds presented in yields ranging from 50% range according to Table 1.

The modified copolymers showed different aspects (Figure 3).

At the end of each synthesis and evaporation of the solvent solubility tests were performed with different organic solvents. Each compound showed different solubilities, since they have different chemical groups inserted in the copolymer chains.

Table 2 shows the solvents used, and the behavior of each compound.

It was observed that compound 3 was soluble in the most polar solvent (water) due to carboxyl groups present in the copolymer chains, that made strong hydrogens bonds interactions with water. However, other less polar compounds were soluble in solvents of low to medium polarity. The different solubilities of the modified copolymers indicate that there was modification of the starting copolymer properties. FTIR spectroscopy indicated

Table 1.
Yields of modified copolymers.

Copolymers	Yields(%)
COPMET (1)	66,10
COPACET (2)	49,11
HYDROLIZATE (3)	97,09
COPHAL(4)	55,33

(1) (2) (3) (4)

Figure 3.
Modified graft copolymers: COPMET (1), COPACET (2), HYDROLIZATE (3), COPHAL (4).

Table 2.
Solubility Test of the modified graft copolymers.

Copolymer	Water		Ethanol		Acetone		diethyl ether		Chloroform		Hexane	
	T$^{a)}$	T$^{b)}$	T$^{a)}$	T$^{b)}$	T$^{a)}$	T$^{b)}$	T$^{a)}$	T$^{b)}$	T$^{a)}$	T$^{b)}$	T$^{a)}$	T$^{b)}$
COP GRAFT						X	X	X				
1												
2					X	X			X	X		
3	X	X										
4					X	X	X	X				

a) room temperature.
b) heating temperature.
The areas marked with the letter X of the table indicate that the corresponding compounds are soluble in the solvent.

that all derived copolymers showed the absorption band related to the bond C - OH in approximately 3500 cm^{-1} equal to this absorption band in Cop GRAFT, but low intensity, except compound 3 (Hydrolyzed) having a more broad absorption band due introduce a carboxyl group which carries strong bonds between the carboxyl hydrogens leading to dimer formation. It was also possible to observe the decrease in the band related to the stretching of the bond C-O of primary alcohol at about 1050 cm^{-1}. Interestingly, the attenuation band was significant for compound 3 in which the bond CO was partly replaced by bond C-Cl with the appearance of the absorption band at 750 cm^{-1}. Compounds 1 and COP GRAFT showed the same absorption band related to the stretching bond of the C=O in approximately 1750 cm^{-1}, as was to be expected. Compounds 2 and 4 showed two absorption bands relating to bond C=O at about 1750 cm^{-1} (already present in COP24h), and an average intensity at 1700 cm^{-1} due to the electron withdrawing effect of groups Cl and $OCOCH_3$. The compound 3 had the appearance of absorption band C=O typical of carboxyl and intense band at 1700 cm^{-1}. For different values of absorption bands relating to the bonds C- OH and C=O is possible to notice the chemical modification of the graft copolymer PMMA -g- PEG (Figure 4).

Figure 5 shows the TGA and DSC curves of the graft copolymer before modification reactions of its structure with new inserts of organic groups.

The analysis of the TGA curve shows a COP GRAFT with two sharper weight loss, the first starting around 50 °C and the second at around 250 °C, with no apparent residue. The DSC curve shows an endothermic peak on the melting temperature of the graft copolymer around 50 °C and exothermic transitions above 200 °C which

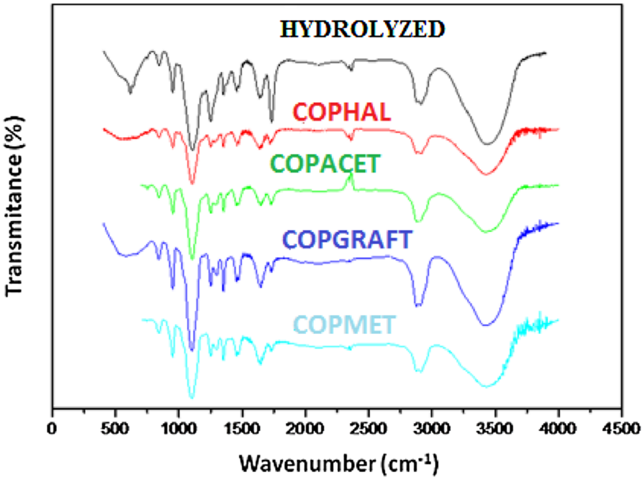


Figure 4.
IR spectra of modified copolymers and COPGRAFT.

may be related to a crystallization process and subsequently thermal degradation of the sample. In the TGA and DSC curves in Figure 6 it is possible to perceive a change in the thermal behavior of the graft copolymer after insertion of organic functional groups of high, low and medium polarity on the polymer chain. These groups have led to a modification of the initial degradation temperature of the COP GRAFT from 50 °C to about 100 °C. The results obtained by DSC and TGA showed that the modified copolymer presented endothermic transition temperature and degradation behavior profile compatible with the polymer chains.

