Radiation Effects on Polymer Materials Commonly Used in Medical Devices

Report of the 1st RCM for CRP F23035

Virtual

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1. INTRODUCTION

Polymers are widespread in healthcare products, such as single-use medical devices, implants, drug delivery and packaging systems, because of their versatility and economic advantages, including low weight and ability to withstand sterilization processes. Around 50 percent of all single-use polymer-based medical devices manufactured worldwide are sterilized using ionizing radiation from two main sources: the cobalt-60 radioisotope (gamma irradiation), or an electron accelerator, using either e-beams or, less commonly, X-rays. While all the above irradiation modalities are recognized in the applicable ISO standards, gamma irradiation dominates the radiation sterilization market and accelerator-based sterilization methods are only utilized for around10% of products.

There are multiple reasons for the historical underutilization of accelerator technologies for sterilization, and the lack of knowledge about the radiation effects on polymers for e-beam and X-ray is one of them. To address this issue and fill the knowledge gap, the IAEA launched the Coordinated Research Project F23035. Its goal is to better understand the mechanisms underlying radiation effects from gamma, e-beam, and X-ray irradiation of polymers and to improve the legislative landscape and standards related to the accelerator-based sterilization of medical products and devices, which in turn will help increase access to accelerator-based sterilization.

This meeting was the first Research Coordination Meeting of the participants of the CRP F23035 “Radiation Effects on Polymer Materials Commonly Used in Medical Devices”.

2. PRESENTATIONS AND DISCUSSIONS

Seventeen teams from thirteen countries are participating in this CRP, and sixteen of them were able to attend this virtual RCM (see Annex I). During the first three days, the teams introduced their research groups, facilities, and equipment, they presented their work plans relevant to the CRP, and they showed preliminary results. Each presentation was followed by questions and suggestions from other teams. The last two days were dedicated to the discussion of important technical issues to consider and the following steps of the project (see Annex II).

Different teams explored different products and used different irradiation modalities as well as different equipment for pre- and post-irradiation analysis. To better understand opportunities for potential collaborations between the teams, two matrices were created: one to compare the polymers and products under investigation (see Annex III) and one to compare the facilities and expertise of each team (see Annex IV). These matrices describe not only the equipment used for experimental work, but also expertise in Monte Carlo simulations and modeling of dose rates and overall doses within the irradiated products. In addition, they include the teams’ planned analysis (functionality, physical changes, mechanical changes, etc), dosimetry standards and interest in the intercomparison studies.

It was decided to store the interaction matrix in the shared space (the DIIF Nucleus platform[1]) and update it periodically to monitor the CRP progress and facilitate interaction. The same platform was

[1] https://nucleus.iaea.org/sites/diif/Pages/Home.aspx

proposed to be used to deposit relevant publications from the participants, IAEA, and other research groups and organizations.

The CRP assumes periodic meetings; the tentative project schedule includes the 2nd RCM taking place in Winter 2022/2023, the 3rd and final RCM taking place in Fall 2024, and a TM taking place in Fall 2023. While the RCMs are planned to take place in Vienna, several participants tentatively proposed that they would host the TM at their facilities. The advantage would be to provide a tour of irradiation facilities and organize hands-on activities using various analytical tools and equipment. In addition to the planned meetings involving all the CRP participants, it was proposed to use the upcoming ICARST 2022 meeting[2] to gather the participants and discuss the progress made, possibly in smaller groups. Additionally, it was suggested to the IAEA staff to consider the opportunity to organize a side event during the ICARST. A short 1-1.5 hours event focused on radiation effects on polymeric materials would be of interest not only to the CRP participants, but to other attendees.

As the purpose of this project is to compare different irradiation modalities, it is important to ensure the use of identical methodology and practices for dosimetry. These issues were discussed in detail and an interlaboratory comparison of the dosimetry was proposed to be carried out. Such a comparison would help ensure that the dosimetry is done properly and allow awareness of various impacting/influencing factors, as well as dosimetry methodology improvements for many teams. Participants from the Aerial facility agreed to lead this activity pending the budget discussion.

A separate subject actively discussed involved the comparison of peak or instantaneous dose rate to average dose rate. While this is not an issue for gamma irradiation, it can be a great concern for electron beam or x-ray irradiation due to the pulsed structure of the electron beam and, in some cases, beam scanning/rastering. It was agreed that for the sake of meaningful comparison, it is important to use consistent definitions of the total dose, average dose, peak dose, etc, defined from the time structure of the electron beam and its motion. In addition, knowing the time structure of the beam is important to compare with the typical lifetime of oxydation kinetics (seconds) and radical formation (nanoseconds). In most cases, polymers are semi-crystalline, resulting in complex kinetics of long-lived free radicals, which is a separate and complicated situation.

Several other technical issues were brought up by the participants. For example, it was emphasized that special attention must be paid to the mechanical and thermal history and formulation of the polymers. Knowledge of additives in commercial polymers is also very important and would also need to be as complete as possible for each product. A special case when sterilization and synthesis occur simultaneously requires a separate discussion. For post-irradiation analysis, not only surface effects need to be considered, but also volume ones, since chemical reactions at the surface can be greatly influenced by the atmosphere in which irradiation occurs and may differ from the ones in the volume/bulk in quantity or type. Timing of the post-irradiation analysis was also discussed in detail. As the thermal and mechanical properties of the irradiated product change over time, investigating the ageing effects and the shelf life of the irradiated products is critical. Moreover, temperature, humidity, and other storage conditions can also affect the ageing of the irradiated products.

[2] https://www.iaea.org/events/icarst-2022

It is clear that irradiation affects the polymers, but at which point do the changes induced in the material cause the final product to be functionally unacceptable? Change in some polymer properties (especially mechanical) can be easily quantified – for example, the threshold of 50% loss of mechanical stress at a certain dose (D_{50}) could define when the changes are unacceptable. Other parameters cannot be quantified that easily. In addition, some functional properties may not be critical for applications and uses of a particular product.

Given the breadth of the project, the variety of polymers and products to investigate, use of several irradiation modalities, and the numerous post-irradiation analytical methods, it was proposed to prepare a publication to review the relevant studies performed up to date and to identify the gaps and means to fill them.

3. *CONCLUSIONS*

The 1st RCM was very successful and allowed the participants to become familiar with each other's work, as well as to identify the major technical challenges and important issues to be aware of during their research work. The following conclusions were reached by the participants:

1. Strong collaboration between participating institutes is vital for the successful progress of the CRP. A matrix summarizing each group's capabilities, facilities, expertise, etc. has been generated to aid in collaboration efforts. In addition to the already planned RCMs, it would be important to meet at the TM and use other opportunities, such as a side event at the upcoming ICARST 2022.
2. A dedicated shared space (for example the MS Teams folder, established during the 1st RCM, or the DIIF Portal) would be a useful online tool to exchange and centralize information and to share files between participating parties.
3. Following the same standards and using the same language and well-structured definitions is crucial and would define a baseline for comparisons. A list of established standards (e.g., ISO ASTM 31645-15) to be used in each case would be helpful. Moreover, an inter-laboratory comparison of the dosimetry (dose calibration and dose measurement) would be important to ensure the use of identical methodologies and dosimetry practices.
4. The effect of formulation, additives, and the manufacturing processing conditions (i.e., extrusion, molding) of polymeric materials are parameters to be considered, among others, when investigating the radiation effects on medical devices.
5. The applicability of the medical device, such as for treatment or diagnosis, as well as if there is intended internal or external use in the human body, either temporary or permanent, should be considered. Associated risk levels according to the device type are also relevant.

4. *RECOMMENDATIONS*

Based on the discussion among the participants of the 1st RCM of the CRP F23035 "Radiation Effects on Polymer Materials Commonly Used in Medical Devices" the following recommendations were made:

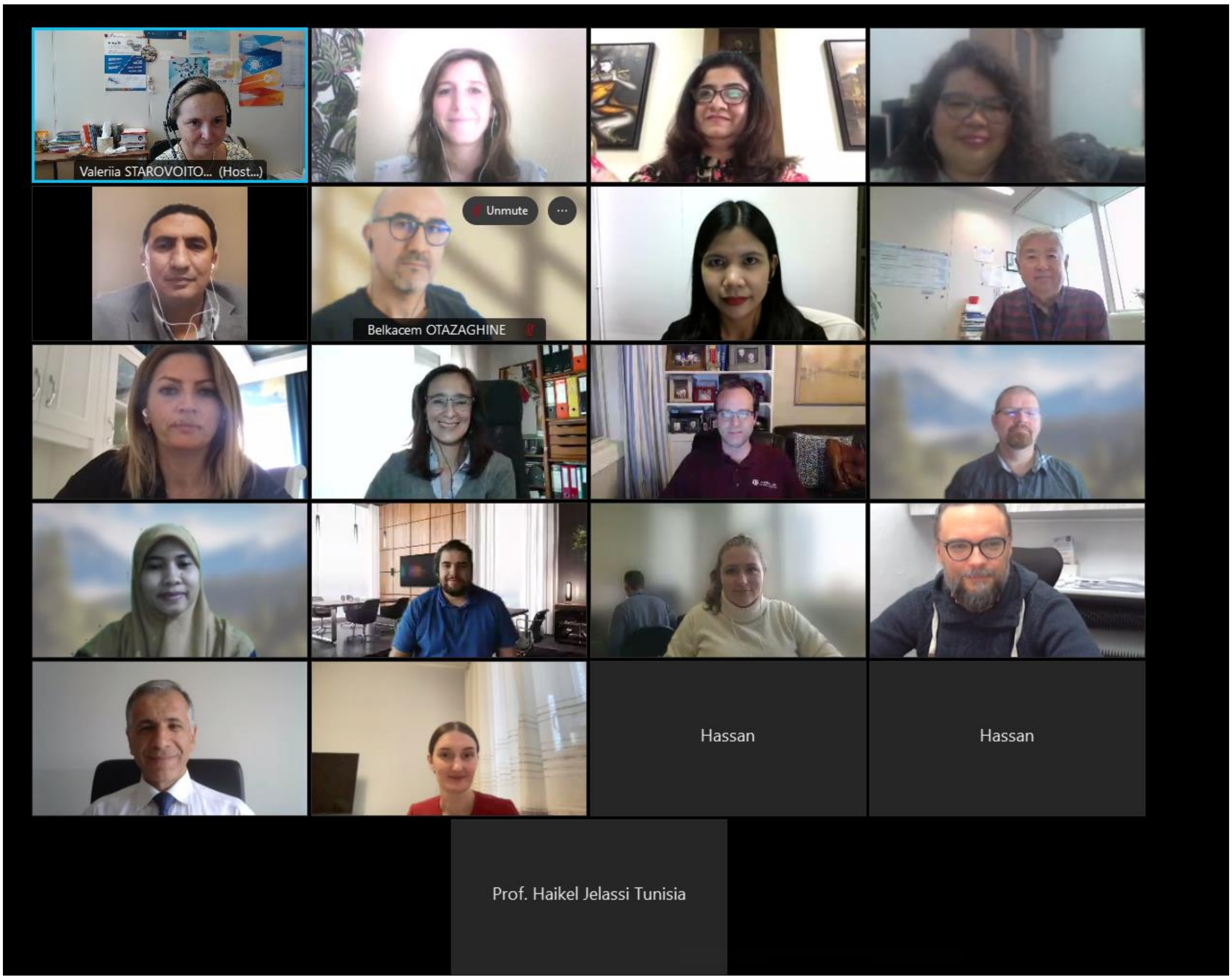
1. To assist in organizing an interlaboratory comparison of the dosimetry (together with Aerial, an IAEA Collaboration Centre)

2. To create a shared space (for example the MS Teams folder, established during the 1st RCM, or the DIIF Portal) dedicated to this CRP to be used as an online tool to exchange and centralize information and share files between participating parties.

3. To enhance the communication between the CRP participants by a) organizing a TM to be hosted by one of the CRP participants to provide a tour to irradiation facilities and organize hands-on activities using various analytical tools and equipment; b) organizing a side event during the ICARST-2022; and c) organizing periodic "unofficial" meetings, perhaps every 6 months via Webex.

4. To prepare a publication to review the relevant studies performed up to the date and identify the gaps and means to fill them.

5. For all activities, to keep in mind and try to involve young professionals.



5. *COUNTRY REPORTS*

Argentina

RADIATION-BASED STERILIZATION AND ITS EFFECTS ON POLYMER MATERIALS

M.N. CIÁVARO[1], M.V. VOGT[1], M.F DEL GROSSO[2,3], A.J. PACHADO[1]

[1]Radiation Science and Applied Technology Management, CAE, National Atomic Energy Commission, Ezeiza, Argentina

[2]Research and application Management, CAC, National Atomic Energy Commission, Buenos Aires, Argentina

[3]National Scientific and Technical Research Council

ABSTRACT

Even though photons (gamma source and X ray), or particles (electrons) can be used for sterilization of medical devices, throughout the last decades ^{60}Co, has been used as a source of gamma ionizing radiation for a wide variety of applications, and it has become one of the most used methods for the sterilization of medical devices.

In Argentina, radiation sterilization technology is based on ^{60}Co sources but there is a growing interest in electron beams and X-rays not only just for sterilization purposes but also for irradiation of packaging and food, among others. In order to encourage the use of electron accelerators as a sterilizing method, it is important to know the effects that they generate on the materials of medical devices. In this coordinated research project, some polymers commonly used in medical devices and health care products such as polypropylene (PP), acrylonitrile butadiene styrene (ABS) and polylactic acid (PLA), will be analyzed. These polymers will be irradiated under different conditions (dose, dose rate) with gamma rays and electron beams, under vacuum and air environment. The mechanical properties will be analyzed through mechanical test (tensile, compressive, flexural), thermal and chemical properties (differential scanning calorimetry: DSC and fourier transform infrared spectroscopy: FTIR, yellowness index, biocompatibility assay and its accelerated aging will also be analyzed. Finally, at least one medical device or health care product made up of one of the selected polymers will be studied. The minimum sterilization dose and functionality of a selected product will be analyzed and Its primary packaging will be evaluated by airtightness tests to study if it can preserve the sterility of the product.

1. OBJECTIVE OF THE RESEARCH

The project aims to investigate and compare the effects of gamma sources and electron accelerators on some polymers commonly used in medical devices, in order to spread the acquire knowledge and encourage industries to sterilize their products using electron accelerators in the near future.

2. INTRODUCTION

Nowadays, in the global market, a 30 % of the medical devices is sterilized by ethylene oxide, a 30 % using ionizing radiation, a 30 % using moist or dry heat and a 10 % is sterilized using other modalities such as hydrogen peroxide and ozone, among others. Particularly, in Argentina, radiation-based sterilization technology is mostly carried out using ^{60}Co sources, but there is a growing interest in electron beams and X-rays for sterilization of medical devices, food irradiation and polymers modification.

During 2019, what was sterilized and decontaminated in the Semi Industrial Irradiation Plant at of the National Atomic Energy Commission, a 60 % of the irradiated products were pharmaceutical, such as physiological solution, a 1 % were laboratory supplies (such as gloves) and a 9 % were medical products. Within the sterilized medical products, a 44% were dental implants, a 9 % biological tissues, and a 47 % were medical devices (such as huckle implants, cannulas, etc). A high percentage of the sterilized medical devices were made of different polymers such as polyethylene, polyurethane, collagen. Moreover, their primary packaging was made of a lot of different polymers such as polystirene (viales), polichloride vinil (widely used in blisters), high density polyethylene, different elastomers (which usually are used to provide airtightness to the packages) and collagen (a natural polymer usually used in medical grade paper).

Considering that the sterilization market is growing really fast, the development of new sterilization facilities will be needed in Argentina. Therefore, the development of x-rays and electron beams facilities could be part of the solution. In order to promote the electron beam irradiation, in this coordinated research project we are going to compare the effects of electron beams and gamma rays on different polymers (PP, ABS and PLA).

