V. Conclusions
The main conclusions of the present work can be summarized as follows. The numeration corresponds to the different goals and the derived papers:

1.1. An alternating copolyester constituted by glycolic acid and 4-hydroxybutyric acid units has been prepared with high yield and moderate molecular weight from a thermal polycondensation that has the formation of metal chlorides as a driving force.

1.2. The polymer is semi-crystalline with a melting point close to 110 °C and a glass transition temperature of around -15 °C. Thermal properties and chemical constitution enhance the interest in this copolyester as a new biodegradable material. Furthermore, the polymer has a high thermal stability, which makes its melt processing feasible and diminishes the risk of degradation reactions during polymerization.

1.3. The polymerization kinetics of the sodium, potassium and cesium salts of 4-chlorobutyric acid carboxymethyl ester has been analyzed. The activation energy decreases by increasing the size of the cation. The three salts have a similar mechanism (R₃ model) which is the best shape factor in order to simulate the experimental results.

2.1. An alternating copolyester consisting of glycolic acid and 6-hydroxyhexanoic acid residues has been synthesized with high yield and high molecular weight from the condensation of metal salts of the chloroacetylhydroxy acid.

2.2. The new synthesis avoids the occurrence of transesterification reactions and allows obtaining samples with regular sequence and high crystallinity.

2.3. Poly[Glc-alt-6HH] has a glass transition temperature intermediate between those found in the corresponding homopolymers, whereas the melting point is low and similar to that of polycaprolactone. The polymer has a high thermal stability, the temperature at which decomposition starts being clearly higher than both the reaction and melting temperatures.

3.1. Crystallization of poly[4Hb-alt-Glc] from the melt renders different types of spherulites depending on the crystallization temperature. Maltese cross spherulites with
a fibrillar texture and negative birefringence, or ringed spherulites with positive birefringence, could be obtained at high and low supercoolings, respectively.

3.2. A regime III to regime II transition is detected with the Lauritzen and Hoffman analysis of spherulitic growth rate data. This transition can be correlated with the observed morphological changes.

3.3. Calorimetric studies point out to the existence of two crystallization regimes with secondary nucleation constants similar to those deduced from optical microscopy experiments. The values of the Avrami exponent for isothermal crystallization range between 1.9 and 2.9, suggesting heterogeneous nucleation and three-dimensional spherulitic growth in agreement with optical microscopy observations.

3.4. The melting behaviour of the two kinds of spherulites is quite different. Thus, fibrillar spherulites show multiple melting peaks due to reorganization during heating, whereas the ringed spherulites melt in a single peak, that is, lamellar recrystallization was not detected.

4.1. Nonisothermal crystallization experiments performed at different cooling rates allow the spherulitic growth rate to be determined over a large temperature range by means of optical microscopy. Analysis of the experimental data with the Hoffman-Lauritzen theory allows determining a regime II-III transition, which is in full agreement with data obtained from isothermal experiments. The spherulitic morphology clearly changes according to the crystallization regime and the optical birefringence.

4.2. DSC studies reveal that a lamellar reorganization takes place at some degrees before fusion. Avrami analyses of the glass and melt nonisothermal crystallization give rise to apparent exponents for primary crystallization, which are higher than those previously evaluated from isothermal experiments. However, more reliable exponents can be obtained by the Cazé methodology. In this case, exponents become close to 2.5 and suggest a spherulitic growth with heterogeneous nucleation.

4.3. An isoconversional approach allows the temperature dependence of the effective activation energy for both cold and hot nonisothermal crystallization to be estimated.
V. Conclusions

5.1. The simultaneous SAXS/WAXD experiments performed with poly[4Hb-alt-Glc] show that the nonisothermal crystallization from the melt leads to the simultaneous appearance of the crystalline and the long period peaks. During all the different assayed thermal treatments the spacing of crystalline reflections remains practically constant as expected for a single crystalline structure.

5.2. Synchrotron studies reveal that a lamellar reorganization takes place at some degrees before fusion. The SAXS profiles indicate that the long period increases during this reorganization process from an initial value close to 8.4 nm until approximately 10.9 nm, whereas the WAXD curves allow estimating a maximum degree of crystallinity, between 30-40 % depending on the sample preparation. This crystallinity is reached at the end of the reorganization process.

5.3. Poly[4Hb-alt-Glc] crystallizes according to an orthorhombic unit cell of dimensions $a = 0.521$ nm, $b = 0.774$ nm and $c = 0.860$ nm. A deviation from the all-trans molecular conformation can be deduced taking into account the value of the $c$ parameter. A $P2_12_12_1$ space group appears compatible with the observed data. The unit cell contains two molecular segments with a statistic up and down distribution.

