STUDY OF STRUCTURAL MODIFICATIONS IN POLY(L-LACTIDE) INDUCED BY HIGH-ENERGY RADIATION

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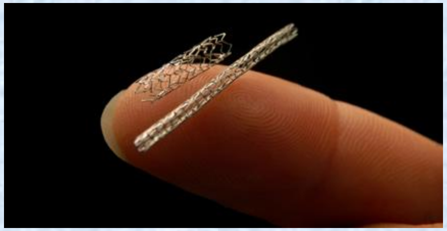
Coronary Heart Disease (CHD)

- Coronary heart disease is the leading cause of death worldwide.

- Plaque in blood accumulates against the walls of the coronary artery, which returns oxygen rich blood from lungs to heart. If left untreated, it could lead to blood clots/heart attacks.

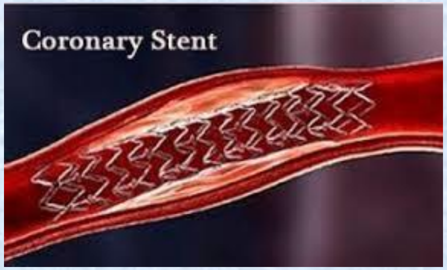
CHD treatment options:

- Surgery (Bypass, High Risk)
- Medication treatment (Less Effective)
- Angioplasty



Angioplasty:

Minimally invasive procedure; heart stents, usually made of a metal mesh, are inserted into the body thus enabling the blood flow increase.



Possible problems with metalic and metal-mesh stents:

- Effective, but often delay natural healing process of the arteries.
- If metal mesh is not placed in suitably, plaque may build up on the stent, eventually killing 1 in 200 patients in procedure.

Possible solution:

- The use of a biodegradable polymer drug eluting stent (DES) mainly produced out of **biodegradabile polylactide**. These stents are designed to completely dissolve into the bloodstream within 2-3 years after procedure (no need for additional surgical procedure) and are found to be safer than metal stents (the risk of stent thrombosis and heart attack are significantly reduced).

Abbott

The sterility of the product - one of the **main concerns** with respect to the successful application of implanted biomaterial

- Several different sterilization procedures were proposed.

- In the case of polymer implants, their high sensitivity to heat, moisture and radiation should be taken into account when a particular method is applied.

- Amongst conventional methods, dry and moist heat sterilizations are not suitable for thermosensitive polymers as they lead to thermal degradation and structural changes.

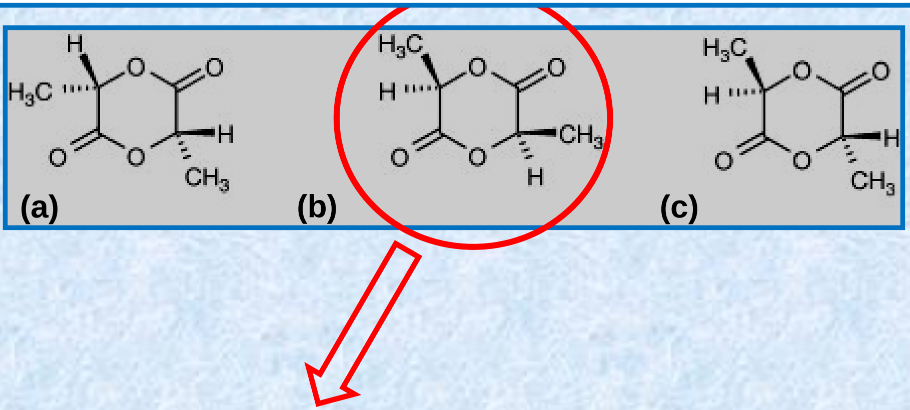
- Ethylene oxide (EO) is broadly used for polymeric devices although including drawbacks such as its toxicity, changes in morphology and the presence of gas residues, which requires long aeration time.

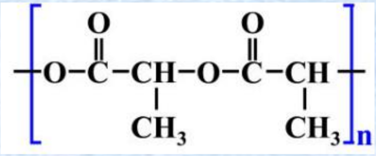
- Contrary, due to the excellent penetration characteristics of **high-energy ionizing radiation** (in the form of **gamma radiation** from a suitable radioisotopic source such as ^{60}Co or of **electrons** energized by a suitable electron accelerator). **Radiation sterilization eliminates problems which may appear with other methods** like high temperature, need for quarantine, problems associated with residuals and EO gas penetration, uniformity of sterilization etc. Problems with the radiation sometimes evolve as a result of its damaging effects on materials.

Experimental: Materials

Polylactide (PLA): linear thermoplastic aliphatic polyester derived from renewable resources such as corn starch. It is extensively employed as a biomaterial in numerous applications including tissue engineering three-dimensional scaffolds, implantable medical devices and carriers in controlled drug delivery systems, to the environmentally friendly packaging ones. Degradation of this **biocompatible** and **biodegradable** polymer lead to non-toxic products as it enters the Kreb's cycle inside the human body and is eventually removed as **carbon dioxide** and **water**.