Taking into account the three modalities of radiation-based sterilization, γ-Irradiation using a 60Co source has a low dose rate, much lower than that of electron beams. Therefore, sterilization of products takes much longer by using gamma rays instead of electron beams. On the other hand, gamma rays have a higher penetration than e- beams, which allows them to irradiate bulky products, but gamma irradiation involves the handling of a radioactive source.

X ray irradiation can overcome the penetration limit of electron beams and the fact of handling a radioactive source. However, the conversion from electron beam to X ray is a low efficiency process, so X ray irradiation has become commercially feasible with the progress in high energy and high beam power electron accelerators.

PLA is commonly use in absorbable sutures, implants and it also is used in packaging in film sheets. This is a radiation sensitive polymer. It was found that after increasing doses of radiation there is an important decrease in its mechanical properties that can be attributed to the decrease in the molecular weight of the PLA chain.

PP is used in non-absorbable sutures, syringes, inhalers, lids. It is a well-known radiosensitive material that leads to chain scission. PP polymers are slightly less stable against gamma irradiation in relation to electron beams but the oxidative degradation generated post-irradiation, is considerably lower with electrons [1]. This polymer is susceptible to degradation exhibiting poor resistance to aging,

ABS is used in nebulizers, non-absorbable sutures, tendon prostheses. It is a radioresistant polymer. Gamma radiation affects the mechanical properties of ABS, it seems to crosslink as the radiation dose increases, this could be seen as an increase in viscosity and in a higher elastic limit.

Studying the effects of radiation in the properties of these polymers, a reduction in the lack of knowledge regarding the effects of electron beams on polymers will be achieved.

This research project will be carried out jointly with the University of Maryland, the Buenos Aires Technological Institute (ITBA), the National Scientific and Technical Research Council (CONICET) and two Argentinian private companies: Terragene SA and Pablo Cassará.

3. MATERIALS AND METHODS

A biodegradable and bio-based polymer: PLA and two non-biodegradable and fossil-based polymers: PP and ABS will be studied. The gamma irradiation will be carried out with a ^{60}Co source (820 kCi) in semi-industrial irradiation plant located in Ezeiza Atomic Center (Argentina). The doses to be used will be between 0 kGy and 60 kGy with dose rates of 20 kGy/ h, approximately. Electron beam Irradiation will be carried out in the University of Maryland (USA) with an electron accelerator facility.

- Mechanical properties of the selected polymers will be analyzed before and after being irradiated in vacuum and air environment. Flexural, tensile or compressive essays will be done in order to determine the tensile strength, strain at break and Young’s elastic modulus.

- A DSC will be done in order to carry out the thermal analysis. The glass transition temperature, melting temperature and crystallinity of the polymers will be analyzed.
- The appearance and decay of functional groups by the corresponding absorbance bands of the polymers after and before being irradiated, will be determine by fourier transform infrared spectroscopy.

FTIR analysis

Table 1: Possible functional groups to analyze and their signals in the spectrum

Polymer	Functional group	Wave number (cm^{-1})
PP	R-CH3	2958
	R-CH3	2885
	R-CH2-R	1461
	R-C=O-R	1670-1690
PLA	R-C=O-O-R	1756
	-OH	3506
ABS	R-OH	3650
	R-C=O-R	1650-1680

- The yellowness index of the polymers will be analyzed in order to measure their possible radiation- induced color change.
- Accelerated aging will be carried out in a climatic chamber at controlled temperature and humidity. This way, a rapid determination of the effects of irradiation on the integrity of the polymers due to the passage of time will be done. Before subjecting the polymers into accelerated aging, the properties previously described will be analyzed.
- Size exclusion chromatography and rheological techniques will also be used to analyze scission and crosslinking reactions
- A packed health care product / medical device made up of some of the polymers described will be chosen and its minimum sterilization dose will be determined. Furthermore, its functionality will be analyzed too. In addition, it will be analyzed if its primary packaging preserves sterility by airtightness and sterility tests.
- Biocompatibility testing: Cytotoxicity in Vero cells will also be carried out too. If applicable, a sealing force test will be carried out on the primary packaging.

All tests will be done according to the corresponding ASTM or ISO standard.

4. PRELIMINARY TESTING OF GAMMA IRRADIATED SAMPLES.

Until now, some preliminary tests have been done in air conditions. The polymers are still under study.

FTIR analysis

- PP analysis

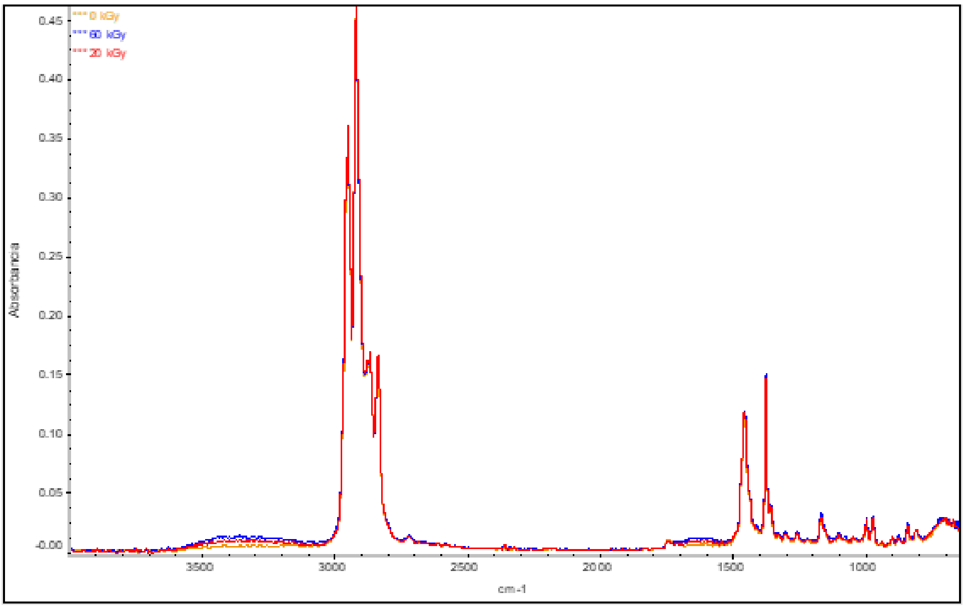


Figure 1: PP control and irradiated samples

FTIR assay of control and irradiated PP samples was done to see if there was a noticeable chemical change in their structure. It was found an apparently change of PP in the 1500–1800 cm−1 range. The range 1600–1700 cm−1 is usually connected with a C=C bond and the area 1700–1770 cm−1 with C=O in aldehydes, ketones or in carboxylic acids. It is perceivable that chain scission leads to a C=C formation at the end of a chain and that a small amount of oxygen could react with macro-radical rendering a C=O bond [2].

- ABS analysis

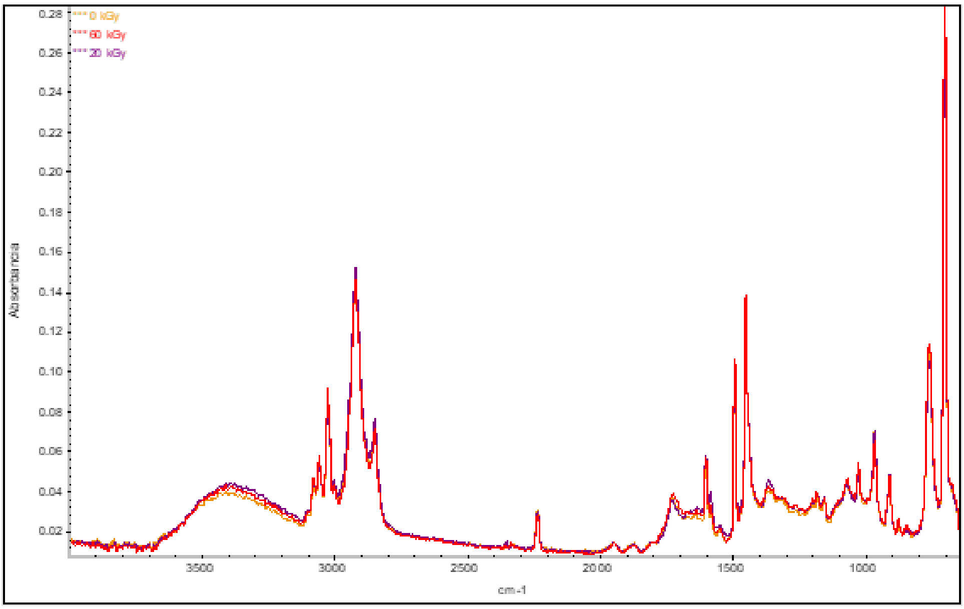


Figure 2: ABS control and irradiated samples

FTIR assays of control and irradiated ABS samples were done and it haven't been found any noticeable chemical change in their structure yet. The samples are still under study.

DSC analysis

- PP analysis

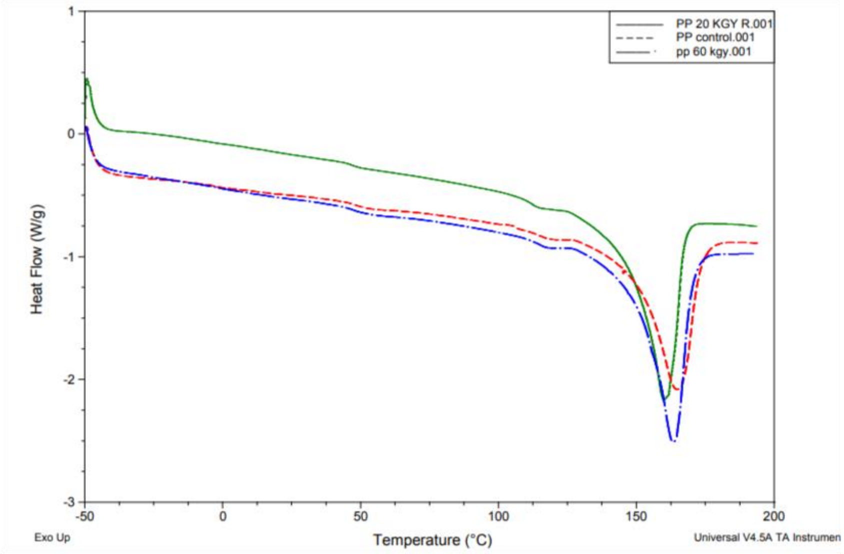


Figure 3: PP control and irradiated samples

It was found an increase in PP crystallinity and a decrease in its melting temperature with increasing doses of radiation (table 2). This probably is related with chain scission reaction.

It wasn't possible to determine the PP glass transition temperature. Therefore, it might be lower than 50 °C.

Table 2: PP crystallinity

Dose (kGy)	Tf (°C)	ΔHf(kJ/kg)	%C
0	165	65,6	31
20	160	69.24	33
60	163	72,49	35

- ABS analysis

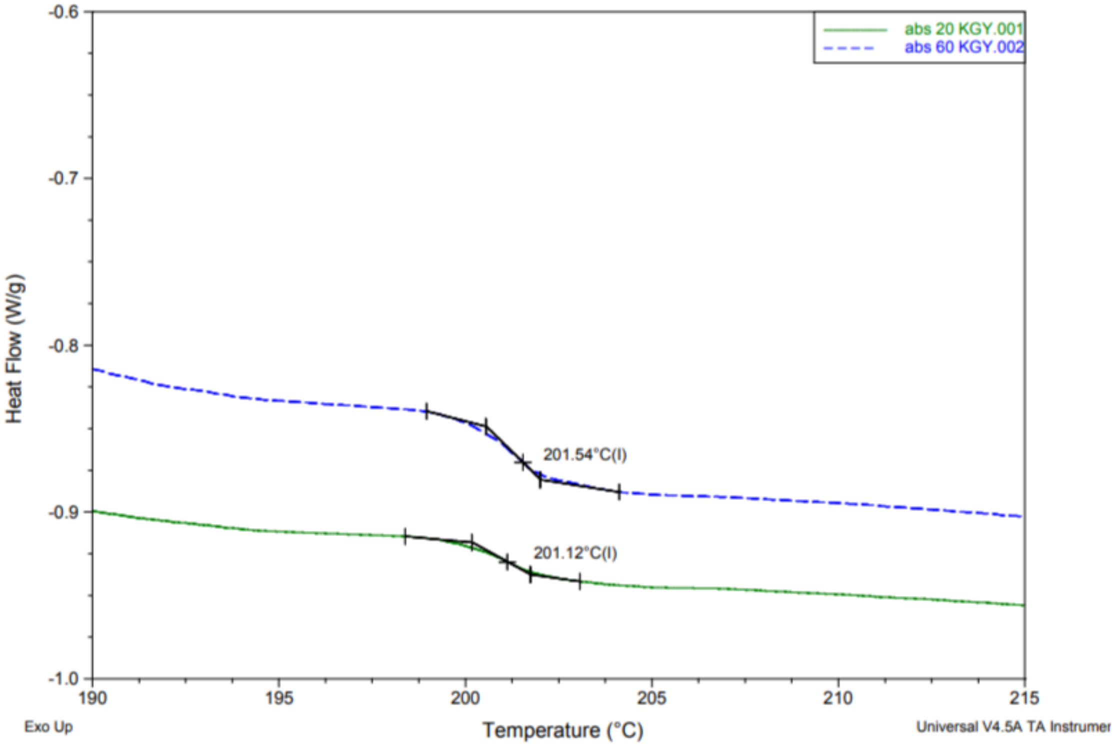


Figure 4: ABS irradiated samples

We still haven't found any noticeable changes in the FTIR spectrum of ABS. The glass transition temperature of control and irradiated samples was of 201 °C (table 3). This fact is consistent with ABS being stable against radiation.

Table 3: ABS crystallinity

Dose (kGy)	Tg (°C)
0	201
20	201
60	201

Tensile properties

- PP assay

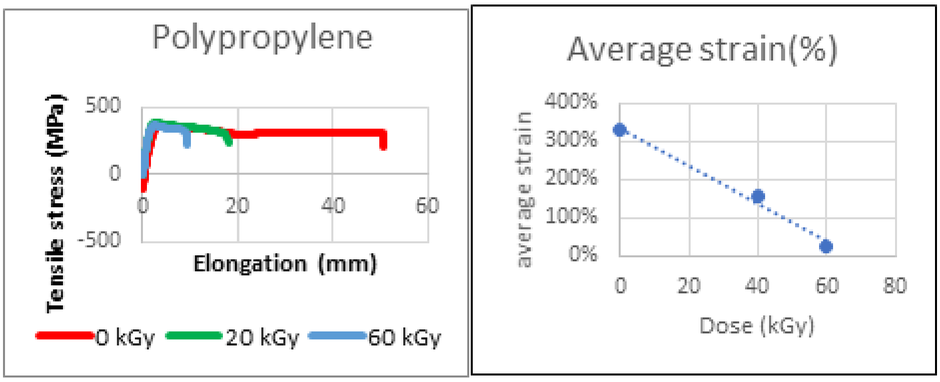


Figure 5: PP strain- stress curve

Tensile properties of PP control and irradiated specimens were studied. It was found a noticeable decrease in strain with increasing radiation dose. The decrease in strain might be related with the increase of crystallinity with increasing radiation dose. Tensile strength and young's elastic modulus haven´t been studied.