In the case of TGA curves it was observed two levels of weight loss for all copolymers, where the second level showed a sharp inclination in approximately 90 °C. In those cases the number of stages in which degradation occurs is related to the mechanism of degradation of the samples. It was also observed that the modification of the graft copolymer chain resulted in a decrease of its thermal resistance, in addition to presenting an increased amount of residues samples. The transitions observed in the DSC curves showed peaks of broad base with characteristic of materials with high molecular weight and medium sizes chains.

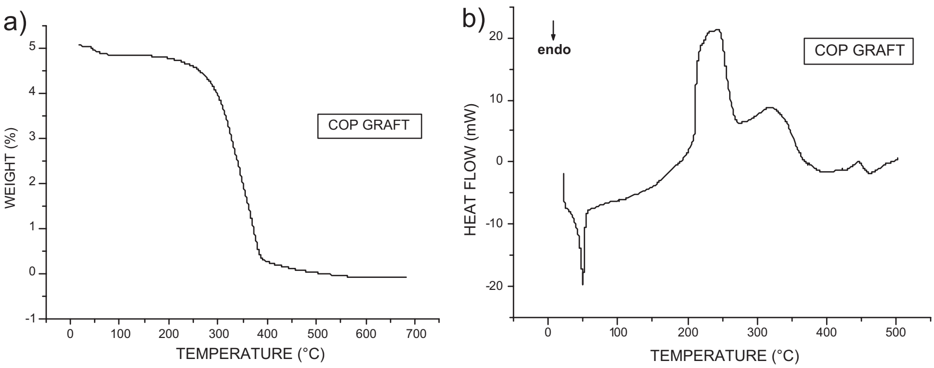


Figure 5.
Curves (a) TGA and (b) DSC of COP GRAFT.

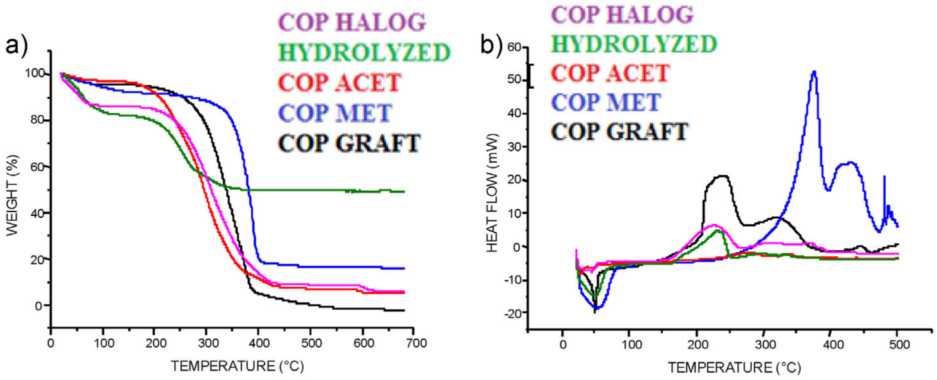


Figure 6.
Curves (a) TGA and (b) DSC of derivatives copolymers from COP GRAFT.

In the DSC curves endothermic transitions referring the melting temperature of the copolymers at temperatures between 28 °C and 60 °C (Figure 6) may be observed. The displacement of the melting transitions is a evidence to the efficiency of the reaction modification of graft copolymer chain. The differences between the profiles of the transitions related to the melting temperatures of the modified copolymers are given by inserting groups of high, low and medium polarity in the polymer chains of the graft copolymer that before modification by organic reactions have only polar groups in their chains. These differences can be observed by widening of melting peak. The inclusion of apolar character groups results in a variation of melting temperature of the graft copolymer, and consequently on modification of the structure and thermal behavior of this copolymer. The exothermic transitions observed in the temperature ranges between 200–275 °C and 350–475 °C may be related to the crystallization of the samples, which is accompanied by the