PLA exists in two stereo-isomeric forms: (a) D-PLA (PDLA) and (b) L-PLA (PLLA), and (c) a mixture of D- and L-lactic acid also exists as D,L-PLA (PDLLA)





The polymers, which are **derived from** optically active **D and L monomers**, are **semi-crystalline** while the optically inactive **D,L-PLA is amorphous**. Generally, L-PLA is preferred in applications where high mechanical strength and toughness are required, e.g. sutures and orthopedic devices. In contrast, due to the amorphous nature of D,L-PLA, it is usually considered for applications such as drug delivery systems, as it is important to have a homogeneous dispersion of the active species within a monophasic matrix.

Polymer obtained from L-lactide - PLLA was used in this study: Commercial granular poly L-lactide (Fluka, Germany; M_w=100,000, M_n=60,000)

Experimental methods:

1. Scanning electronic microscopy (SEM)
2. Gel permeation chromatography (GPC)
3. Differential scanning calorimetry (DSC)
4. Wide-angle X-ray diffraction method (WAXD)
5. Fourier transform infrared (FTIR) spectroscopy
6. Electron spin resonance (ESR) spectroscopy

Results and discussion

Scanning electronic microscopy (SEM)

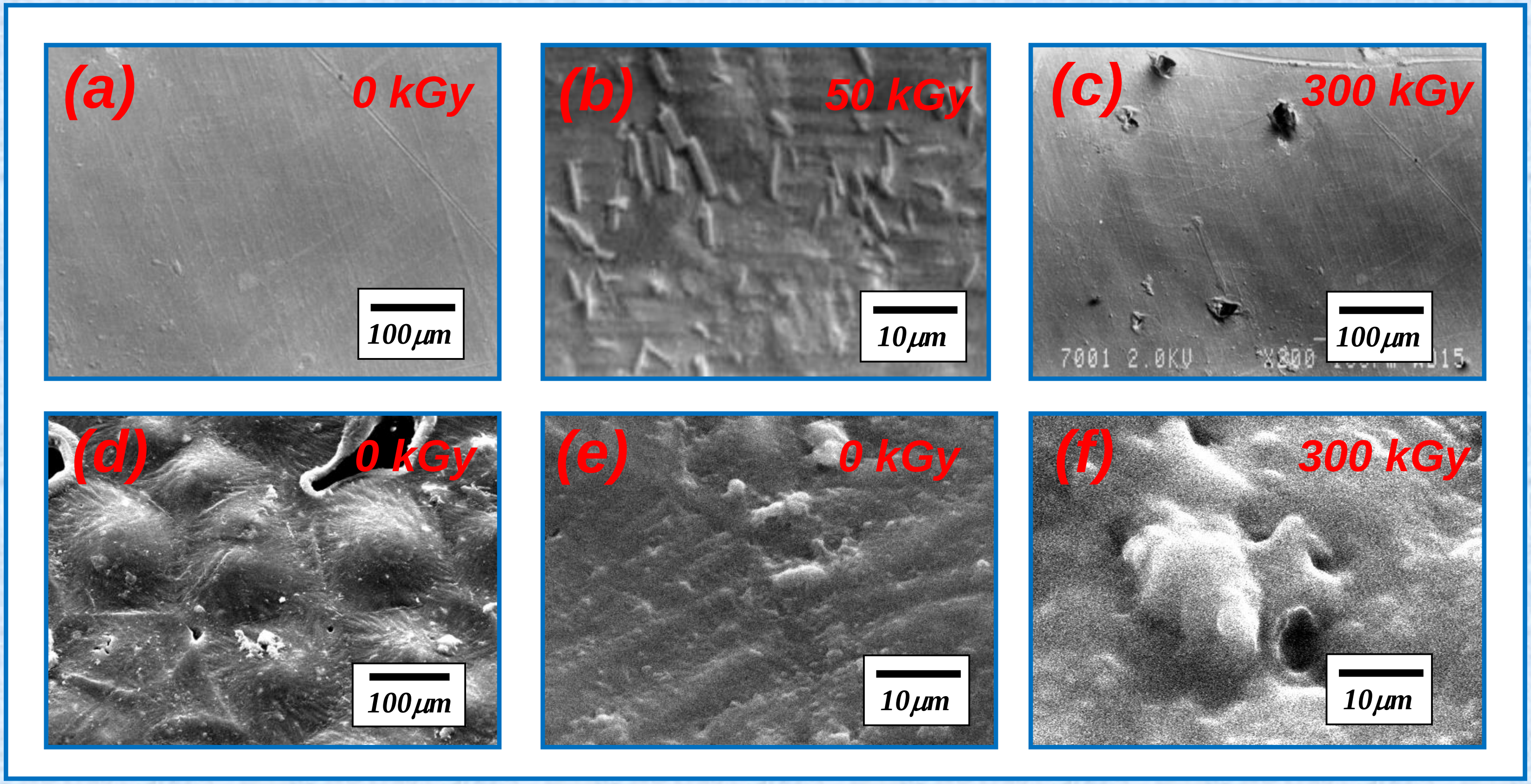


Figure 1. SEM images of (un)irradiated samples obtained by: **(a-c)** quenching from the isotropic melt in the ice-water mixture and **(d-f)** slow cooling to the room temperature keeping the sample between the press platens;

Gel permeation chromatography (GPC)