- ABS assay

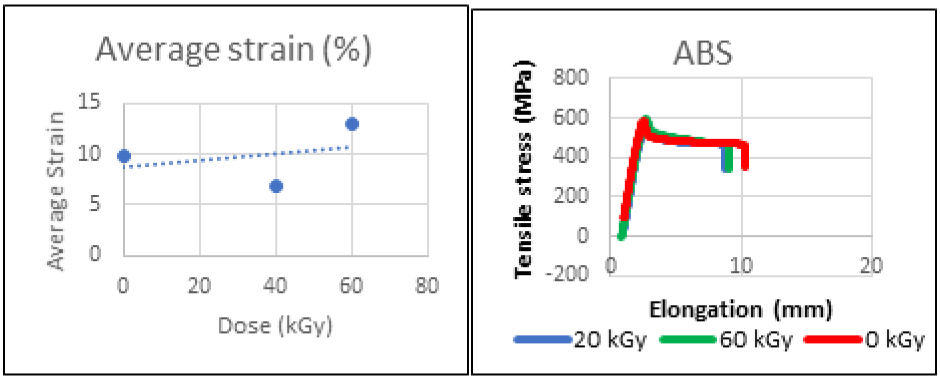


Figure 6: ABS strain- stress curve

No noticeable change has been found in the tensile properties of ABS. This is consistent with the ABS being stable against radiation. The samples are still under study.

5. CONCLUSIONS

In the present research, an investigation and comparison of the effects of gamma rays and electron beams on some polymers used in medical devices will be done. This will be of great contribution to encourage industries to sterilize their products using electron accelerators, and in a near future spread the acquired knowledge.

FTIR, DSC and tensile preliminary tests were done on gamma-irradiated PP and ABS samples.

It was found a noticeable decrease in PP strain with increasing radiation dose. This might be related with the samples increase of crystallinity. An apparently change of PP in the 1500–1800 cm−1 range was detected. This might be related with the development of chain scission reactions.

No noticeable change has been found in the chemical structure, thermal and tensile properties of ABS. This is consistent with ABS being stable against radiation.

All the samples are still under study.

6. ACKNOWLEDGEMENT

This research will be possible thanks to the collaboration and support of Dr Mohamad I. Al-Sheikhly, from Maryland University. Furthermore, this research will be possible by the collaboration of ITBA, CONICET, Terragene SA, Pablo Cassará and different researchers and professionals from the Constituyentes Atomic Center and the Ezeiza Atomic Center.

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[13] ASTM D 3078 "Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission"

[14] ASTM F 88/88M *"Standard Test Method for seal strength of flexible barrier materials"*

Brazil

MEMBRANES AND OTHER POLYMERIC AND BIOPLYMERIC SUBSTRATES MODIFIED BY IONIZING IRRADIATION FOR MEDICAL MATERIALS

A.B.C. GERALDO[1], M.S. FERREIRA[1], E. MOURA[1], M.B. MATHOR[1], S. SOMESSARI[1], P. VASQUEZ[1], J. PACHADO[2], M.V. VOGT[2], C. CARRASCO-VILLANUEVA[3]

[1] Instituto de Pesquisas Energéticas e Nucleares – IPEN-CNEN-SP, 05508-000, São Paulo, Brazil

[2] Comisión Nacional de Energía Atómica (CNEA), Buenos Aires, Argentina

[3] Universidad Mayor de San Andrés (UMSA), La Paz , Bolivia

Abstract

Polymers are a kind of material that is submitting to continuous improvement in terms of backbone changing, novel additives mixing to improve specific properties and developing reactional features to evolve functional groups or even to modify them. In this way, ionizing irradiation is an important energetic resource to carry out these chemical conversions. In this work, irradiation process will be applied in polymeric substrates commonly used in medical stuffs to modify them in specific chemical routes and to improve chemical-physics-biological properties in these materials. Polypropylene (PP), polyethylene (PE) and polyvinylchloride (PVC), that are popular in medical devices, will be coupled with chitosan from natural sources to increase its biocompatibility and-or polarity. These polymeric substrates in distinct shapes (membranes, rods, woven and others) will be modified to give them a biocompatible character for distinct medical applications. The cooperation with researchers in Latin America will be necessary to develop important aspects of chitosan-polymer substrates.

1. INTRODUCTION

Polymers are well used in medical and healthcare fields, specially commodity polymers as polyvinylchloride (PVC), polyethylene (PE) and polypropylene (PP).

PVC is a low cost polymer used in medical-surgical devices and consumable materials (urine bags and catheters, transfusion tubing) [1], due its high biocompatibility, chemical stability and mechanical properties as high flexibility and transparency. Also, polyolefins (PE and PP) are a low cost polymer class and due its high mechanical resistance and low chemical reactivity it is applied to both disposable and durable materials, replacing glass or metal due its ease of molding in intricate shapes, where micromolding is the challenge to produce tiny parts.

The demand for the use of synthetic polymers as implants or another medical device is the possibility for low degradation process in biological fluids media, once foreign materials in body may be hydrolyzed and the product of this process, generally carbon dioxide, is responsible for local pH decreasing, resulting in cell and/or tissue necrosis and other unwanted immunogenic response.

Biopolymers may be an alternative to be used, as conjugated to other material or even been the main material to assume the composition of medical devices. Biopolymers are isolated or extracted from living organism (animals, vegetables, fungi and microbes) and also, may be synthesized from biological systems. Renewability and biodegradability are evident advantages. Biopolymers can be classified as polysaccharides (starch, cellulose, alginate, agar, chitin/chitosan, hyaluronic acid, xanthan, dextran and others), proteins (silk, collagen/gelatin, elastin, polyaminoacids), polyesters and natural resins (polylactic acid, natural rubber, shellac) [2].

In this work, chitosan, a cationic polysaccharide, is the biopolymer to be explored. Chitosan is obtained from deacetylation of chitin (founded easily as exoskeleton of crustaceans and insects) and it is known not only for its antibacterial/bacteriostatic characteristics, but also its biodegradability and biocompatibility, specially hemocompatibility. Therefore this biopolymer is important in tissue engineering. Coatings of chitosan and heparin have been studied to promote the acceleration of re-endothelization and healing process after coronary stent implants in porcine iliac artery [3]. Chitosan-based matrices can be applied in bone regeneration, despite its mechanical weakness; therefore chitosan needs to be combined with another materials. Li and co-workers [4] developed a chitosan-alginate scaffold and it was observed an increase in mechanical strength in these scaffolds due to the ionic interaction between these both biopolymers.

Brazilian working group is obtaining chitosan from different animal sources by ionizing irradiation process. The advantage of irradiation process is low time of chitin's deacetylation reaction, that normally is performed in 6-12 hours. We also developed a chitosan-polymer substrate from PE and PP pre-irradiation process (gamma rays and electron beam) to perform irradiation grafting. The chitosan-polymer material presented bacteriostatic properties.

Irradiation grafting is a method where is possible to modify polymer backbone, macromolecules and to build new geometries of macromolecules. Stimuli-responsive polymers [5], with an interpenetrating network is formed from a monomer grafted on polymer substrate, like those developed by Nava-Ortiz et allii [6], where polymeric supports of PP and PE, which are functionalized with cyclodextrin from grafting of glycidyl methacrylate by polymer pre-irradiation method; these materials can be applied to prevent *Candida albicans* biofilm formation when miconazole, an anti-fungal agent, is loaded in these grafted polymers. Sutures of PP were gamma grafted using distinct monomers (N-isopropylacrylamide (NIPAAm), 2-hydroxyethylmethacrylate (HEMA) and N-vinylimidazole (NVIm)) [7]; the modified PP samples do not affected physical and mechanical properties, besides biocompatibility characteristics, compared to original PP, on the contrary, it was observed advantageous characteristics as water affinity and stimuli-response without compromising cell viability.

Bolivian workgroup in IIDEPROQ (UMSA), was obtaining a derivative chitosan as exopolysaccharide produced by *Candida maltosa* [8]. Other potentials biopolymers also studied are polyhydroxybutirate (PHB) from a novel *Halomonas boliviensis* - throught agroindustrial wastes as substrates [9].

2. OBJECTIVES

The aim of this research is modify commodities polymers commonly used in medical devices by irradiation process to give them properties of biocompatibility and antibacterial/bacteriostatic characteristics. Specifically, chitosan from distinct sources will be grafted onto a polymer substrates and the grafted products will be submitted to biocompatibility tests and microbiological assays. These objectives will have technical contributions of workgroups in Bolivia and Argentina. Bolivia's cooperation will be in terms of specific chemical processes and that of Argentina, in the different types of irradiation processes and cytotoxicity and biocompatibility tests.

3. MATERIALS AND METHODS

3.1 Chitin Sources

Chitin was obtained from different animal exoskeletons: insect (cockroaches) and crustaceans (shrimps, squids and crabs). Squid pens and shrimp (specie: *Litopenaeus vennamei*) shells were obtained from fish markets (shrimps and squids). Crab shells (*Charybdis hellerii* – known as "siri bidu" at Brazilian coastline that is an invasive species that threatens our native coastal fauna) were provided by technicians staff from IP (Instituto de Pesca)-SP (Fishing Institute of São Paulo). The cockroaches (Genre: Blaberus) were obtained in pet food stores (dry or frozen individual units).

The exoskeletons (shrimps shells, squid pens and cockroaches) were cutted in small pieces (dimensions about 10 mm). Crab shells were ground in a hand grinder; the particles were sieved and separated in different grain sizes. For this work was selected particles size of 32 mesh.

3.1.1 Chitin isolation:

The shells were treated from two sequential steps – demineralization (shells were dipped in chloridric acid solution to remove inorganic salts) and deproteinization (exoskeletons were dipped in sodium hydroxide solution to remove proteins-oligoproteins).

3.1.2 Radiation process

The finely divided and isolated chitin samples were irradiated from gamma source (Gamma Cell 220N – AEC Ltd. (Canadian) – dose rate: 0.47 $Gy.s^{-1}$; absorbed dose: 20 kGy) and electron beams (RDI Dynamitron Accelerator JOB188 – 1.5 MeV – 37.5 kW - dose rate: 22.4 $kGys^{-1}$; absorbed doses: 10-70 kGy)

3.2 Chitosan synthesis

Chitosan is obtained from chitin desacetylation process. This chitin conversion is developed mixing chitin particles in 60% sodium hydroxide solution; this mixture is submitted to reflux by 1 h (irradiated samples) and 6 h (non-irrdiated original samples). After this procedure, the product is filtered and washed in water until neutral pH. The samples are purified by precipitation in sodium hydroxide solution.

Chitosan was characterized by FTIR to determine deacetylation degree (DD) and by viscosimetry to determine molecular mass (MM). All results were compared to chitosan low MM provided by Sigma-Aldrich (SA).

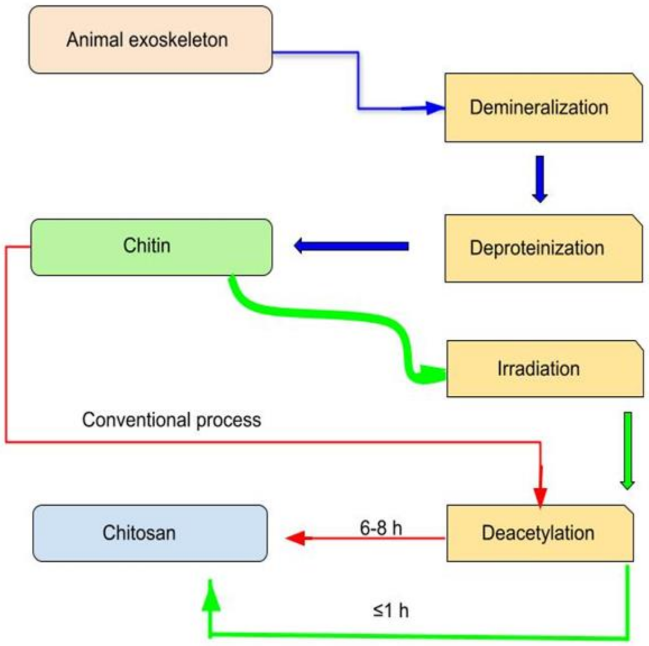


Figure 1: Chitin conversion to chitosan methodologies.

3.3 Chitosan grafted onto polymeric substrates

Pre-irradiated films (EB, 22.4 $kGy.s^{-1}$, 50 kGy) of polypropylene and polyethylene were immersed in a chitosan solution (distinct immersion times) and after, they were washed in distilled water and dry under room temperature.

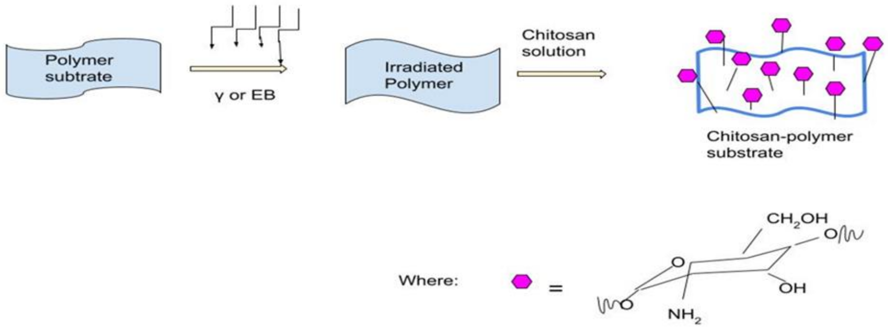


Figure 2: Chitosan grafting onto polymer substrate process.

3.4 Microbiological assays

Antibacterial activity was tested from two kinds of bacteria:

1. Gram-negative (*Escherichia coli* - W3110 – Hormone Laboratory (CB-IPEN-CNEN-SP) – Luri-Bertani Miller (LBM) broth in glicerol);

2. Gram-positive (*Staphilococcus aureus* – Universidade Federal de São Paulo (UNIFESP) – LBM broth (Becton, Dickinson & Co)).

   The bacteria were subcultured in LBM-agar broth at 37 ^{o}C for 18 h (*E. coli*) and 14 h (*S. aureus*). After, the bacteria were inoculated in 5 ml LBM broth at 30 ^{o}C (*E. coli*) and at 37 ^{o}C (*S. aureus*), with shaking of 150 rpm for 24 h. Viable cells were enumerated after incubation (Turbidity method - DO600 = 1.0 – 8.106 CFU)

   Chitosan solutions were prepared in acetic acid with final concentration of 10 µg⁄ml

3.4.1 Determination of MIC (Minimum Inhibitory Concentration)

The MIC was determined from chitosan solution added to LBM broth in concentrations of: 2.5 µg/ml; 2.0 µg/ml; 1.5 µg/ml; 1.0 µg/ml; 0.5 µg/ml; 0.25 µg/ml and 0.125 µg/ml.

The incubation were performed in room temperature and samples were analyzed by turbidity after 22 h.

3.4.2 Antibacterial activity of chitosan-polymer films

Chitosan-polymer films were cutted in circular geometry, disinfected in 70% ethyl alcohol and autoclaved. Each kind of chitosan-polymer was immersed in LBM broth and incubated in aerobic conditionsf at 30 ^{o}C (*E. coli*) and at 37 ^{o}C (*S. aureus*), with shaking of 150 rpm for 72 h, that was stored at 40 ^{o}C.

The bacteria growth kinetic was measuring by spectrophtometry (UV-vis spetrophotometer 2100PRO Amersham Bisociences) for 18 h, 20 h, 22 h and 27 h.

4. RESULTS AND DISCUSSIONS

All results are reported to chitosan from crab shells, once chitosan from other sources described in 3.1, are in processing. These results are obtaining from Brazilian preliminary studies.

4.1 Chitosan characteristics

The FTIR spectral bands at 3450 cm^{-1} and 1655 cm^{-1} are characteristics for hydroxyl and amide groups respectively, presents in chitosan spectra. The Deacetylation Degree (DD) is obtained from relation of absorption values of these bands, were DD is the result of a mathematical equation (proposed by Rojas [10], based on Moore [11] studies), that include this bands relation. Table 1 shows DD parameter calculated from spectra of commercial sample (Chito SA), non-irradiated (Chito 0 kGy) and gamma (30 kGy) and EB (10 kGy, 20 kGy and 70 kGy) irradiated samples.

The samples presented DD values about 70%, except that from chitin irradiated at 20 kGy EB. These results are expected for successful chitin conversion in chitosan.

TABLE 1: Deacetylation Degree (DD) of chitosan from crab shells – commercial sample, non-irradiated and irradiated samples. Evaluation from Roja's method [10].

