APPLICATION OF TIME-RESOLVED X-RAY TO STUDY THE CRYSTALLIZATION PROCESS OF TWO NEW BIODEGRADABLE POLYMERS.

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Object of the study

Our research group develops new polymers with applications in the biomedical field. This work involves different steps: a) Synthesis of new polyesters and poly(ester amide)s; b) Characterization of main physicochemical properties; c) Study of crystallization processes; d) Determination of the crystalline structure by means of X-ray and electron diffraction; and e) Study of applications as drug delivery systems. This research has been supported by CICYT grants MAT2003-01004 and MAT2006-02406.
The main purpose of the performed synchrotron experiments was to get insight the crystallization behaviour of two similar polymers that belong to the indicated polyester and poly(ester amide) families:

a) Poly(gly-amh): -[$OCH_2CONH(CH_2)_5CO]_n$-
b) Poly(glc-cap): -[$OCH_2COO(CH_2)_5CO]_n$-

Both polymers can be easily obtained by a new synthetic method that has been patented by our group which is based on a thermal polycondensation with formation of metal halide salts as a driving force. Samples are biodegradable, being degradation rate and thermal properties clearly different.
Crystallization behavior of polymers is usually studied by means of DSC and optical microscopy (HSOM) in both isothermal and nonisothermal conditions. However, time resolved SAXS/WAXD experiments are nowadays also employed since information on the lamellar structure, and on the amorphous and the crystalline phases can be easily obtained (e.g. Polymer 2005, 46, 9831-9839; Eur. Polym J. 2003, 39, 2091-2098; Polymer 2001, 42, 8965-8973).
The study of poly(gly-amh) by the above indicated DSC and HSOM methodologies was performed by our group (Eur. Polym J. 2006, 42, 1595-1608). It was stated that cystallization from the melt state (hot-crystallization) can be well evaluated in the 115-135 ºC temperature range, whereas crystallization from quenched samples (cold-crystallization) can be experimentally measured in the 30-60 ºC temperature range. Studies on poly(glc-cap) are in a more preliminary state, but the results of the hot-crystallization experiments performed between 30 and 55 ºC indicate a complex melting behavior after crystallization, two melting peaks being usually observed.

Methodology

The SAXS detector was placed to collect reflections close to 10 nm that are associated to the lamellar spacing. WAXD detector was only able to collect a restricted reciprocal space (0.6-0.3 nm). This zone was enough to get information about the molecular chain packing which is defined by strong 110 and 020 reflections around 0.44-0.36 nm. However, the 00*l* reflections that give a direct measure of the chain repeat period could not be observed. Diffraction profiles were corrected considering the empty sample background in order to avoid an overestimation of the amorphous content.
SAXS experiments allow to determine the lamellar long period from the position of the peak maximum (L_B) in Lorentz corrected patterns as well as from the first maximum (L_γ) of the normalized one-dimensional correlation function. This is evaluated after

correction for background SAXS intensity and considering the Porod's law. Analysis of the correlation function renders also the degree of crystallinity within the stacks of lamella, X_c^{SAXS}, the crystalline lamellar, l_c, and the amorphous layer thickness, l_a, according to the relationships:

$$X_c^{SAXS}\,(1-X_c^{SAXS})\,L_\gamma = A$$
$$X_c^{SAXS}\,L_\gamma = l_c$$
$$L_\gamma = l_c + l_a$$

where A corresponds to the first zero value of the correlation function.
In order to study in detail the structural changes during crystallization, the standard Gaussian peak-fitting routine can be applied in WAXD spectra. In this way, deconvolution of spectra can be performed and consequently broad reflections associated to the amorphous phase can be well differentiated from the Bragg reflections corresponding to the crystalline phase. Domain dimensions in the directions perpendicular to the (*hkl*) planes, L_{hkl}, can be easily obtained from the Scherrer's formula:

$$L_{hkl} = 1 / (\delta_{hkl})$$

where δ_{hkl} is the full width at half maximum of the corresponding peak.
Integration of the area corresponding to the crystalline peaks at different stages of crystallization should allow to get a relative degree of crystallinity when the value obtained at the end of the crystallization process is considered. Values can be subjected to an Avrami analysis and compared with the results attained from DSC studies. Finally, synchrotron experiments should be useful to associate the change of crystallization regimes or to relate the complex melting behavior with a polymorphism induced by temperature.