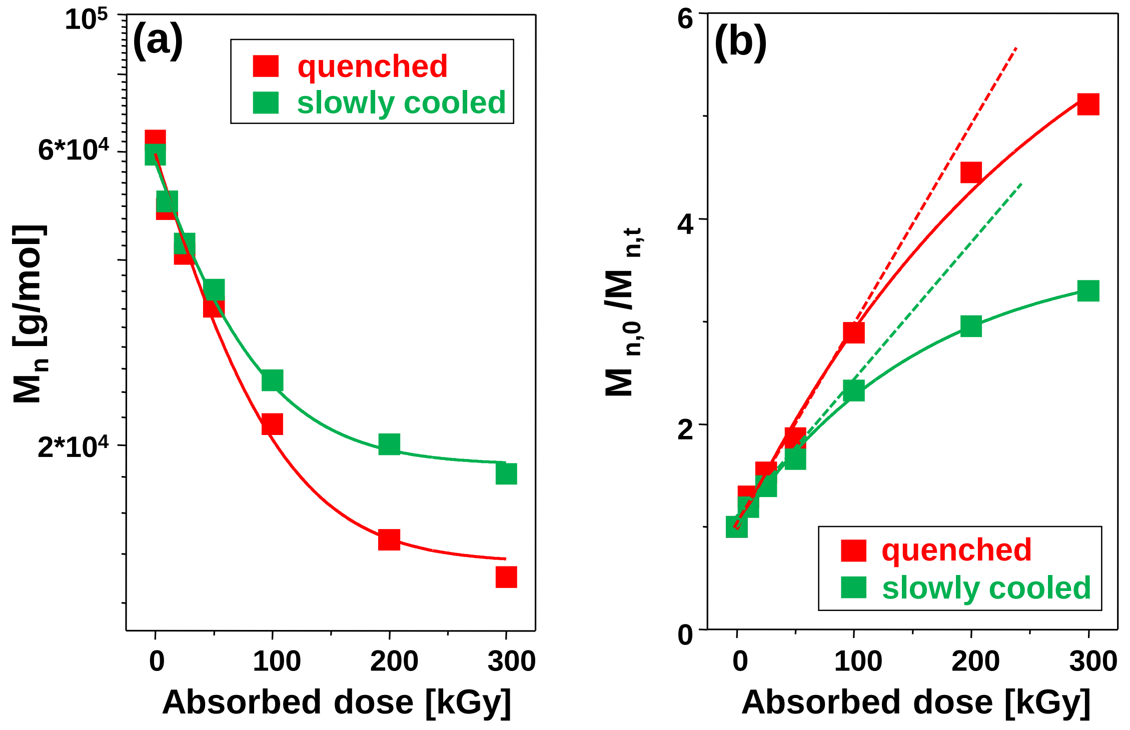


Figure 2. (a) Number average molecular weight (M_n) as a function of absorbed dose for quenched and slowly cooled samples and (b) $M_{n,0}/M_{n,t}$ ratio as a function of absorbed dose, where $M_{n,0}$ and $M_{n,t}$ are molecular weights of the unirradiated and irradiated samples, respectively.

Differential scanning calorimetry (DSC)