Sample	A_{1655}	A_{3450}	DD (%)
Chito SA	6.4	15.6	69%
Chito 0 kGy	2.7	7.3	72%
Chito 10 kGy	3.2	8.9	73%
Chito 20 kGy	4.3	8.0	59%
Chito 20 kGy (Gamma)	4.3	10.8	70%
Chito 70kGy	0.82	2.23	72%

The evaluation of Molar Mass (MM) by viscosimetry are shown in Table 2.

TABLE 2: Molar Mass of chitosan from crab shells – commercial sample (Chito SA), non-irradiated (Chito 0 kGy) and irradiated samples (gamma source – mentioned - and EB).

SAMPLE	MM (KDa)
Chito SA	212 (±129)
Chito 0 kGy	27,1 (±3.58)
Chito 10 kGy EB	25,2 (±6.44)
Chito 20 kGy EB	16,5 (±2.99)
Chito 20 kGy (Gamma)	6,48 (±1.66)
Chitosan 70 kGy EB	12,9 (±2.09)

The MM value obtained for commercial sample (Chito SA), is compatible with the same results from its product specification sheet provided by the manufacturer.

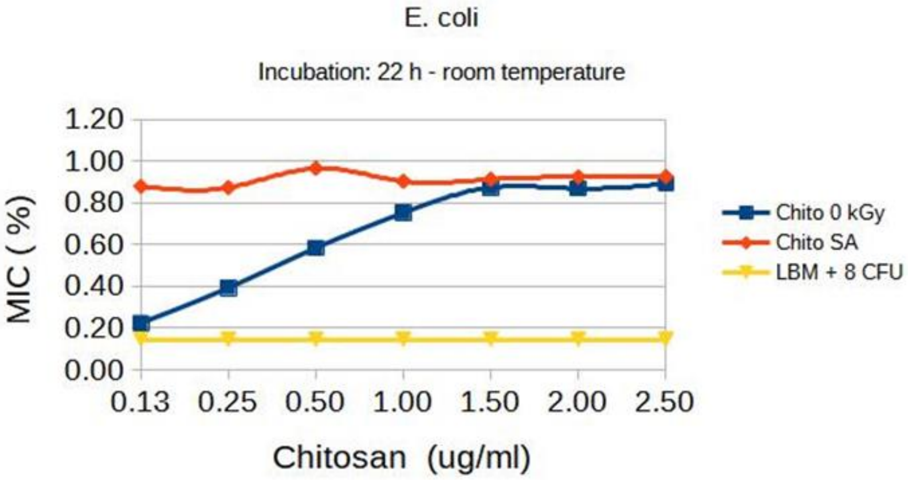
The non-irradiated sample presented low MM value, that indicate this sample is classified as oligochitosan [12]. For irradiated samples, the results shows not only that the products are an oligochitosan, but also, that MM values decrease with the increase of absorbed dose. Then, the higher dose, the greater the degradation.

Comparing gamma irradiation and EB irradiation at 20 kGy, a lowest value is obtained by the first irradiation method. This result suggests a dose rate influence, where in low dose rate (gamma irradiation) the chitosan degradation is important.

4.2 Determination of MIC

The percentage of MIC of chitosan samples against *E. coli* and *S. aureus* bacteria is shown in Figure 3. The commercial chitosan sample presented an inhibitory action under low product concentration to both bacteria types. The chitosan from non-irradiated crab shells has an inhibitory action from 1.5 ppm for both bacteria assayed.

a)



b)

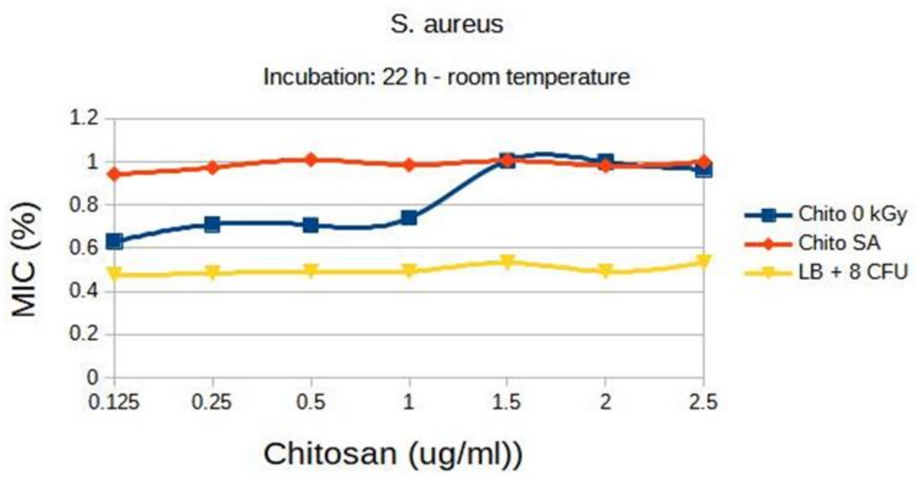


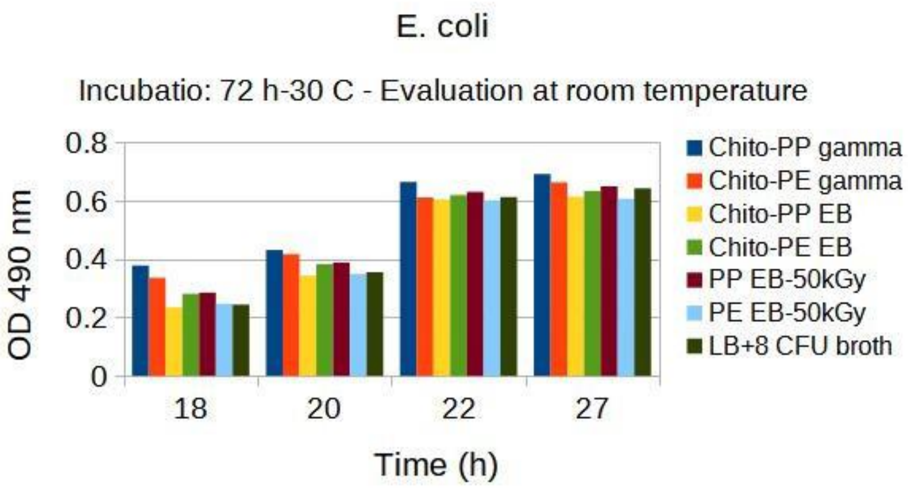
Figure 3: Percentage of Minimum Inhibitory Concentration (MIC) for chitosan (from non-irradiated crab shells and commercial), against a) *E. coli* and b) *S. aureus*.

This result may be related to distinct chitosan MM values and it is according to the literature [12], where oligochitosans presented low antibacterial activity.

4.3 Antibacterial activity assays of chitosan-polymer films

Figure 4 shows the results of antibacterial activity assays for chitosan from crab shells irradiated at 20 kGy by gamma rays (gamma) and electron beam (EB) irradiation grafted onto polypropylene (PP) and polyethylene (PE). These results are compared to irradiated polymers (by EB-50 kGy-22.4 $kGy.s^{-1}$), that were the polymer substrate for chitosan grafting and to bacteria growth media (LB + 8 CFU broth) in each condition of incubation at room temperature.

a)



b)

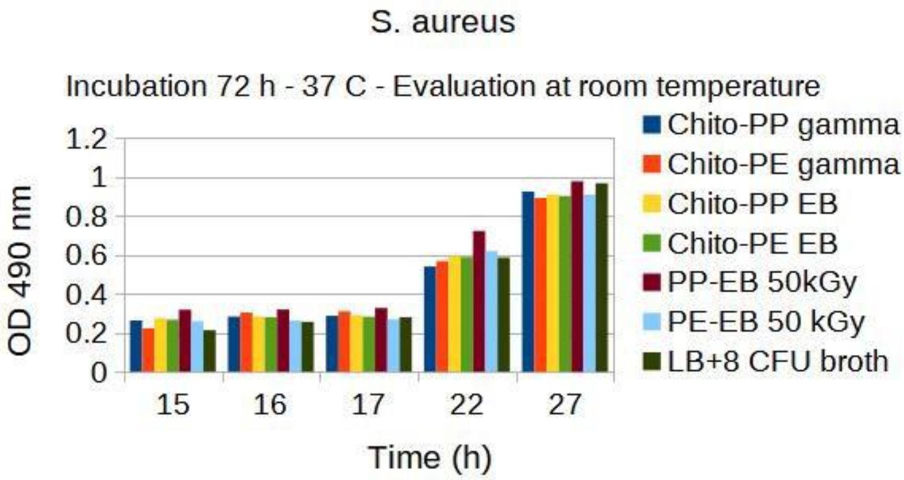


Figure 4: Antibacterial activity of chitosan-polymer films against a) *E. coli* and b) *S. aureus*. Evaluation of incubation at room temperature after 72 h at 37 ^{o}C,

These results show an antibacterial activity of some chitosan grafted films:

1. Chito-PP EB presented in all times of incubation at room temperature against *E. coli*, absorbance values below to that of control sample;

2. All chitosan grafted polymers presented absorbance values below to that of control samples after 22 h of incubation at room temperature against *S. aureus*.

As discussed above, the oligochitosans presented low antibacterial activity, but this was not an impediment to not observing an antibacterial activity in some samples. These results show chitosan grafted onto PP and PE was a successful process, where even in favorable conditions for bacteria growth, some grafted films tended to inactivate bacteria. .

5. CONCLUSIONS

The chitosan obtained by the irradiation process has the advantage of obtaining a product quickly and with good quality in terms of DD. However, it is necessary to have control over the main irradiation parameters (dose rate and absorbed dose), since the degradation of the material is evident.

It is possible to graft chitosan in polymers such as PP and PE. This composite of a biomolecule with biological/biochemical characteristic allied to the polymers with high chemical and mechanical resistance have important requirements to be applied in medical field, mainly as disposable antibacterial materials, in materials for topic use, such as wound dressing and even as part of materials for tissue engineering and implants.

6. OUR CONTRIBUTION FOR THIS CRP

This work expect to contribute to radiation technology not only in obtaining chitosan, but also, obtaining supports for this macromolecule, that may be useful in medical application. Then, our working group will focus on the following issues:

- to optimize obtaining chitosan by irradiation process from distinct natural chitin sources;
- to improve chitosan grafting onto commodities polymer, including PVC;
- to develop chitosan-g-polymer in distinct geometries (tube, sheet, rod, woven, corners, concavities, tipsand others);
- to evaluate microbiological tests, as biocompatibility and cytotoxicity, in such grafted polymer objects for specific application.

ACKNOWLEDGMENTS

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Egypt (Abd El-Rahim Hassan)

Comparison of the gamma radiation and electron beam effect on medical nonwoven polypropylene polymers

H.A. ABD EL-REHIM*, N.M. DEGHIEDY
Radiation Research of Polymer Chemistry Department, National Centre for Radiation Research and Technology (NCRRT),
Atomic Energy Authority, Cairo,
Egypt
*ha_rehim@hotmail.com

Abstract
Comparison study of electron beam irradiation with gamma processing for medical gowns material treatment was carried out. Nonwoven Isotactic polypropylene was subjected to gamma rays and electron beam irradiation at different doses and storage for 14 months. The tensile strength and elongation at break of PP materials was determined. The irradiated Nonwoven polypropylene mechanical properties were significantly changed specially for those treated with gamma rays when exposure to dose up to 15kGy.Also, the damage effect of gamma irradiation on PP is higher if compared with that of EB. The amount of radical formed by radiation using electron is less than that formed by irradiation using Gamma rays. Moreover, the structure change on PP treated with gamma and Eb at the same dose of 25kGy was investigated. Two characteristic peaks for C=O and OH were appeared in the PP treated with gamma rays. Meanwhile, such peaks were not clear for the samples treated with EB at the same irradiation dose. Although the main interaction with matter is basically the same for gamma and high-energy electrons, some differences between the two modes remain.

1. INTRODUCTION

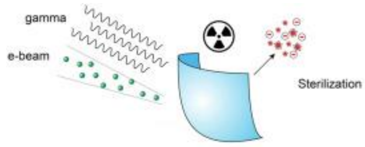
Radiation sterilization has been used in the industrial market for many years. Gamma sterilization is one of the most common radiation systems in use today. What made gamma radiation so attractive is its controlled doses which can penetrate deeply into many materials and high energy output. Although its use is widespread, there are inherent problems with the use of gamma radiation. It can be dangerous if not protected from workers in the area. The difficulty for obtainingthe ^{60}Co sources as a result of restricting by nuclear security issues and the ban on their production and transportation. Also, due to the high gamma production nature, material properties can change in undesirable ways as well. Color (yellow indicator), hardness, tensile strength, elongation and rupture strength can change during the gamma sterilization process. These drawbacks resulting from the use of gamma rays make the thought of using other available sources of ionizing radiation imperative. Turning to use of electron beam accelerator and x-ray allows for more controlled doses to ensure only desired property changes occur.

Although the accelerator and x-ray technologies in sterilization processes are mature and reliable technology, they still constitute a small share of the sterilization market. However, Improvements in accelerator technology in general, attributed to an increasing rate of growth for the accelerator-based sterilization, over the last decade. They experienced limited use when compared to gamma rays due to gaps in data, processes, knowledge, and certifications, and improvement in these areas is important because it directly encompasses the health and safety of hospital patients and consumers of healthcare products. It influences the future availability of alternative sterilization technologies that can solve production capacity issues for the Cobalt 60 that may restrict by nuclear security issues as well as residual EO in medical products that may cause serious illness Therefore, the type of information that may be missing and may impede medical device manufacturers from moving to expedited sterilization should be determined. There are multiple reasons for this insufficient use of accelerator technologies for sterilization, including large capital investment. Also due to the lack of the characteristics between the radiation methods, and knowledge of the polymer effects of the electron and x-ray beam, and Educating workers in the industry about the similarities and differences in treatment. The primary goal of this primary is to investigate radiation effects on polymer materials commonly used in medical devices by comparing gamma, and e-beam,. This research focus on polymers commonly used in the medical industry, such as, polypropylene. The experimental design of the studies is taken into account irradiation conditions, namely total dose and its uniformity, dose rate, temperature, and irradiation environment (normal or oxygen-free). In addition, evaluation of the irradiated samples should involve physical and chemical analysis and ageing studies.

2. METHEDOLOGY

2.1. STERILIZATION OF PP NON-WOVEN FABRICS CLOTHES USING GAMMA OR ELECTRON BEAM IRRADIATION

A commercially available isotactic polypropylene Surgical Gown -S.M.S type (size 50cm x 1m) from MMARAMCO Medical groups was used and analyzed. During the production of the non-woven material, dyes (masterbatch containing blue pigment not more than 2%) and antioxidants (up to 1) were also introduced into the polymer composition%). the colouring of such clothes have been done using master batch. This grade is formulated to be sterilized by radiation. its, applications include medical gowns, gloves, wipes, wound dressings, filters, hygiene products. Polyvel's Additive Master batches is maybe used for Polypropylene Nonwovens that under investigation.



3. RESULTS AND DISSCUSSION

Some products especially those need higher doses irradiation namely medical closes like gowns from isotactic polypropylene have been turned to EB for sterilization. Before this step, validation study was performed to determine the proper EB doses required for sterilization. Also, the change in materials functionality and properties if any that resulting from applying EB radiation have been investigated and compared with that resulting from gamma radiation treatment.