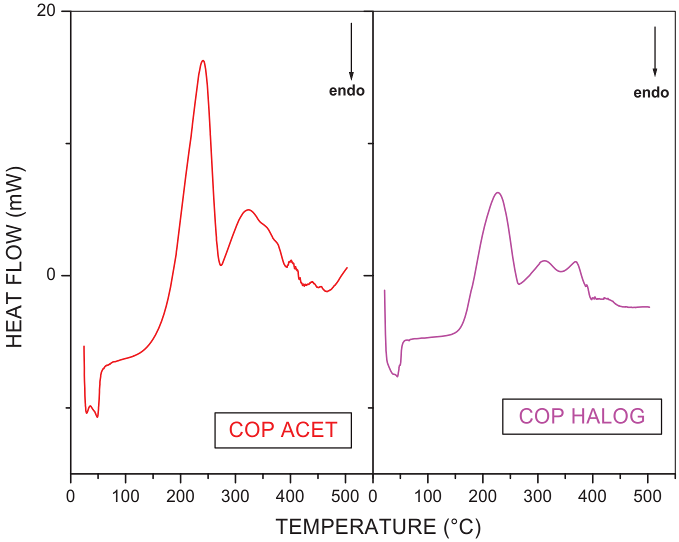


Figure 7.
DSC curves COP ACET and COP HALOG.

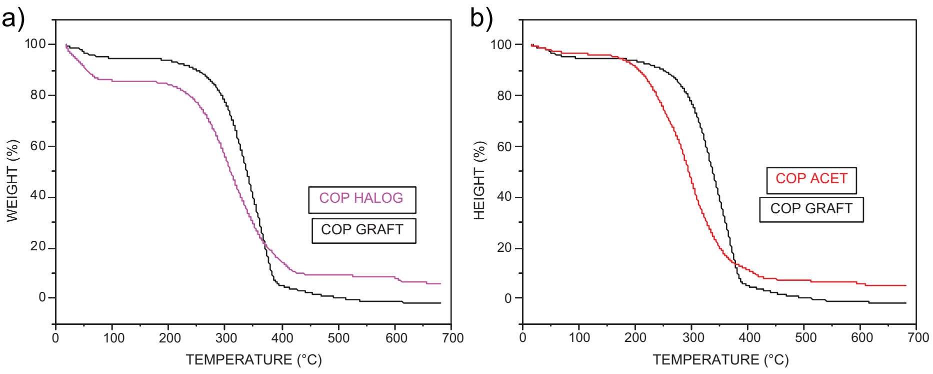


Figure 8.
DSC curves of the derivatives copolymers from COP GRAFT/COP ACET and COP GRAFT/COP HALOG.

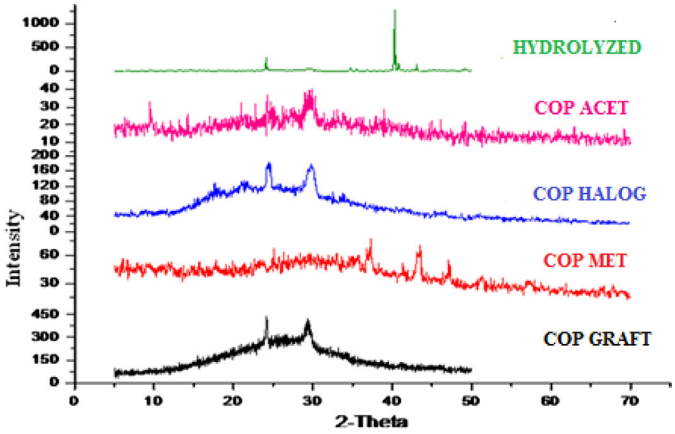


Figure 9.
X-ray diffractograms of derivatives copolymers from COP GRAFT.

release of latent heat process, generating an exothermic peak. These exothermic peaks appearing during heating of the samples before decomposition of them. This behavior is illustrated in Figure 7, showing the thermal transitions of the COP ACET and COP HALOG.

Thermogravimetric analysis showed the degradation of the graft copolymer with a initial weight loss of about 5% at 50 °C and a second weight loss of 95% in the range of 250 ° to 450 °C. Figure 8 shows the curves of the COP ACET and COP HALOG with weight losses in the range of 10° to 100 °C and 250° to 450 °C. The difference between the temperature ranges of the copolymers happens by the decreasing of the polar character of graft copolymer due to the inclusion of groups of low polarity and higher carbon chain, which decreases the strength of intermolecular graft copolymer chains and consequently decreases its temperature initial degradation, thus proving the efficiency of the modification of its chains. Considering the efficiency of purification performed by extraction and characterized by other technique such as FTIR, not mentioned in this work, we can evaluate that the first weight loss is related to copolymer chains and not to weight loss of water molecules.