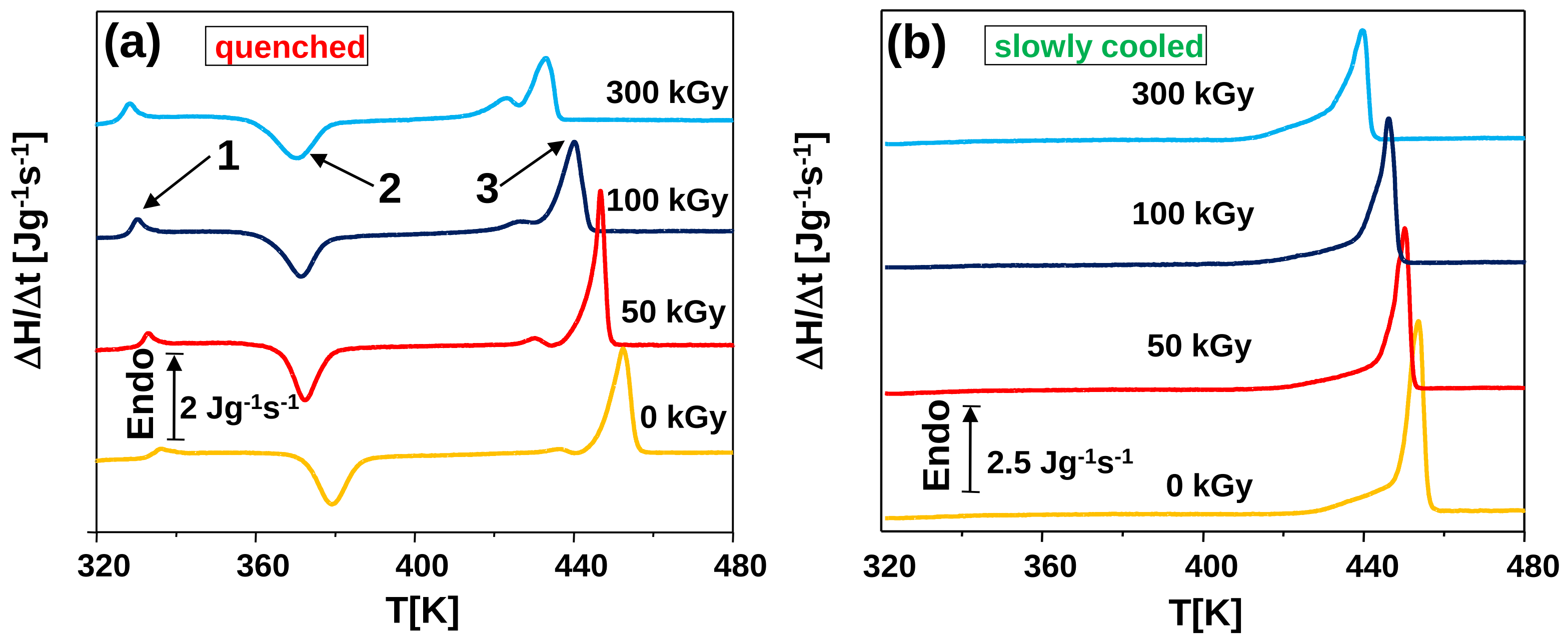


Figure 3. DSC heating thermograms of **(a)** quenched and **(b)** slowly cooled samples for various absorbed doses.

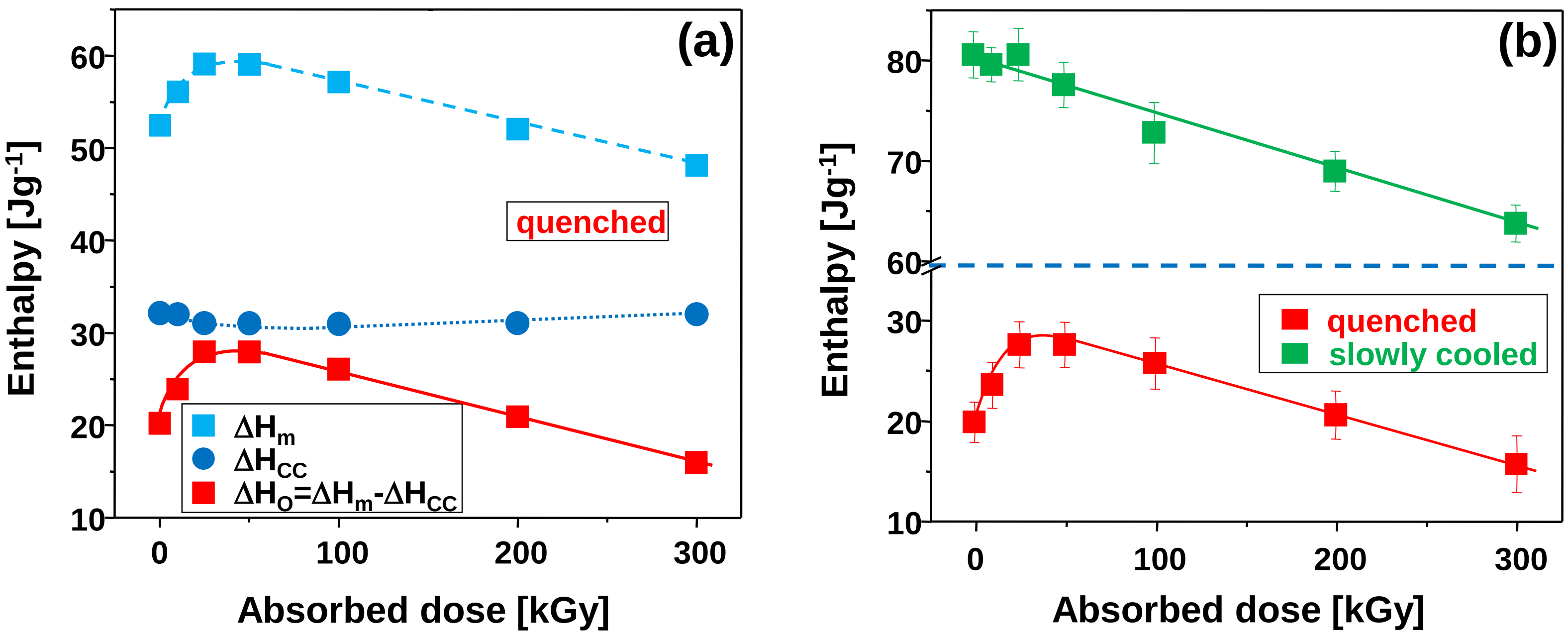


Figure 4. (a) Melting (ΔH_m) and cold crystallization (ΔH_{cc}) enthalpy and $\Delta H_o = \Delta H_m - \Delta H_{cc}$ of quenched samples as a function of absorbed dose and **(b)** ΔH_0 enthalpy of the quenched and slowly cooled samples.