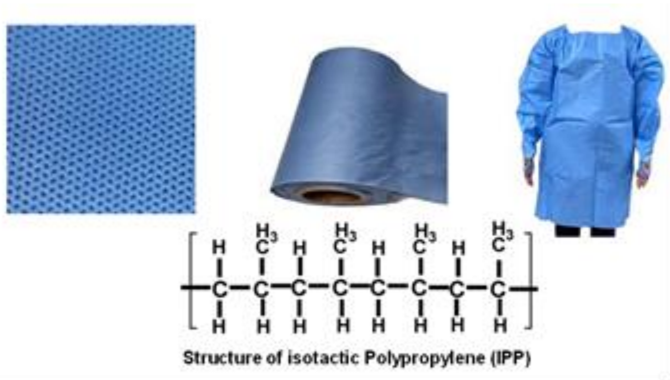
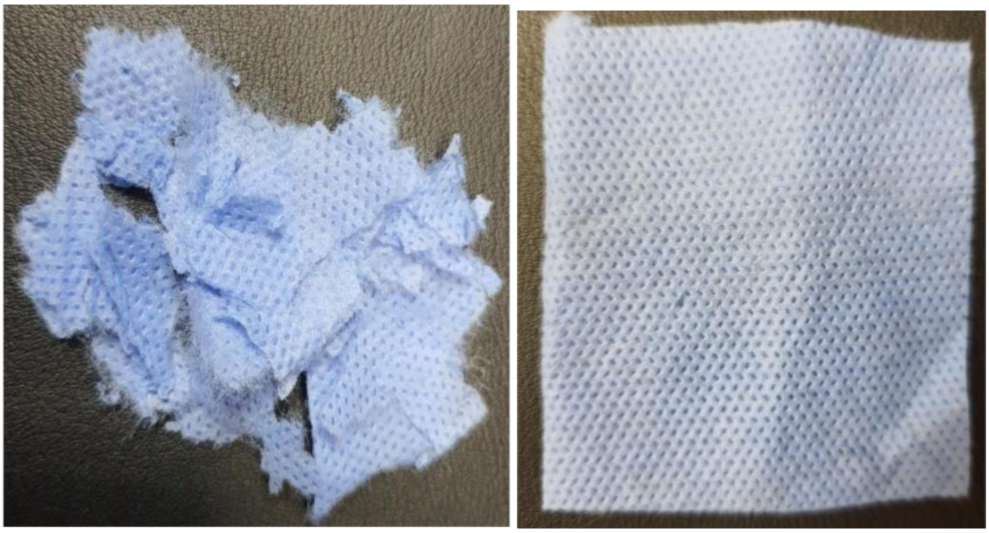


FIG. 1. Non-woven polypropylene products and its chemical structure

Samples of blue color PP materials have been irradiated to different doses up to 25 kGy using gamma and electron beam irradiation and were tested for tensile strength and elongation at break after 14 months storage. Fig.2 shows sever degradation happened after14 months storage period for the samples irradiated with gamma rays, meanwhile, the sample irradiated with electron beam seems to be slightly affected by EB radiation.



(a) (b)

FIG. 2. Photographs of the irradiated PP nonwoven sample after 14 months storage using: (a) gamma irradiation (b) electron beam irradiation

3.1. MECHANICAL PROPERTIES

Table (1) showed the comparison study between the effects of gamma and EB on the tensile strength of PP. Appling low gamma or electron beam irradiation doses less than 15kGy resulted in a slight effect on the tensile strength. Thereafter, as the irradiation dose increases, the mechanical properties for the irradiated sample increases and significant changes were observed for the mechanical properties of PP materials treated with the sterilized dose. Also, it is clear that the tensile strength and elongation at break for the materials were affected by radiation type. The EB irradiation has a less damage effect if compared with the damage caused by gamma rays. It could be concluded that there are serious changes in PP chemical structure were observed when the materials expose to 25kGygamma-ray if compared with EB. The same behavior for elongation at break properties of nonwoven PP after irradiated with both gamma radiation and electron beam.

TABLE 1. Tensile strength percent (%) of un-irradiated and irradiated PP with gamma and electron beam at different irradiation doses after storage for 14 months.

Dose (kGy)	Gamma	EB
0	100	100
10	86	96
15	73	90
25	19	76

3.2. ESR STUDIES

ESR studies for the irradiated samples were carried out to determine the amount, stability and decay of the radical formed during irradiation processing by gamma rays and electron beam. It can be seen from the Table (2) that the amount of radical formed by radiation using gamma rays is much higher than that formed by radiation using EB. The radicals formed during irradiation process using gamma rays or EB were decayed by time. After one month storage, the radical's decay for both samples irradiated with gamma and electron beam reached to 90%. The shape and position of ESR signal suggested that peroxyradicals is the main radicals formed by both gamma and EB radiation (Figure 3). After the 14 months the peroxyradicas signal disappeared and a new wider signal radicals on other position is appeared. This signal in the spectra can be ascribed to polyenyl radicals, which are left after the alkyl radical's decay

TABLE 2. Comparison between the peak height of EB and gamma irradiated samples at irradiation dose 25 kGy

Time (day)	Peak height For EB	% decay	Peak height for GR	% decay
0	315	0	931	0.00
1	147	53	547	41
3	95	62	388	59
9	73	84	203	87
15	52	85	104	89
25	36	90	67	93

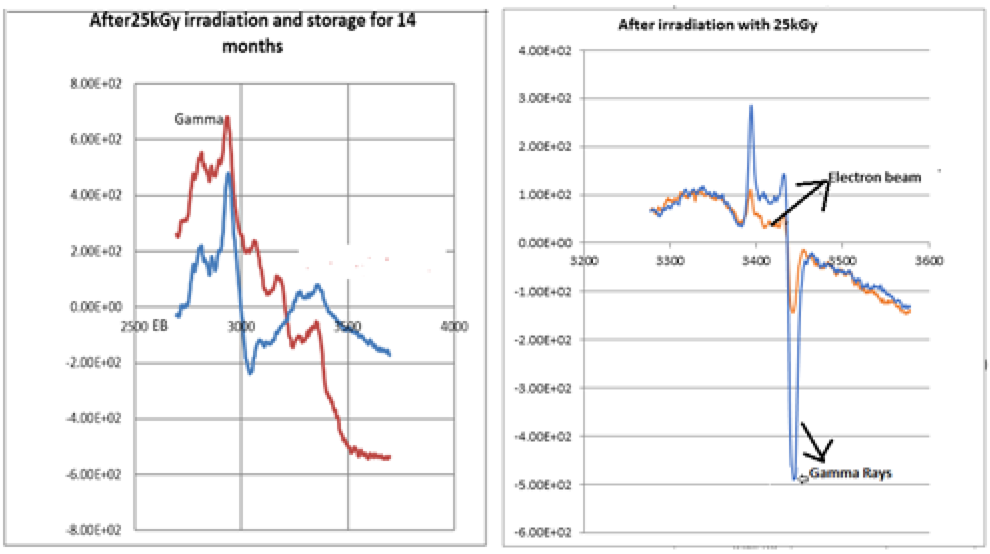


FIG. 3. ESR spectra of irradiated non-woven polypropylene using gamma and electron beam radiation after 14 months storage.

3.3. FTIR STUDIES

The change in chemical structure of the irradiated polymers could be followed by measuring FTIR. Accordingly, the FTIR studies of irradiated PP at different gamma ray doses was carried out. The Carbonyl groups and hydroxyl groups were observed indicating the oxidation of PP by using radiation at different doses (Figure 4). The structure change on PP treated with gamma and EB at the same dose of 25kGy was also investigated. As seen from the Figure 5, two characteristic peaks for C=O and OH are appeared in the PP chemical structure treated with gamma rays. While, such peaks are not clear for the samples treated with EB at the same irradiation dose. This means that, radiation sterilization by EB is regarded to be less damaging to PP compared with gamma radiation sterilization. This is because of limited oxygen diffusion during PP sterilization using EBand consequently the autoxidation process is restricted.

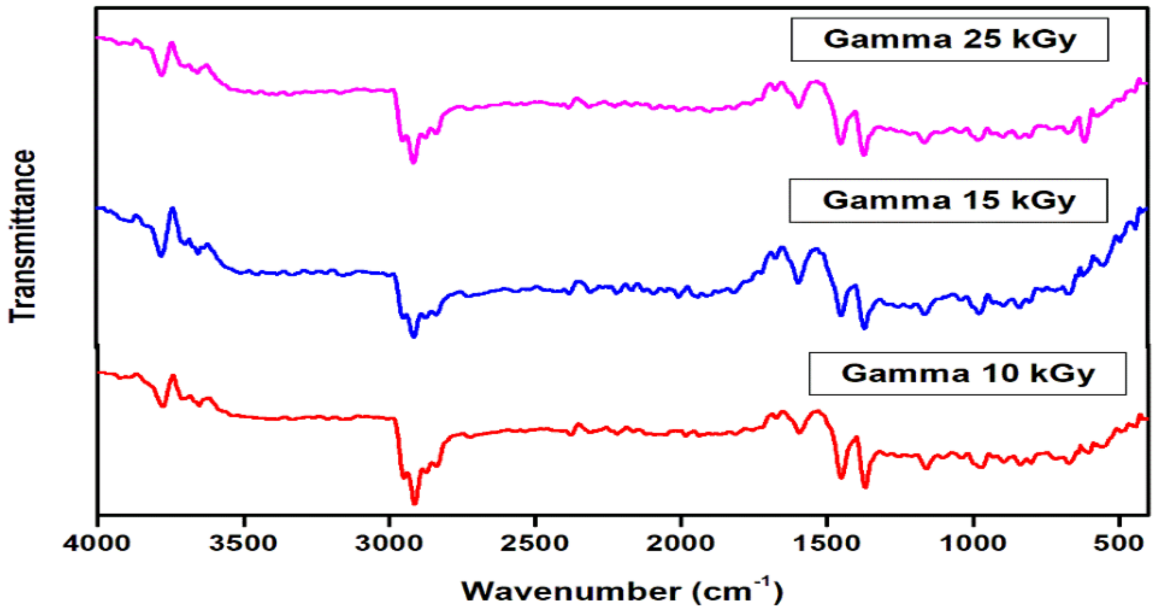


FIG. 4. FTIR spectra of gamma irradiated PP polymers at different irradiation doses.

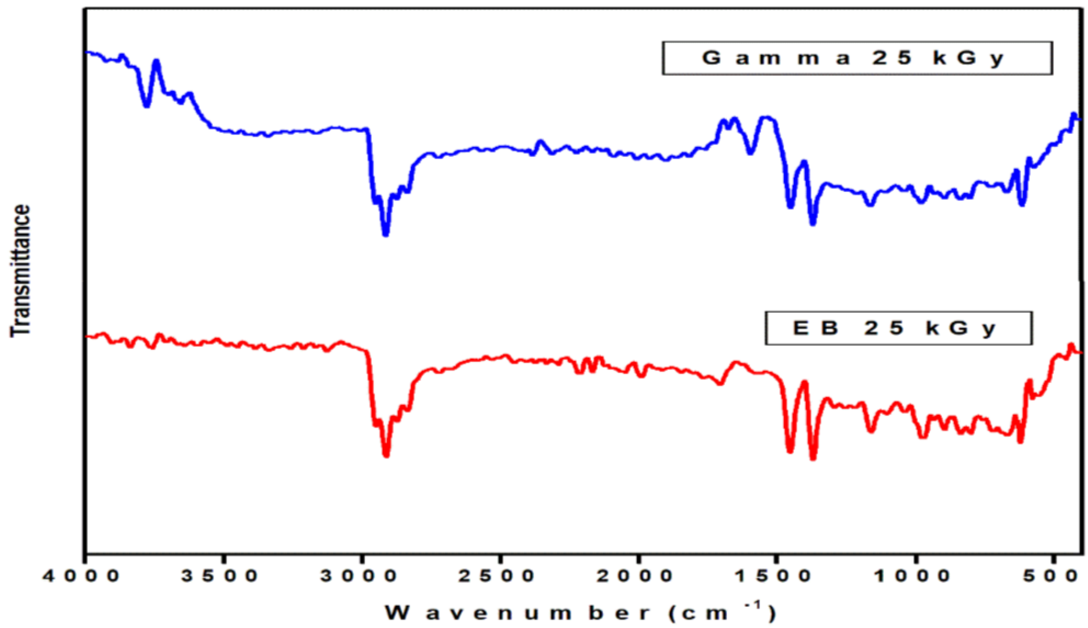


FIG. 5. FTIR spectra of PP polymers irradiated using gamma and electron beam irradiation

3.4. MECHANISM OF PP DEGRADATION

When the PP sample is irradiated in air, the oxidation processes begin simultaneously because of the oxygen diffusion during the irradiation. An intermediate species between alkyl and peroxy is observed and the last one becomes more important as the oxygen concentration increases. General oxidation reaction by radiation consists of four main steps: initiation, propagation, chain branching, and termination. In the initial step, free radical is formed by PP -radiation interaction. In chain propagation step, the free radical reacts with oxygen to produce peroxy radicals and generate hydroperoxide and new alkyl radical. The alkoxy, hydroxyl, hydroperoxy, and other radicals' species may be formed if the reaction becomes aggressive. In the chain branching step, the formation of alkoxy radicals and hydroxy radicals can be formed. Hydroperoxides are unstable species and undergo homolytic decomposition, and leads to new radicals (chain branching radicals). All the radicals formed in this way initiate new reactive chains, taking part in new reaction. In termination step, cross-linking or creating functional groups is a result of the reaction of different free radicals (Figure 6).

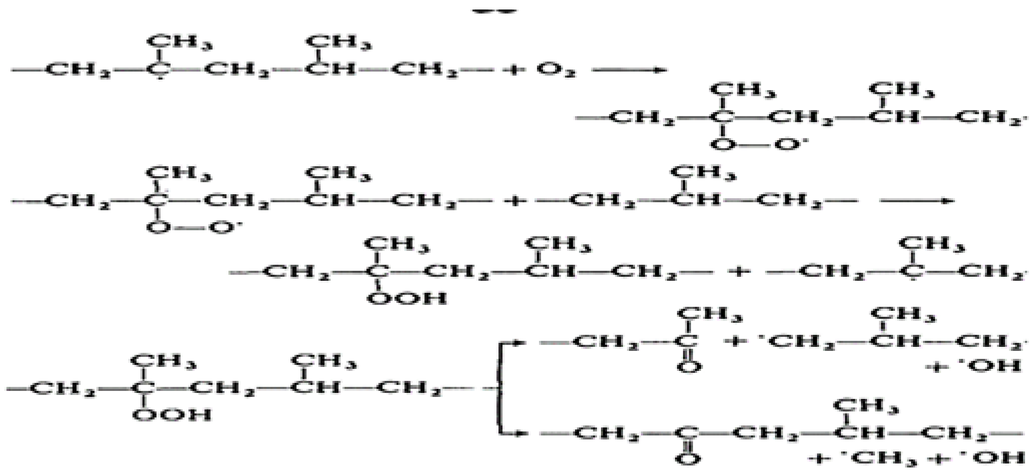


FIG. 6. General mechanism of oxidation reaction of PP by radiation

3.5. COMPARISON OF ELECTRON BEAM IRRADIATION WITH GAMMA PROCESSING FOR NON-WOVEN POLYPROPYLENE

Although the main interaction with matter is basically the same for gamma and high-energy electrons, some differences between the two modes remain. It is therefore the objective of this study to quantify these Gamma rays and EB differences, especially towards PP material degradation. Irradiation with EB results in much higher active species and their probability to recombination and termination is high taken in consideration that the high temperate under EB widow help to fast termination of such active species and the termination step in these cases is faster if compared with gamma. This prevents the diffusion of O_2 to surface and bulk of polymer and reduced the formation of proxy radical and minimizes the oxidation processing of polymers. However, by using gamma rays, the active species is slowly formed depending on the irradiation dose rate, the lower the dose rate the lower the active species formation as consequently radical termination rate is very low. This condition is more suitable for O_2 to interact with active spices

At room temperature and under low dose rates, the active species concentrations are quite low; hence, the termination reactions are relatively unimportant. However, at higher temperatures where the main polymer chains are quite mobile or under high dose rate conditions, through the high initiation rate, the active species concentration can be quite high and thus the termination reactions can be fast. At the higher temperatures, the free-radical recombination and termination reaction is expected to be much faster than that at near room temperatures, resulting in less polymer degradation. Moreover, the much-shortened irradiation duration would limit significant oxygen migration into the PP sample, compared with long time for gamma irradiation. Less oxygen availability would naturally lead to less oxidative degradations. On conclusions temperature, dose rate, and total irradiation dose as well as O_2atmosphere has a great effect on the oxidation process of PP.