5.4. Single crystals of poly[4Hb-alt-Glc] can be obtained by isothermal crystallization at 57 ºC from dilute hexafluoroisopropanol solutions. Crystals have a lozenge morphology and appear as multilayered growths with both right- and left-handed screw dislocations. The angle between the {110} growth faces is in full agreement with the deduced cell dimensions.

5.5. A preliminary structural model has been built taking into account the X-ray and electron diffraction data. The calculated $hk0$ electron density map agrees with the postulated statistical arrangement of up and down molecular chains with a non planar conformation.

6.1. Isothermal hot crystallization of poly[Glc-alt-6HH] is characterized by an Avrami exponent that ranges between 2.4 and 2.9. An heterogeneous nucleation and a three-dimensional spherulitic growth is inferred in agreement also with optical microscopy
observations, which revealed the formation of small Maltese cross spherulites. These are athermally nucleated and have a fibrillar texture with negative birefringence.

6.2. Hot crystallizations experiments performed between 35 °C and 56 °C show a single crystallization regime when the Lauritzen and Hoffman treatment was applied.

6.3. SAXS and WAXD peaks appear simultaneously during isothermal crystallizations, indicating that nucleation and crystal growth is the predominant growth mechanism. Both, long period and lamellar thickness decrease with crystallization time and then reach a plateau value at the final stage of crystallization. Differences between SAXS and WAXD crystallinities suggest the existence of a significant amorphous fraction located between the lamellar stacks.

7.1. Degradation studies performed with poly[4Hb-alt-Glc] and poly[Glc-alt-6HH] confirm that the two samples can be degraded under both hydrolytic and enzymatic conditions.

7.2. Under enzymatic conditions poly[Glc-alt-6HH] degrades at higher rate than poly[4Hb-alt-Glc] because of the distinct binding capacities of the enzymes to the substrates.

7.3. A relative cytotoxic response was found for poly[4Hb-alt-Glc], which can be attributed to the 4-chlorobutyryl units released during degradation. Thus, polymers synthesized using chloroacetyl chloride appear advantageous due to the higher reactivity of the derived monomers, the lower ratio of terminal groups and the lower toxicity of the final polymer.

7.4. Cell proliferation and adhesion was observed in both polymer surfaces as well as the formation of a tissue-like structure maintained by numerous elements of cell interconnection similar to filopodies.

8.1. Poly[4Hb-alt-Glc] and poly[Glc-alt-6HH] have proved to be adequate for preparing microspheres with sustained release of hydrophobic drugs such as triclosan. The release
V. Conclusions

in a hydrophobic cell medium is well described by the Baker and Londsdale model, which is based on a diffusion process in spherical particles.

8.2. Degradation data allow release controlled by polymer erosion to be ruled out. The different release behaviour of the two studied polymers may reflect differences in porosity and hydrophobicity since both factors enhance the release from the hydroxybutyric acid derivative.

8.3. Triclosan has a good affinity with the two studied polymer matrices and seems to be present in both amorphous and crystalline phases. The prepared charged microspheres have a high crystallinity, which can hinder drug release.

8.4. The two copolyesters show very different thermal properties, a feature that may enhance the interest in this family of materials.

9.1. Butane-1,4-diyl bis(chloroacetate) and butane-1,4-diyl bis(bromoacetate) have a practically identical structure. Both crystallize according to the monoclinic system. The main difference corresponds to the expected slight increase (4 %) in the unit-cell volume of the bromo derivative. The two compounds crystallize according to a $P_{2_1}/c$ space group. Their packing is characterized by a network of weak intermolecular hydrogen bonds along a direction parallel to the crystallographic $b$ axis.

9.2. The compound $N,N'$-Butane-1,4-diylbis(bromoacetamide) crystallizes according to a $P_{2_1}/c$ space group. Its packing is characterized by the establishment of strong hydrogen bonds between amide groups along a single direction.

10.1. Morpholine-2,5-dione adopts a distorted boat conformation and crystallizes according to a $P_{2_1}/n$ space group. The molecular packing is stabilized by the establishment of strong intermolecular $\text{NH}^\cdots\text{OC}$ hydrogen bonds, which give rise to centrosymmetric dimmers, and a network of weak $\text{CH}_2^\cdots\text{OC}$ hydrogen bonds, where each dimmer interacts with eight neighbouring morpholine-2,5-dione rings.