Wide-angle X-ray diffraction method (WAXD)

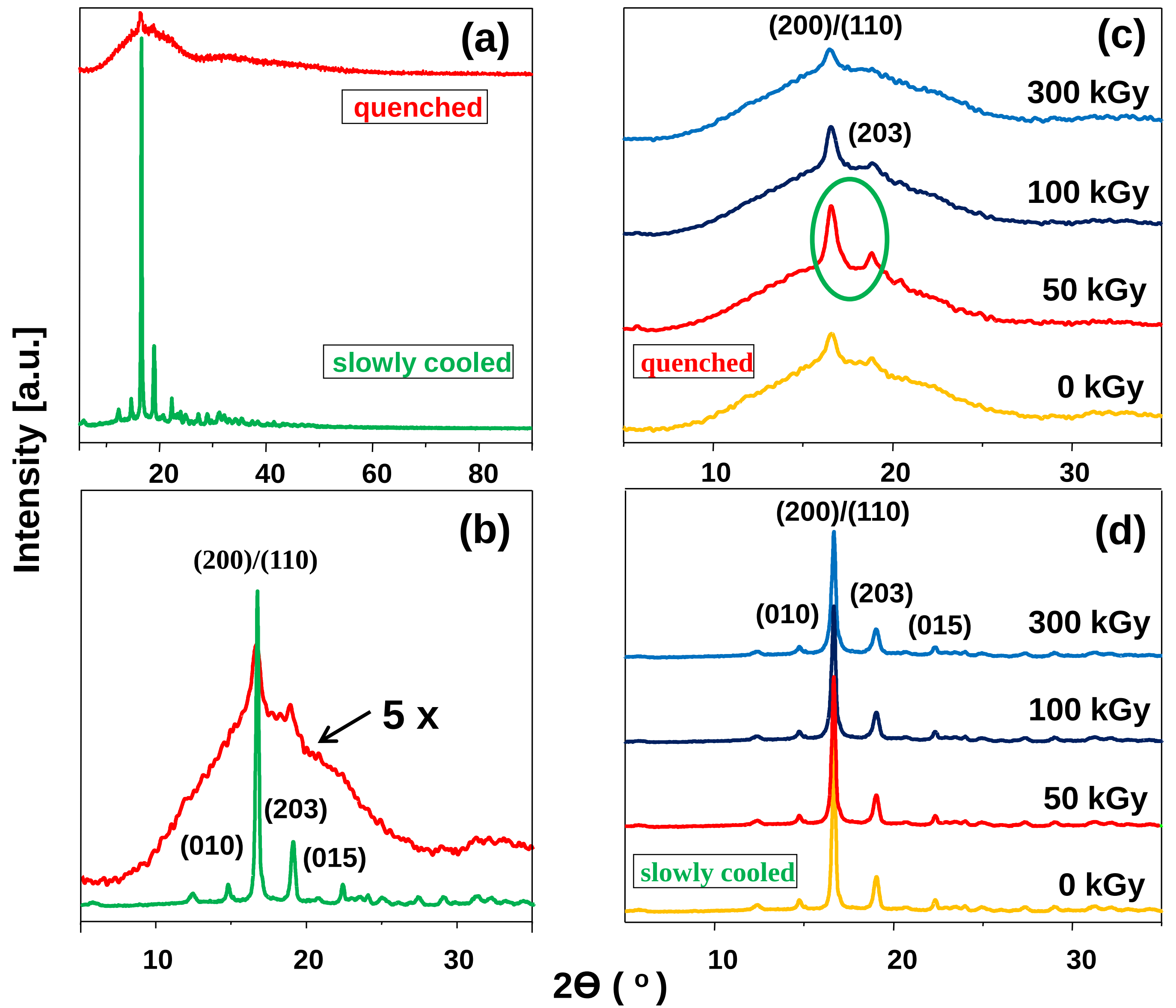
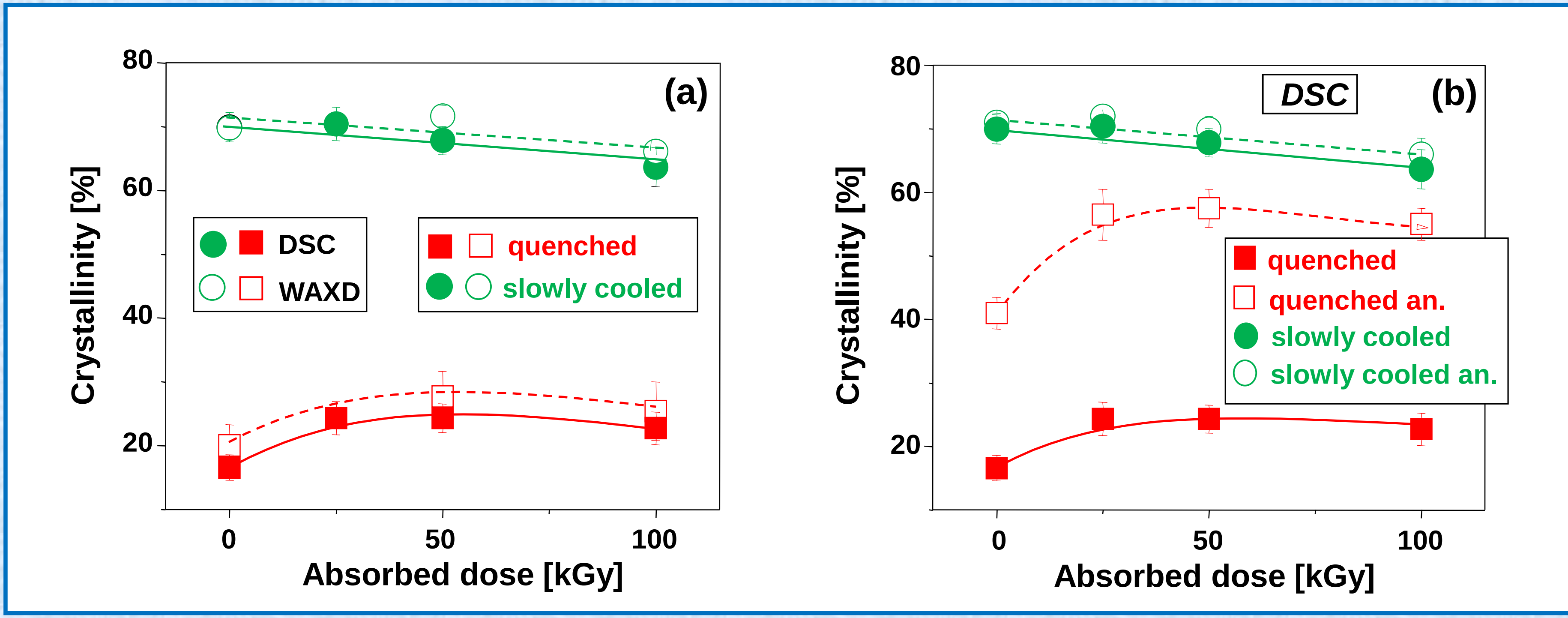