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Egypt (Ayman Massoud)

Technical Report for CRP-Research Project – F23035

ON

"Radiation Effect on Polymer Materials Commonly Used in Medical Devices" Under CRP Projects- IAEA

1. Title:

"Effect of Gamma Radiation and Electron Beam on Raw and Manufactured Polymeric Materials Commonly Used in Medical Devices and Tools"

Covering Period: June 2021 to June 2026

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Recipient: International Atomic Energy Agency (IAEA)

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Project Team: Ayman Massoud (PI)

Nabila Maziad (Co-PI)

Moussa Osman (Member)

Contact(s): Ayman Massoud, PhD

Associate Professor

Nuclear Chemistry Department

Egyptian Atomic Energy Authority, (EAEA)

P.O. Code 13759, Cairo, Egypt

Cell phone: +201063825713

Email: ayman_mass@yahoo.com

Official email: ayman.massoud@eaea.org.eg

2. Summary:

Gamma irradiation, electron-beam, and x-ray have been used for sterilization of medical devices and tools. Gamma radiation is the most common method used for this purpose. The objective of this project is to provide more information about the effect of radiation on the polymeric materials commonly used in medical devices.

Therefore, the effect of radiation of gamma-rays, and electron-beam on the raw and manufactured polymeric materials commonly used in medical devices will be investigated. Numerous parameters such as the effect of dose, effect of dose rate, and the effect of radiation type on the mechanical, thermal properties, and physicochemical stability of polymeric materials will be evaluated. Moreover, the effect

of radiation on the biocompatibility and aging of irradiated samples will be studied. Besides, the effect of irradiation on the functionalities of the whole product will be estimated. As a result, this CRP project will increase the existing knowledge base of radiation effects on the polymeric materials commonly used (medical devices and tools) and also identify optimal doses for the sterilization of medical devices and tools.

3. Background Information:

Currently, **polymeric materials** are rapidly replacing or are used in conjunction with other materials such as metals, alloys, and ceramics in device preparation.[1-3] Table 1 provides a list of polymers used in implantable devices along with their preferred sterilization methods and applications. Biodegradable polymers such as polyesters, polycarbonates, polysaccharides, etc. are preferred over non-biodegradable polymers as they are cleared from the body over time thus allowing the neighboring tissues to restore their functionality following treatment with the implantable device. Infection is a major problem associated with implantable devices and involves bacterial, device, and host-related factors.8 Commonly found bacteria include Staphylococcus aureus, Staphylococcus epidermidis, Eschericia coli, etc.[4] Several device factors such as shape, size, and location can also facilitate virulence. To prevent infection, sterilization is a critical step in the manufacturing of MD’s and also in the preparation for reuse of MD’s (such as suction tubes, endoscopes, etc.). Failure in sterilization for an MD can leave the patient exposed to various nosocomial infections, which could in turn be life-threatening. It is important to consider sterilization and related issues early on in the development of the MD as opposed to the final stages to ensure the safety and effectiveness of the device. This review article focuses on established as well as novel sterilization techniques for polymer-based implantable MD’s providing an emphasis on the impact of these techniques on polymer stability and degradation [6].

Medical devices (MD) are regulated in the US by the Food and Drug Administration (FDA) under the Medical Device Regulation Act of 1976 and by the subsequent amendments made to the Federal Food, Drug, and Cosmetics Act of 1938. The MD’s have been organized into three classes by the FDA, namely Class I, II, and III based on the risks involved, and the degree of regulatory control necessary to ensure a device’s safety and effectiveness [7]. **Class I** devices such as bandages, gloves, and hand-held surgical tools are considered low-risk and are subjected to the lowest level of regulatory control. **Class II** devices such as pregnancy test kits, condoms, and powered wheelchairs are considered higher-risk compared to Class I devices and thus require special controls for labeling, guidance, tracking, design, performance standards, and post-market monitoring. Many Class II devices require premarket notification 510 (k) to demonstrate substantial equivalence (i.e. that they have the same intended use and technological characteristics) to a legally marketed device. **Class III** devices such as implantable glucose sensors, pacemakers, and breast implants are considered the highest risk and require stringent regulations. Most Class III devices require premarket approval (PMA). PMA examines a variety of factors in weighing the probable health benefits from the intended use of a device versus the probable risks. Figure 1 shows a flowchart of the classification of MD’s and steps involved in the approval process.

Implantable MD’s fall under Class II/III devices and are defined as devices placed inside the body for a short or long-term period to serve their intended purpose. Based on their application, implantable MD’s are divided into three groups: Orthopedic implants, Cardiovascular implants, and implants for other use [8]. The US implantable device market is expected to be worth $73.9 billion by 2018.5 Orthopedic implants are the most commonly used medical implants and have the largest market share [9].

Sterilization is defined as the process by which all-living cells, viable spores, viri and viriods are either destroyed or removed from an object. Sterilization can be achieved through the use of a passive process (aseptic processing) or an aggressive process (terminal sterilization). As aseptic processing is expensive, terminal sterilization is the most commonly used method. Sterilization of implantable MDs is performed to eliminate pathogenic organisms and thus minimize the risk of infection. Sterilization efficiency or sterility is measured in terms of the Sterility Assurance Level (SAL). A SAL limit of 10^{-6} is generally acceptable for pharmacopoeial sterilization procedures and is defined as ‘the probability of finding not more than one viable microorganism in one million sterilized materials [10]. Upon optimizing an existing sterilization technique or developing a novel technique, method validation studies have to be performed. The validation studies should document that the product can achieve the required SAL post sterilization by the proposed method. **In the industrial setup**, sterilization validation is generally evaluated by: i) determining the qualitative and quantitative bioburden after product manufacture; ii) determining the rate of killing using fractional-run sterilization; and iii) determining the duration required to achieve 10^{-6} SAL. In fractional-run sterilization, the product is exposed to a fixed dose of sterilant, following which the number of resistant microorganisms is reported graphically on a semi-logarithmic plot, and by extrapolation, the dose and time required to achieve 10-6 SAL is estimated [10].

Radiation sterilization can be of two types depending on the source of radiation: Gamma sterilization and Electron beam sterilization. Gamma radiation utilizes high-energy gamma rays, which have excellent penetration powers. Electron beam sterilization employs a constant stream of high-energy electrons. Radiation sterilization is a fast process, requiring only one dose between 15-45 kGy, thus resulting in ease of application. 25 kGy is a typical dose commonly employed to destroy the microbial load. Although radiation is an effective sterilization technique, the initial capital costs for setting up a radiation facility are very high. Radiation kills bacteria by breaking down the bacterial DNA thus inhibiting bacterial division. Radiation can also kill bacteria by the formation of free radicals [11].

4. Overall Objective:

This project aimed to expand the existing knowledge base and identify optimal doses of sterilization for medical devices.

5. Specific Research Objectives

- Survey of the previous publication for most polymers commonly used in medical devices.

- Bring the polymeric samples from the companies currently used in medical devices and also their raw materials of polymeric devices.

- Selection of appropriate measurements and analytical methods to detect the effect of radiations on the polymeric materials and their radiation degradation as by-products.

- Calculation and assessment of radiation doses used for irradiation of polymeric materials.

- Irradiation of polymeric raw materials and medical devices (implants) by different irradiation techniques including gamma rays, and electron beam.

- Measurements of irradiated polymeric samples and medical devices using analytical techniques such as Scanning electron microscope (SEM), Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), Dynamic viscosity measurements (Rheological analysis), tensile strength (dynamic direct tensile test), spectrophotometric colorimeter (Colorimetry) and Shore durometer (hardness) then evaluate the effects of radiation on their mechanical, thermal, structural, and physicochemical properties.

- Theoretical models maybe apply to the obtained experimental data

6. The facility in our institute:

The collected samples will be irradiated in the gamma cell and electron beam:

- We have more than gamma sources with different dose rates. Therefore, we can easily study the effect of doses and dose rate on polymeric materials.
- We have also an electron accelerator with a 3MeV industrial linear accelerator beam 3mA, with a minimum dose of 3 kGy without a maximum dose. The applications of this accelerator are treatment and sterilization.
- Characterization of the polymeric samples:

1. XRD- model Shimadzu 6000, made in Japan
2. FTIR model Nicolet iS10 FT-IR spectrometer (USA)
3. SEM model no. JEOL JSM 5600 LV, made in USA
4. TGA-DTA model Shimadzu DTG-60 thermal analyzer
5. Hardness tester

7. Planned Activities

- Survey of the previous publication for most polymers commonly used in medical devices.
- Bring the polymeric samples from the companies currently used in medical devices and also their raw materials of polymeric devices.
- Selection of appropriate measurements and analytical methods to detect the effect of radiations on the polymeric materials and their radiation degradation as by-products.
- Calculation and assessment of radiation doses used for irradiation of polymeric materials.
- Irradiation of polymeric raw materials and medical devices (implants) by different irradiation techniques including gamma rays, electron beam, and X-ray.
- Measurements of irradiated polymeric samples and medical devices using analytical techniques such as Scanning electron microscope (SEM), Fourier transform infrared spectroscopy (FT-IR), X-ray diffraction (XRD), Dynamic viscosity measurements (Rheological analysis), tensile strength (dynamic direct tensile test), spectrophotometric colorimeter (Colorimetry) and Shore durometer (hardness) then evaluate the effects of radiation on their mechanical, thermal, structural, and physicochemical properties.
- Theoretical models maybe apply to the obtained experimental data

8. The current stage of the project:

Currently, we have collected the polymeric raw materials samples and manufactured medical devices and tools from different companies in our country. Next step: we will divide the collected samples into many groups according to the irradiated doses. Then, the samples will be irradiated with different doses and dose rates based on the calculated doses.

Acknowledgments:

The project team would like to express our deep thanks to the International Atomic Energy Agency for supporting the project. The project team also would like to extend their deepest appreciation to Ms. Valeriia Starovoitova and other organizing members for the achievement of the meeting.

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France (Belkacem Otazaghine)

Assessment of the impact of the irradiation process on the final properties of radio-resistant and customized polypropylene materials used for medical devices

1. Partners of the project

The project is led by a French consortium of industrial and academic partners:
IMT Mines Alès: Aurélie TAGUET, Rodolphe SONNIER and Belkacem OTAZAGHINE
IMT Mines Saint Etienne: Jean GERINGER
Aix-Marseille University: Nathalie DUPUY and Sylvain MARQUE
IONISOS: Sophie ROUIF
AERIAL: Nicolas LUDWIG and Florent KUNTZ
MEDTRONIC: Xavier BOURGES and Yves BAYON
SARTORIUS: Samuel DOREY

2. Introduction

The project concerns the conversion from the current sterilization method using ethylene oxide (EO) to irradiation methods for PP containing medical devices. Indeed, the environmentally friendly radiation procedure, and the possible reduction in costs through faster (more flexible and time effective) sterilization make irradiation processes of great interest to medical devices or biopharmaceuticals manufacturers. Current PP formulated for medical devices and sterilized by radiation contains antioxidants to gain radio-resistance. While the effects of irradiation on virgin polypropylene and on some generic antioxidants are well established, when it comes to commercial grade of polypropylene, effects of irradiation are far from being fully understood. Radiation induced release of these antioxidants could lead to potential extractable products coming into contact with human body.
Hence, the objective of the project is to assess irradiation impact on the (micro)structure and mechanical properties of antioxidant formulated PP. This will be performed for the three irradiation modalities: gamma, e-beam and X-rays in order to find equivalences or inquire about differences between these methods and to define suitable conditions for the PP sterilization.

3. Academic and industrial partners of the project

This project will be carried out in collaboration with several academic and industrial partners who have strong expertise in irradiation technologies and process control (IONISOS and Aerial) as well as in the manufacturing and evaluation of medical devices and biopharmaceutics intended products (MEDTRONIC and SARTORIUS). The academic partners (ICR and IMBE Laboratories of Aix-Marseille University, IMT Saint Etienne and IMT Mines Alès) have the knowledge and the equipment to study and evaluate the different phenomena that occur for polymers during irradiation and to understand the impact of each of the technologies used on the properties of the materials treated.

4. Description of research objectives

The project concerns the evaluation of irradiation procedures for the radiation sterilization of polypropylene (PP) materials used for medical devices applications.
Generally, for long-term medical device applications, PP is sterilized with ethylene oxide (EO). The high toxicity of EO gas and the possible reduction in costs through faster and flexible processes make irradiation processes of great interest to medical devices manufacturers. Nevertheless, commercial PP formulations which can be used for radiation sterilization are not adapted to be used as implant for more than twenty-eight days (short-term implants). Indeed, to be suitable for radiation sterilization, PP

must be stabilized with antioxidant additives to mitigate the degradation of the polymer matrix during the irradiation. Antioxidant molecules and products formed by their reaction during irradiation step can have toxicity for the human organism. Moreover, the irradiation process also consumes the antioxidants used to improve the durability of PP and limits long-term applications.
PP is the second thermoplastic polymeric material that is devoted to medical device and instruments. Sterilization of every article containing PP is a problem for manufacturers as the PP material suffers from changes in properties due to EO treatment, the usual sterilization method. In addition, to compensate the antioxidant consumption the volume of the manufactured PP objects is artificially increased in order to limit some of the deleterious effects of γ irradiation on mechanical properties. So, optimization of both the irradiation process and the formulation of the PP should reduce the consumption of PP.
The objectives of the project are: 1) to assess the impact of various irradiation modalities (e-beam, X-rays and gamma) and conditions on the structure and the final properties of PP materials used for implant and medical devices applications, 2) to study the effectiveness of antioxidant formulations for the stability of PP and 3) to evaluate the release of antioxidants or their degradation products from the irradiated PP materials 4) to reduce the volume of PP products used as medical devices (and thus reduce the environmental impact of the consumption of this polymer) while keeping their long-term functional resistance.
Recommendations for the radiation sterilization of stabilized PP materials are expected. Indeed, the applications of this material are very diverse and the expected properties vary accordingly. The evaluation of the impact of the irradiation process on the final properties of the PP will make it possible to disclose sterilization conditions recommendations for the different medical devices (parietal implants, sutures, single-use systems including bags and filters).

5. Scientific Scope of the project

This project aims to understand the processes involved in the irradiation sterilization step using gamma, E-beam and X rays and to assess their effects on the properties of PP materials (including stabilized PP) in order to respond to the following questions:
- What are the physico-chemical modifications undergone by PP during the irradiation process (formation of radicals, decomposition of polymer chains or additives, modification of crystalline zones, etc.)?
- What are the effects of the different irradiation methods (e-beam, gamma, X-rays) on the properties of PP? Can equivalences between these modalities be found or can the sterilization of polypropylene be optimized in terms of treatment conditions?
- How can the modifications undergone for the stabilized PP material modify its interaction with its environment (adsorption and absorption or release of chemical molecules) and affect its aging?

6. Work Plan for the first year

During the first year, standard specimens from commercial PP formulations will be prepared and irradiated over a large range of doses using different irradiation methods (i.e. gamma, e-beam and X-rays). The irradiation plants at IONISOS and Aerial will make it possible to compare the three irradiation modalities while applying defined dose and dose rate levels.
The PP mechanical properties will be assessed over a period of 12 months. The maximum acceptable dose will be defined for each irradiation modality and each PP formulations. The maximum acceptable dose is defined according to the relevant standards (i.e; ISO 11137)
Processing equipment (twin-screw extruder and injection-molding devices) will be used to prepare standard specimens.
Mechanical characterization will be mainly carried out using Universal Testing Machines.
The objective is to identify if the mechanical properties are impacted only by absorbed dose or also by other factors (like dose rate or combination of factors like Dose x Dose rate) requiring specific recommendations to be made depending on the irradiation method.