Results of the studied systems

We had some experimental limitations since a cryogenic Linkam holder was not available and consequently cold-crystallizations from quenched samples could not be performed. Furthermore, the low crystallization temperature of poly(glc-cap) samples caused some problems that fortunately were solved by using a water refrigeration circuit. Spectra corresponding to the hot-crystallizations of both proposed polymers could be well recorded. At this moment we are finishing with processing the collected data.
Two different samples (PE 88: -$[O(CH_2)_8OCO(CH_2)_6CO]_n$- and PADAS: -$[NHCH(CH_3)COO(CH_2)_{12}OCOCH(CH_3)NHCO(CH_2)_8CO]_n$-) were also studied to take maximum profit of the beam line. In addition, spectra corresponding to samples used as drug delivery systems were also recorded.

a) Poly(glc-cap): Isothermal hot-crystallizations were studied at temperatures of 30, 35, 40, 45, 50 and 55 ºC. The crystallization process took place between 15 and 150 minutes depending on the crystallization temperature. Both SAXS and WAXD spectra could be well recorded and appeared suitable for performing an accurate analysis of the crystallization process. In this way, the lamellar long period was clearly observed around 9.0 nm. WAXD patterns were indicative of a single crystalline structure and a crystalline domain that clearly increases with the crystallization time. Data acquired at the different crystallization temperatures can be subjected to a typical kinetic analysis and compared with DSC and HSOM data to perform a suitable publication.

b) Poly(glc-amh): Isothermal hot-crystallizations have been studied at temperatures of 115, 120, 125, 130, 135, 140, 145, 150 and 160 ºC. Processes took place in a wide time interval that varies from 2 minutes at the lowest temperature to 2.5 hours at the highest temperature. Spectra corresponding to posterior heating runs (melting behavior) were also recorded, a recrystallization just before fusion being in some cases detected. WAXD patterns were in full agreement with the structure previously deduced (J. Polym Sci. Part B: Polym. Phys, in press) that was characterized by strong 020 and 110 reflections at 0.437 and 0.418 nm, respectively. Additionally, synchrotron spectra showed a splitting of the first reflection after recrystallization. SAXS analysis appeared suitable although the long period (11 nm) was in this case observed very close to the beam stop. Results of the experiments seem to be suitable for a publication that completes the previous published works concerning DSC experiments and structure analysis.

c) PE 88: Isothermal experiments have been performed at 60, 65 and 70 ºC. Well developed peaks were clearly observed in both SAXS and WAXD spectra and appear suitable for a posterior analysis. Crystallizations took always place in a very narrow time interval, although the induction period clearly increased when temperature was lowered. Nonisothermal experiments were also carried out using cooling runs of 8, 10 and 15 ºC/min. A detailed hot crystallization study appears suitable considering both analyses. A slight change during heating of WAXD spacings is also noticeable and merits a posterior discussion.

d) PADAS: A recrystallization process was detected during heating scans. WAXD spectra indicated that only the reflections associated to the molecular packing were affected. Lamellar long spacing and chain repeat reflections could not be observed. Results may be interesting in order to understand the complex melting behavior of this sample but are insufficient to perform a kinetic analysis due to the very low degree of crystallinity that could be attained. In fact, the lateral methyl groups of the polymer chain clearly hinder the crystallization process.

e) Drug release: Microspheres of polyester derived from glycolic acid were charged with a triclosan drug and then exposed to a phosphate medium. WAXD spectra were obtained from the charged sample and compared with those corresponding to the polymer and the triclosan. In this case, synchrotron spectra were taken in order to verify that microcrystals of the drug did not grow inside the microspheres used in the release. The data should appear as a minor point in a general drug release work.