Figure 5. WAXD spectra of unirradiated quenched and slowly cooled samples in the 2θ range: **(a)** 5°-90° and **(b)** 5°-35° (quenched samples are presented magnified for clarity); the evolution of WAXD spectra with absorbed dose for **(c)** quenched and **(d)** slowly cooled samples.



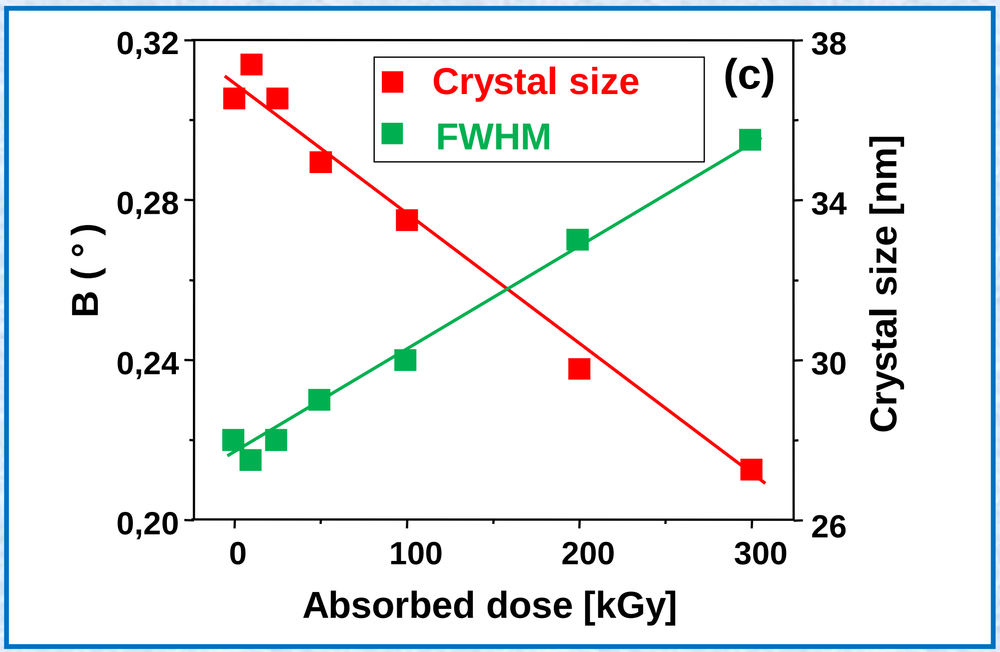


Figure 6. Crystallinity of: **(a)** quenched and slowly cooled samples obtained by DSC and WAXD measurements, **(b)** quenched and slowly cooled (un)annealed samples (in air, at 80 °C for 2 h after irradiation); **(c)** FWHM (B) and crystal size as functions of absorbed dose.