7. Work Plan for the second year

During the second year, the influence of irradiation conditions (dose, dose rate, atmosphere, irradiation methods, i.e. e-beam, X-rays, gamma) on PP structure will be assessed for several commercial and/or lab-made PP formulations. It includes the following characterization methods: solid and liquid NMR, gel fraction, Dynamic Scanning Calorimetry, FTIR spectroscopy, Electron paramagnetic resonance (EPR).
The objective is to identify if the occurrence of a given phenomenon (oxidation, crosslinking, chain scission) or their relative importance depends on irradiation conditions (for the same absorbed dose). This will allow ultimately to propose some equivalences between the irradiation modalities.

8. Work Plan for the third year

During the last year, the issue of antioxidant additives will be addressed, especially how the impact of irradiation on PP material can be modified in presence of these additives. Moreover, their possible release from the polymer matrix during their use is a major problem which must be properly evaluated. A series of commercial or lab-made PP formulations with a well-known amount of antioxidant additives will be characterized by several methods for a couple of irradiation conditions. The influence of the nature and content of antioxidant additives on PP structure and properties will be assessed.
The release of these additives and their degradation products in human body will be assessed by aging tests on PP formulations immersed in solutions mimicking human body fluid.

9. Expected Outputs

Several results are expected for this project:
- Identification and quantitative assessment of the irradiation conditions impacting the structure and properties of PP used as medical devices.
- Identification of the role of antioxidant additives on mechanisms involved in radiation processes.
- Study of the release of antioxidants or their degradation products (formed during the irradiation step) from the PP materials.
- Recommendations about radiation sterilization methods for durable PP material medical devices.
- Optimization of component design for long term resistance

France (Nicolas Ludwig)

Irradiation modality and dose rate effects upon radiation sterilization of commercial polymers used in medical devices.

Introduction

Radiation sterilization using gamma rays, electron beams and X rays are today commercially available, although gamma ray plants are taking precedence over machine sources, and X-rays were implemented industrially only about ten years ago. Machine sources (electron beams and X-rays) become an alternative to irradiation by radioactive sources emitting gamma rays. The interest and acceptance of manufacturers of medical devices, laboratory supplies or consumables for electron beams and X-rays is now evident. While the sterilization efficiency is well established for these three irradiation modalities, their impact on the radio-induced modifications on the polymers used in medical devices, e.g. in implants or devices for biopharmaceutical applications, is far from being understood. In a scientific point of view the principal differences between these modalities is their dose rate. Indeed, both gamma and x-rays release their energy to electrons present in matter when interacting with the matter and these electrons deposit eventually their energy resulting in radiation-induced effects in a similar way than electron beams (direct vs indirect ionization effects). Typical dose rates in industrial irradiation processes are kGy/h for gamma-rays, kGy/min for X-rays and kGy/s for electron beams.

The inherent radiation nature effect ("pure" modality effect) has rarely been studied. Indeed, due to the difficulties of process control with these modalities, studies of their influence are very rare under comparable conditions (control of the dose, dose rate and irradiation conditions). In this goal, this project aims to investigate the inherent radiation nature effect of modality and the combination of irradiation modality and dose rate effect in the radio-induced modifications of polymers commonly used in medical devices. To do so, samples will be irradiated with gamma, X-rays and electron beams with incremental doses with a defined and controlled dose rate. Several commercial grade polymers will be tested in each irradiation condition: LLDPE, HDPE, PA, TPE, PET, PLA, PHB. Physico-chemical modifications of matrices and their mechanical and thermal properties will be evaluated shortly after and over a period of one year after irradiation, in real time and accelerated conditions. Fundamental keys will be obtained through this study to better understand problems encountered in the radiation sterilization field in the context of these technological adoptions.

Scientific scope

This project aims to achieve fundamental results that answer questions having echoes with expectations of manufacturers of medical devices especially for one used as implants and for biopharmaceutical applications:

- What are the principal modifications observed when irradiating several commercial grade polymers?

- How do irradiation modalities and their intrinsic characteristics influence modifications observed on polymers?

- How to mitigate impacts of irradiation by choosing the ‘best’ irradiation modality and optimized conditions?

- What is the impact of irradiation modalities over time, notably during the storage of the devices?

Obtained results will form an original data set which may help industrials considering the radiation sterilization or to choose between existing irradiation modalities regarding their own problematic.

Moreover, this study will although help manufacturers supporting the transition from gamma sterilization to machine source-based radiation sterilization process and offering augmented flexibility in their sterilization mode.

Technical activities

Irradiation will be performed on two different platforms, Feerix platform for both, X-rays and electron beams and Ionisos Dagneux facility for gamma rays :

Feerix Platform at Aerial-CRT in Illkirch, France, is based on a Rhodotron, an electron accelerator (TT300, IBA- Belgium) which beam is used directly to irradiate products on a chain conveyor or converted into an X-rays beam for photon irradiation. Indeed, in this facilities, two different beam lines allow performing treatment with both, 10MeV electrons beam (EB) and X-rays from the conversion of 5 or 7MeV electrons. Dose rates can be targeted between 0.003 and 0.1 kGy/s for X-rays and 0.1 and 20 kGy/s in electron beam.

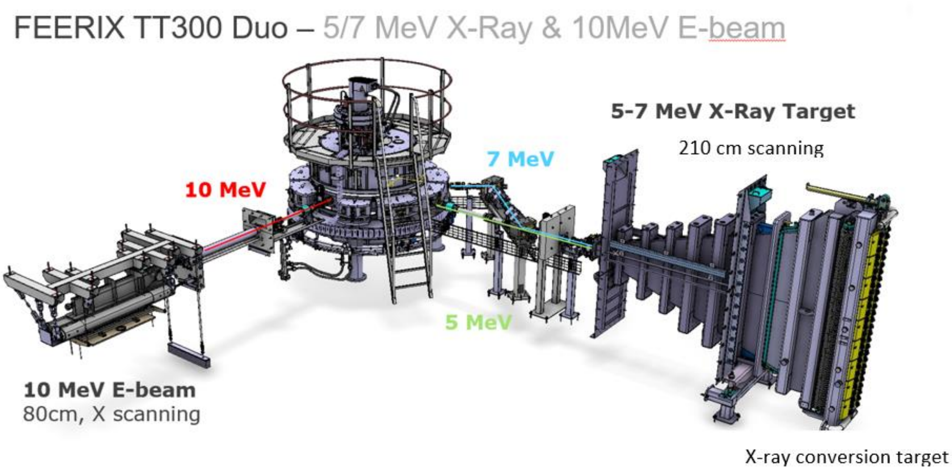


Figure 1: Rhodotron (center), with electron (left) and X-ray (right) beam lines.

Gamma irradiation will be conducted in IONISOS facilitiy in Dagneux, France, based on Cobalt-60 gamma source. Dose rate from 0.1 to 20 kGy/h can be reached.

The actual dose will be controlled after irradiation by alanine/EPR dosimetry, thanks to an MS5000 spectrometer (Freiberg Instruments) with the AerEDE dosimetry dedicated software. EPR spectra of irradiated polymers could also be readily recorded after irradiation to track short lifetime radiation induced radicals.

Irradiation will be conducted at different dose rates, in a range of 6 decades going from 10 to 3. 10^{-5} kGy/s. Due to each irradiation modality characteristics, all dose rate cannot be achieved with each modality. Thus, an irradiation plan which allows to compare irradiation modalities two by two have been designed (Figure 2). Irradiations with Gamma and X-rays will be realized in similar dose rate and irradiation with X-rays and electron beams will be realized in similar dose rate as well.

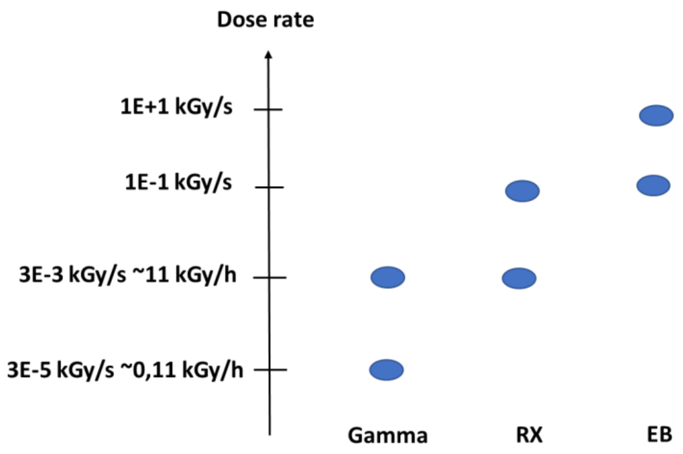


Figure 2: Irradiation plan taking into dose rate achievable with each modality

To evaluate radio-induced modifications in polymers, following physico-chemical characterizations and properties characterizations will be conducted for each of the irradiation conditions:

- Chain scission or crosslinking will be evaluated with gel fraction or HPLC-SEC analysis.
- Chemical modification will be followed by spectroscopic analysis (FTIR, Raman)
- EPR spectrometry will be realized to quantify the amount of radicals remaining in the matrix
- Properties modification: Colorimetry /Mechanical properties / Thermal properties: DSC / DMA
- Leachable and extractables will be analyzed

Detailed work plan for the first year

The first year will be dedicated to the development and optimization of analytical procedures for polymer testing. Physico-chemicals analysis protocols and properties evaluation procedures must be defined for each of the listed polymeric materials. Key indicators to follow could be oxidation rate, presence of radicals, gel fraction, thermal or mechanical properties, extractables and leachables. A first irradiation trial with one single modality will be ran with incremental doses to validate this step and select the more relevant analysis techniques for each of the materials.

The objective of the first year is to define experimental protocols and obtain results with a limited number of irradiations.

Detailed work plan for the second year

Based on the experience acquired during the first year, a comprehensive irradiation plan will be designed to explore potential combination of dose rate and modality effects. This trials will be conducted under typical dose rate encountered with gamma (kGy/h) up to dose rate in electron beam process (kGy/s) in the limit of the possibilities for each of the modalities.

A comprehensive dataset with several dependencies will be obtained

Detailed work plan for the third year

Knowing the potential influence of the modalities, dose rate and their combination on common polymers, additional irradiation parameters such as temperature, atmosphere, formulation, device design (and particularly the specimen thickness), …will be explored in the aim of mitigating their effect. Relevant polymers and irradiation conditions will be selected, and a new set of irradiations and analysis will be defined.

The final goal of this study will be to define general trends of observed modifications on the effects induced by the three irradiation modalities over the product's storage time. These features will be used in order to assess shelf life of materials, and their mechanical specifications overtime.

Finally, acquired knowledge could lead to define most appropriate (the least impacting) irradiation conditions for the studied polymers

Expected outputs

- Obtain an original dataset allowing the efficient comparison between gamma, X-rays and electrons beams irradiation for several commonly used polymers used for medical device.

- Identify the potential role of the irradiation modality, the role of dose rate and the influence of combinations between irradiation modalities, dose rate and other irradiation parameters such as atmosphere and temperature in the overall modifications of common polymers.

- Give recommendations about important parameters to control during a radiation sterilization process to mitigate as much as possible impacts on studied polymers.

- Obtained results will be valorized through publications and/or presentations in scientific conferences (particularly ICARST, IMRP, IRAP, TIHANY, MILLER, …)

Partners

This project is led by Aerial. Aerial-CRT is a worldwide known private R&D organization labelled as Technology Resources Centre by the Ministry of Research and involved in industrial Radiation applications and process control for more than 3 decades. Aerial is recognized as an IAEA collaborating centre and its dosimetry activities are accredited as a secondary Standard Dosimetry Laboratory (Cofrac), the only one in France in this field. Aerial will be in charge of high energy E-beam and X ray irradiations and will manage the dosimetry aspects to make sure of the output's relevancy.

To conduct this CRP, Aerial will be supported by several academic and industrial French partners.

Academic partners:

- IMBE (Mediterranean Institute of marine and terrestrial Biodiversity and Ecology) Joint Research Unit Aix Marseille University/CNRS/IRD/Avignon University. Internal coordinator: Prof. N. Dupuy. Field of expertise: Characterization and study of the aging of natural or formulated products (polymers, membranes) with the highlighting of markers of aging or quality.

- ICR (Institut de Chimie Radicalaire), CNRS / Aix Marseille University. Internal coordinator: Pr. S. Marque. Fields of expertise: Detection of radicals by Electron Paramagnetic Resonance, radical reactivity, and analyzing data.

- PCH (Polymers Composites and Hybrids) from IMT Mines Alès. Internal coordinator: Dr. Rodolphe Sonnier. Field of expertise: 1/ Recycling of polymer materials (polyolefins, ground tire rubber) by radiation-compatibilization, 2/ Promote interfacial compatibilization between polymers and fibers in composites by irradiation, 3/ Impart new functionalities (especially flame retardancy) to fabrics by radiation-grafting FR.

Industrials partners:

- The Sartorius Group is a leading international laboratory and process technology provider covering the segments of Bioprocess Solutions, and Lab Products & Services. The major areas of activity of its Bioprocess Solutions segment cover filtration, fluid management, fermentation, cell culture and purification, and focus on production processes in the biopharmaceutical industry. Internal coordinator: Dr. Samuel Dorey.

- SOFRADIM PRODUCTION (Trévoux), a subsidiary of MEDTRONIC, a world leading company in medical devices, designs, develops and manufactures about 1 million/yr implants for soft tissue repair and hemostats, used for general surgery. It has filed +250 patents on core technologies such as biopolymer and synthetic polymer chemistry and formulation. Internal coordinator: Dr. Yves Bayon.

- Ionisos is a leading company for customized services by cold industrial sterilization. Ionisos runs beside EtO sites, multiple gamma and E beam plants in France and neighboring countries. Internal coordinator: Dr. Sophie Rouif.

India

Radiation Effects on Polymer Materials Commonly Used in Medical Devices

(Project code F23035, CRP No. 2285)

Code of the Coordinated Research Project (CRP) under which Research Contract Should be place

IAEA CRP No. 2285

Gamma-radiation and e-beam induced degradation and probable subsequent growth of microbes in the polymeric structural materials used in the diagnostic catheters

Abstract:

Catheter is a thin tube made from medical grade materials used by inserting it in the human body for the purposes of diagnostics, to treat diseases or perform a surgical procedure. Depending upon application of catheter, a broad range of soft polymeric materials is used for its construction due to their flexibility and biocompatible nature. These polymeric materials are: silicone rubber, polyamide, polyurethane, polyethylene terephthalate (PET), latex, and thermoplastic elastomers. In the proposed project under CRP. The study by the radiation effects on the actual catheters used in the hospitals at dose rate of 25-100 kGy deposited by gamma-rays and electron-beam will be investigated to understand the radiation induced degradation, ageing, and probability of growth of microbes on the catheters after irradiation. These polymer based catheters will be irradiated with gamma-rays from ^{60}Co and electron beam at Bhabha Atomic Research Centre, Mumbai, India and will be subjected to different studies such as Atomic Force Microscopes(AFM) and Field Emission Scanning Electron Microscope(FESEM) for surface morphology, small angle X-ray scattering for bulk physical structure, Thermo-gravimetric Analysis(TGA)/Differential Thermal Analysis(DTA) and Differential Scanning Calorimetry(DSC) for thermal properties, Contact angle measurement for change of hydrophilicity/hydrophobicity, change in its biocompatibility and microbial growth on the surface of the polymeric materials. These properties will be examined after keeping at ambient conditions at desired period of time intervals. The data obtained by these characterizations will be used for understanding the physical and chemical processes involved in the radiation induced changes in the catheters used for the diagnostic objectives.

Key words: Catheters; Electron Beam; Gamma ray; Degradation; Microbial growth.