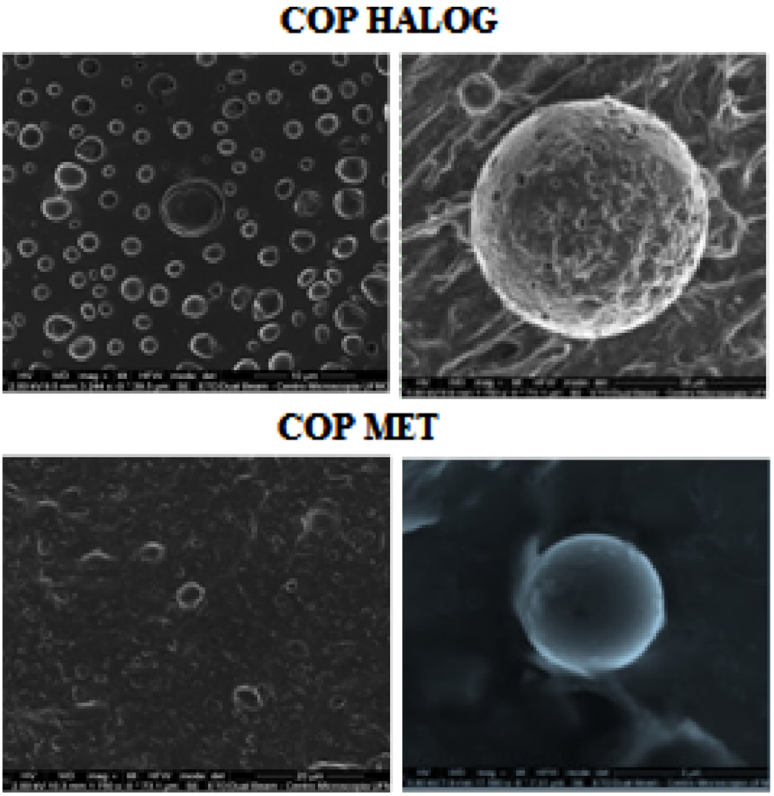


Figure 10.
Photomicrographs of COP HALOG and COP MET.

The X-ray diffraction patterns confirm the results found by DSC and TGA. The hydrolyzed copolymer showed crystalline organization, without amorphous regions that were present in other chains. This behavior is characteristic of semi-crystalline copolymers. All samples showed the peaks related to graft copolymer (Figure 9). Larger peaks of derivatives copolymers indicated a decreased of the chains organization after modification reactions.

Scanning Electron Microscopy was made after the modification reactions of COP GRAFT (Figure 10). From the SEM

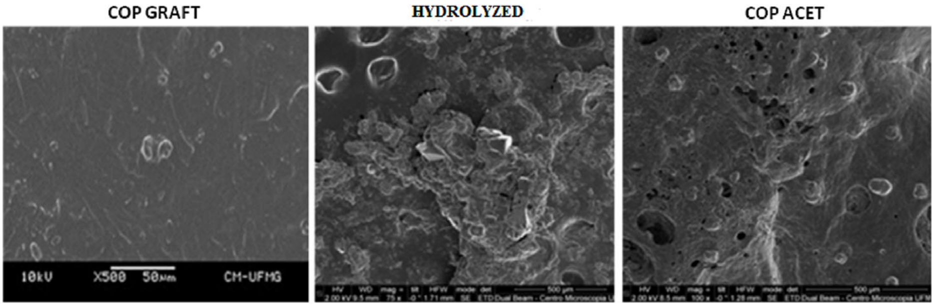


Figure 11.
Photomicrographs of the derivatives copolymers from COPGRAFT.

images of COP HALOG and COP MET was possible to observe the microspheres formation.

HYDROLYZED and COP ACET polymers showed slight microspheres formation (Figure 11) while COP GRAFT showed a smooth surface with few microspheres.

Conclusion

Yields were satisfactory and the use of solvent is essential, because chemical reaction do not happen if the copolymer is not completely solubilized. The COP GRAFT showed different behavior and the formation of new products in the presence of acid or basic characters reagents.

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