Fourier transform infrared (FTIR) spectroscopy

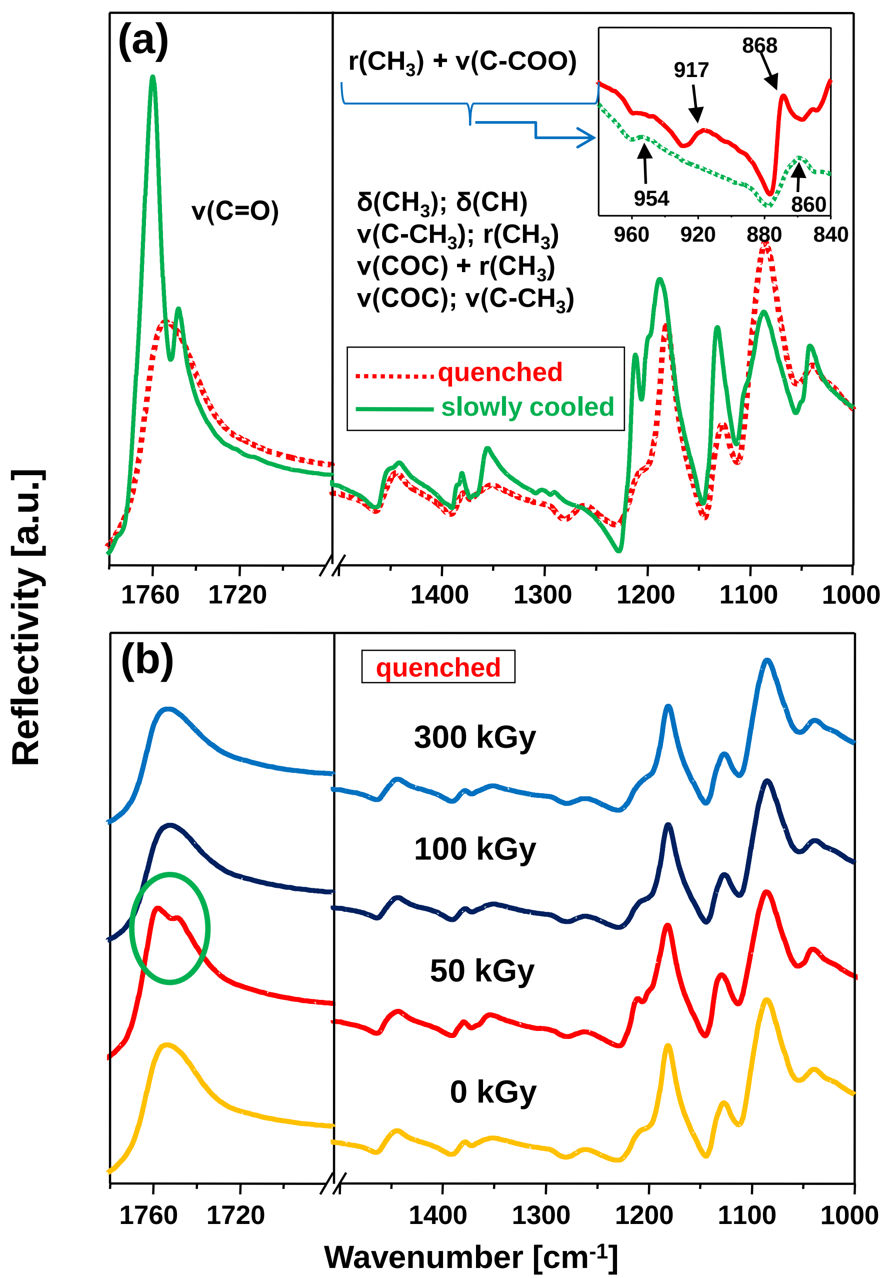


Figure 7. FTIR spectra of **(a)** unirradiated quenched and slowly cooled samples and **(b)** quenched samples for different absorbed doses.

Electron spin resonance (ESR) spectroscopy

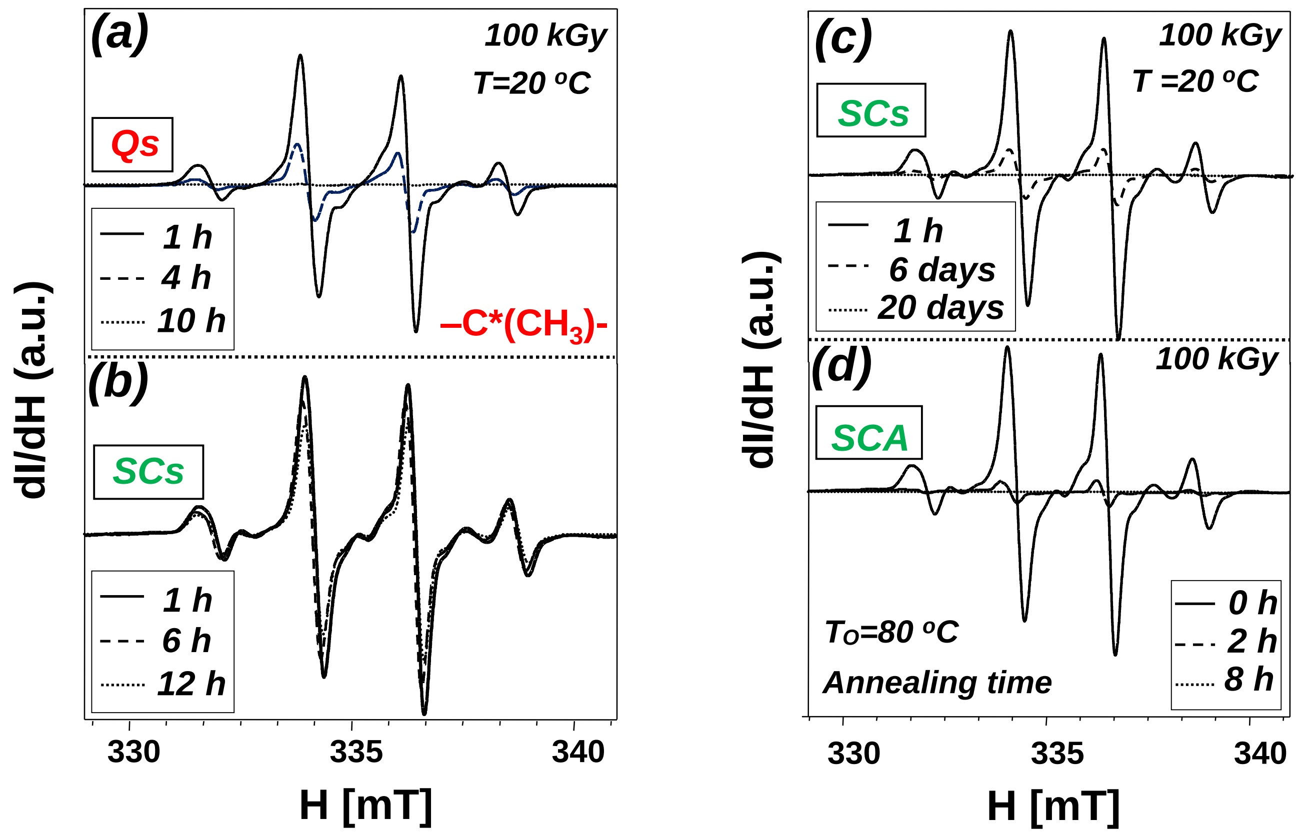


Figure 8. (a) ESR spectra of quenched samples (Qs); ESR spectra of slowly cooled samples (SCs) for **(b)** short and **(c)** prolonged period of time; **(d)** ESR spectra of SCs annealed (SCA) for different periods of time

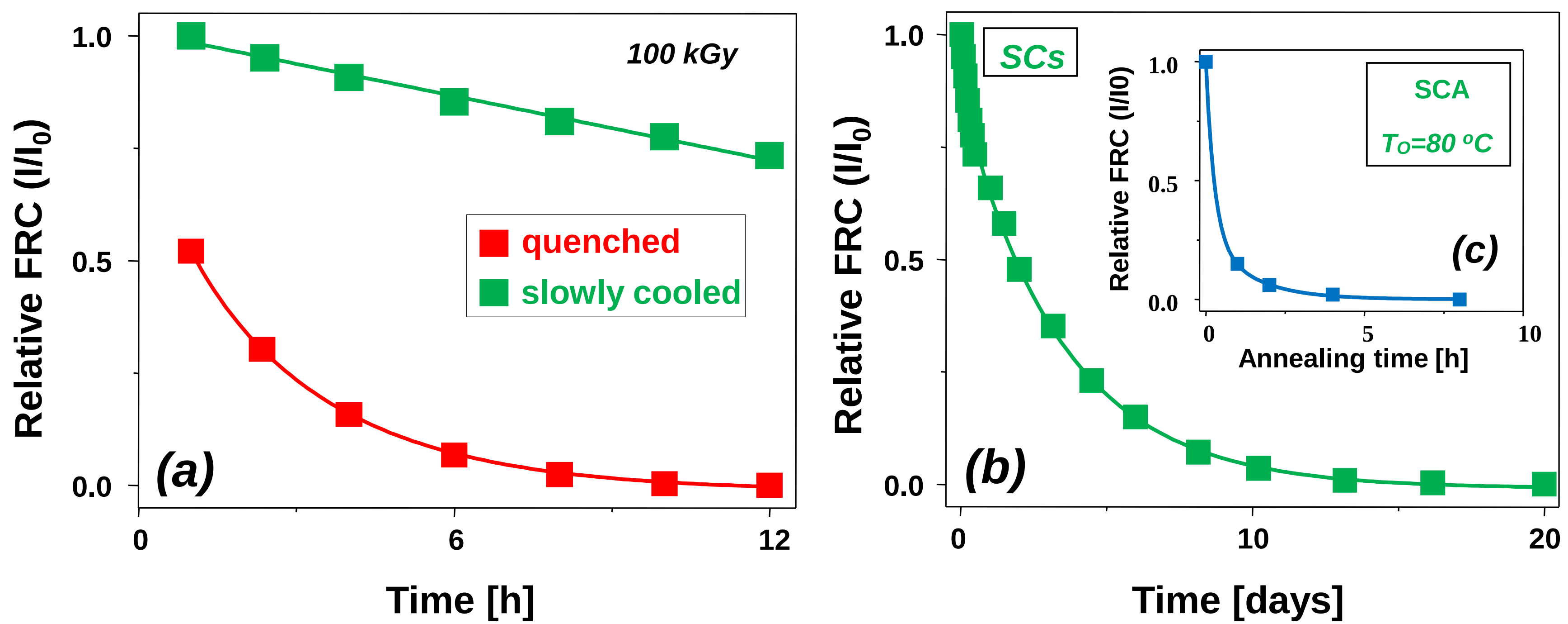


Figure 9. Relative free radical concentration (FRC) as a function of **(a)** short and **(b)** prolonged periods of time; **(c)** Relative FRC versus annealing time.

CONCLUSIONS:

- Depending on the initial preparation conditions, the radiation-induced changes in the structure and properties of PLLA, as well as the evolution of free radicals, differ significantly.

- The low crystalline samples are found to be initially more susceptible to the gamma radiation than the high crystalline ones.

- On the other hand, due to the presence of long-lived free radicals, the high crystalline samples are more prone to the post-irradiation degradation. In addition, the applied annealing treatment substantially reduces the concentration of long-lived radicals, but can also induce additional crystallisation.

- As the gamma radiation leads to quite foreseeable alterations of thermal and morphological properties of PLLA, **the radiation processing can be applied** with the aim of **simultaneous tailoring of required functionality** (e.g. the rate of hydrolytic degradation) **and achieving the sterility of final products**, especially for low sterilization doses where the observed changes are small and tolerable (up to 25 kGy in most circumstances).

Thank you for your attention!

Questions???