Summary of Proposed Research

Introduction:

Implantable technology is very controversial. Use of these technologies opens a rather wide range of questions, dilemma, and arguments revolving around morality vs. legality, business profit versus genuine altruism, religion versus science and technology, animal rights versus human rights, to name but a few. The above example shows that implantable technology blurs further the boundary between what is living (human) and what is non-living (machine). There is a need for an informed discussion about these developments.

Interface between Living and Non-Living Beings

The connection between living and non-living beings has been the subject of human curiosity ever since we became self-aware, and this remains a most fascinating discussion topic today in the world. “Though there appears to be something in the phenomena of living beings which cannot be explained by ordinary mechanical, physical or chemical laws, much may be so explained, and we may without fear push these explanations as far as we can, so long as we keep to the solid ground of observation and experiment”.

A. Scientific Background on Medical Devices

Medical devices are any instrument, apparatus, machine, implant or tool that are used to diagnose, prevent, treat or cure diseases or other conditions. A great technological progress is found in nano-electronics. Implantable devices are becoming smaller, smarter, and more connected with better performance and increased patient comfort. These devices are packed with functions and becoming smarter that is they don't lose their functionality. For example, Internal (temporary) technology reduce the physical distance between machine and human body and spent only limited time within the body. While Internal (permanent) technologies like pacemaker, dental and cochlear implants are permanently inserted in the body by medical procedure and they cannot be removed by the user. These technologies expected to function and co-exist with the natural human organs during the user's lifetime and to have a multi-degree movement for the prosthetics.

Different Medical devices used in diagnosis and treatment in different parts of body of humans and different types of polymers used are listed in the table below:

List of Common Medical Devices/ Implants

Diagnosis Category	**Common Devices**	**Synthetic Polymer Material Used**
Anesthesiology	• Epidural catheters	• Polyethylene • Polytetrafluoroethylene • Polyamide
Cardiovascular	• Pacemaker • Implantable cardioverter/defibrillator • Left Ventricular Assist Device • Mechanical heart valves • Artificial blood vessels • **Catheters**	• Polypropylene • Polyethylene • Polytetrafluoroethylene • Polyamide • Polyethyleneterephthalate • Polydimethylsiloxane • Polyhydroxyalkanoates
Dental	• Dentures • Dental Implants	• Polymethylmethacrylate
Ear, nose, and throat	• Cochlear implants • Stapes implants • Nasal implants for nose reconstruction	• Polydimethylsiloxane • Liquid crystal polymer • Silicone • Parylene • Polyethylene
Gastroenterology and urology	• Penile implants • Neurostimulator in sacral nerve stimulation • Foley catheter • Artificial urinary sphincter implant • Hernia or vaginal mesh	• Polydimethylsiloxane • Polyethylene • Polytetrafluoroethylene • Polyamide • Polyhydroxyalkanoates • Silicone • Polypropylene

General and plastic surgery	• Synthetic blood vessels • Breast implants • Cheek, jaw and chin implants • Lip implant • Titanium surgical implants • Hip implant	• Polypropylene • Polyethyleneterephthalate • Polytetrafluoroethylene • Silicone • Polydimethylsiloxane
Hematology and pathology	• Central venous access device • Peripherally Inserted Central Catheter	• Polyethylene • Polytetrafluoroethylene • Polyamide
Neurology	• Implantable Pulse Generator for Deep Brain Stimulation • Neuro-prosthetics • Cognitive prostheses • **Catheters**	• Polyimides • Polydimethylsiloxane • Parylene • Liquid crystal polymers • SU-8 • Polyethylene • Polytetrafluoroethylene • Polyamide • Polyhydroxyalkanoates
Obstetric and Gynecologic	• Intrauterine Device (IUD) • Intravaginal Rings • Etonogestrel-releasing Contraceptive Implant • Uro-sgynecologic Surgical Mesh Implants • Fetal micro-pacemaker	• Silicone • Polyurethane • Polypropylene
Ophthalmic	• Dexamethasone Intravitreal Implant • Retinal Prothesis • Artificial Intraouclar lens	• Polymethylmetacrylate • Polyethylene • Polytetrafluoroethylene

	• Glaucoma valve • Fluocinolone Opthalmic Implant • Orbital Implant • **Catheters**	• Polyamide
Orthopedic	• Orthopedic Implants	• Polyethylene • Polyether Ether Ketone • Polyhydroxyalkanoates

Medical Devices: Catheters

"Catheter" is a Greek verb meaning "to thrust into" or "to send down". Catheters can be inserted into a body cavity, duct, or vessel, brain, skin or adipose tissue. In general, catheters can be used for functions such as drainage, administration of fluids or gases, access by surgical instruments and perform a wide variety of other tasks depending on the type of catheter. The catheters probes are used in preclinical or clinical research for sampling of lipophilic and hydrophilic compounds, protein-bound and unbound drugs, radiopharmaceutical, neurotransmitters, peptides and proteins, antibodies, nanoparticles and nanocarriers, enzymes, and vesicles.

Catheter is a hollow thin tube made of soft plastic material that can be inserted in the body either enteral, vascular or for draining purposes. Catheters are most referred to as medical devices in hospital settings and prescribed by doctors. Vascular catheters are most widely used devices worldwide in hospitals. Since 1990s, catheter products have significantly changed in their composition, texture, and durability. Catheters are used in three areas of journey such as Radiology, Neurology and Cardiology study. French scale or gauge system unit is commonly used to measure the size in catheters and abbreviated by “Fr” (Diameters in millimeters multiplied by 3 = French size).

I) Catheter Angiography (Radiography) uses a thin plastic tube called catheter is inserted in blood vessel through small incision in the skin. Once the catheter is guided to the area being examined then the contrast material is injected through catheter and captures images using small dose of ionizing radiations (x-rays). The angiography is used to diagnose and treat blood vessel diseases and conditions. Angiography is performed by using x-rays with catheter, computed tomography (CT)/radiography and magnetic resonance imaging (MRI). The use of catheter makes possible to combine diagnosis and treatment in single procedure, Catheter angiography gives a detailed, clear and accurate pictures of blood vessels and help define treatment options. CA is used to examine body vessels in key areas of body for abnormalities are – brain, neck, heart, chest, abdomen (such as kidneys and liver), pelvis, legs and feet, arms, and hands. No radiations stay inside body after an x-ray examination and usually have no side effects in typical diagnostic range. Angiography may eliminate the need for surgery, and if surgery is necessary only then performed more accurately.

II) Neuro Catheters (Neurology) are used to retrieve blood clots in cerebral neuro vasculature by mechanical methods used by neurosurgeons and challenges them to direct catheters to the delicate deep recesses of brain. Concept of soft easily steerable catheter (**Ability to steer the device in any direction they want while navigating the brain's arteries and blood vessels)** that would significantly improve ability to treat brain aneurysms and many other neurological conditions. The device was inspired by nature specifically insect legs and flagella like structures that allows microscopic organisms such as bacteria to swim. **Neuro vascular guide catheters** and thrombus retrieval catheters are designed with different features (diameter, length, variation in material stiffness proximal and distal). According to FDA catheters are put in class 2 of medical device and use of neurovascular guide catheters for thrombus removal may affect the safety and performance, which could result in device failure or serious adverse events such as vessel damage, perforation, or dissection when used in the most distal regions of the neuro vasculature and also difference in the device design

III) Diagnostic (Cardiac) Catheters are designed in such a way so as to meet the needs of patients from simple to complex case and helps to navigate cardiac anatomy, critical cardiac information and to deliver more precise therapy. Diagnostic catheter angiography is for evaluation of brain, head-neck and spine. Guiding catheters generally look stiffer to provide backup support for balloon/stent catheters into the coronary artery and respond differently than diagnostic catheters. Cardiac catheterization or heart cath is also known as cardiac angiogram, outline the heart arteries and angiograms outlines the neck arteries are called carotid angiogram.

Uses of catheters

I. For Diagnosis	II. For Treatment
Angioplasty, **angiography**, **balloon septostomy**, **balloon sinuplasty**, **cardiac electrophysiology testing**, **catheter ablation**. Often the Seldinger technique is used.	**Urinary catheter**: draining urine from the urinary bladder as in urinary catheterization, e.g., the intermittent catheters or Foley catheter or even when the urethra is damaged as in suprapubic catheterization
Direct measurement of blood pressure in an artery or vein	**Drainage of urine** from the kidney by percutaneous (through the skin) nephrostomy
Direct measurement of intracranial pressure	**Drainage of fluid collections**, e.g., an abdominal abscess
	Pigtail catheter: used to drain air from around the lung (pneumothorax)
	Administration of intravenous fluids, medication or parenteral nutrition with a peripheral venous catheter or central venous catheter
	Urinary catheter: draining urine from the urinary bladder as in urinary catheterization, e.g., the intermittent catheters or Foley catheter or even when the urethra is damaged as in suprapubic catheterization

	Drainage of urine from the kidney by percutaneous (through the skin) nephrostomy
	Administration of anesthetic medication into the epidural space, the subarachnoid space, or around a major nerve bundle such as the brachial plexus
	Transfer of fertilized embryos, from in vitro fertilization, or sperm, during artificial insemination, into the uterus
	Administration of oxygen, volatile anesthetic agents, and other breathing gases into the lungs using a tracheal tube
	Subcutaneous administration of insulin or other medications, with the use of an infusion set and insulin pump

III. Performance of surgical procedure:

Imaging and diagnostic catheters are used to investigate and evaluate patients with suspected or known cardiovascular diseases.

Imaging and diagnostic catheters include products such as:

- Angiography Catheters
- MRI Guided Catheters
- Intravascular Ultrasonic Catheters (IVUS)
- EP Mapping Devices
- Cardiac Output Catheters
- Pressure Monitoring Catheters
- Flow Monitoring Catheters
- Oximetry Catheters
- Temperature Monitoring Catheters
- Critical Care Monitoring Systems

Materials Used in Catheters

The structural materials of the catheters are mostly made-up of a board range of polymers such as silicone rubber, polyamide, polyurethane, polyethylene terephthalate (PET), latex, and thermoplastic elastomers. The choice of polymers for the construction of catheters are attributed to it is inert and unreactive to body fluids and a range of medical fluids with which it might come into contact, biocompatibility, flexibility, softness, reasonably good mechanical strength, and possibility of designing it in any shape and sizes. Silicone is one of the most common implantable choices because the reasons stated above. The polyimides are used generally used in vascular catheters for insertion into small vessels in the neck, head and brain. There are many different types of polymeric materials used in catheters for bladder problems. A typical catheter used for above purpose is made from polyurethane and available in different lengths and sizes for men, women, and children. Depending upon specific requirements, some of the catheters have a thin hydrophilic surface coating which swells to a smooth, slippery film making the catheter safer and more comfortable to insert. Some catheters must be packed in a sterile saline solution for the protection against the infections. Some of the examples of the polymeric materials used in the catheters are given in Table 1.

Table 1. Types of Polymers used in Catheters

Types of Catheters	**Types of Polymer used in catheters**
Cournand	Polyurethane
Lehman catheter	
Goodale-Lubin catheter	Polyurethane
Baloon floatation catheters	
Gensini	Polyurethane
Nasal Catheters/ Oropharyngeal	Woven Dacron with Nylon re-enforcement COOK Torcon blue catheter: polyethylene Cordis catheter: polyurethane
Eppendorf catheter	Polyurethane
Lehman ventriculography	
Pigtail angiographic catheter	
Flow directed angiographic catheter	Polyurethane
Shirey transvascular catheter	
Brocken-brough transeptal catheter Double lumen catheter	
Multi-lumen catheter	
Fogarty catheter	
Transducer-tip catheter	
Angioscopic catheter	
Pacing catheter	

Multipurpose catheter	Ppolyurethane
Pigtail catheter	Polyurethane or polyethylene
Grollman pigtail catheter	Polyethylene
Van tassel angled pigtail	Polyurethane
Positrol II pigtail catheter	Polyurethane
Nycore high-flow pigtail catheter	Polyurethane
Ducor high-flow femoral-ventricular Pigtail catheter	Polyurethane
Double pressure Lumen Balloon (Wedge-Pressure catheter)	
Thermo-dilution catheters	Heparin coating(with or without)
Diagnostic vessel sizing catheters	
Berman angiographic catheter	
Reverse Berman catheters	
Impluse diagnostic catheter	
Imager Angiocardiography catheter	
Expo-Diagnostic catheter - Boston	
Siteseer angiographic catheter - Medtronic	Pebax material
Coronary angiographic catheter	

Rationale: Radiation Effects on Catheters

Radiation sterilization of medical devices is an important method. Medical disposable products commonly used in medical devices and sterilized by radiation are syringes, Absorbents, urine bags, **Catheters,** Gloves, drains, tubing, drain pouches, bandages, beakers and laboratory ware, surgical gowns and drapes, hand towel, petri dishes, culture tubes etc. The compatibility of all components must be considered while using radiation for sterilization of medical devices. Ionizing radiations not only kill microorganisms but also affect the material properties. The catheters are mostly made up of many different polymeric materials, composites and sometimes ceramics. Polymeric materials have diverse group and materials exhibit different changes in chemical structure of polymers due to which physical changes occurs. This makes some polymer to cross-links, some to chain-scission while few others are mostly unaffected. Saturated polymers undergo cross-linking and scission while cyclic or ring structures tend to be neutral under radiation in that it is believed that radiation become trapped and resonates within the ring structure. The catheters may also use for the radiopharmaceuticals and desired radiations emitting radionuclide.

Radiations may deteriorate the desired properties of the structural polymeric materials of catheters and higher doses than a threshold may produce damage sites which may promote the adherence of the microbes and promote their growths. Therefore, it is important to study the effects of different doses of radiations on the catheters to achieve the safe uses of the catheters.

Radiation based sterilization is sterilization with an ionizing radiation such as gamma rays or electron beam (e-beam). However, the radiation exposure on materials, especially pharmaceuticals and polymer-containing medical devices, is expected to cause degradation or chemical changes. Therefore, the study on effects of ionizing radiations on a variety of different materials is a growing research area that may lead to a safer technique that reduce radiation damage and increase cost-effectiveness in the future.

B. *Scientific Scope of the Project (Scientific problems to be addressed with overall and specific objectives*

The scope of the project is to study the effects of ionizing radiation on the polymeric materials used in the diagnostic catheters in terms of chemical and physical changes induced by the radiations. In the proposed project under CRP, we will study the radiation effects on the actual polymeric catheters used in the medical diagnostics at dose rate of 25-100 kGy doses to understand the radiation induced degradation and ageing and the probability of the microbial adherence and growth on the radiation damaged sites on the catheters. These polymers will be irradiated with gamma-rays from ^{60}Co and electron beam at BARC, Mumbai, India. These polymers will be subjected to different studies such as Atomic Force Microscopy (AFM) and Field Emission Scanning Electron Microscopy (FESEM) for surface morphology, small angle X-ray scattering for bulk physical structure, Thermo-gravimetric Analysis (TGA)/ Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC) for thermal properties, Contact angle measurement for change of hydrophilicity/hydrophobicity, and microbial growth on the surface of the polymeric catheters. These properties will be examined after keeping at ambient conditions at desired period of time intervals.

❖ Changes observed after irradiation of polymers

Changes Related to Irradiation	**Formed Reactions/Structures in Polymers**
Chemical changes	- Chain scission and crosslinking
	- Gas formation
	-Double bond formation
	-Change of chemical structure of base polymer and additives
Physical changes	- Change in the mechanical properties
	- Color formation
	- Change in the crystallinity properties
	- Thermal transitions
	- Change in the surface roughness

Changes in surface morphology	- Change in the surface hydrophilicity/hydrophobicity
Microbial properties	Safer terminal Radiosterilization
	Change in surface morphology may increase the adherence of microbes on its surface which may lead their growth on the radiation damaged surface after radiosterlization in some polymer depending upon their chemical structures.

Effects of Water Radiolysis

The g-radiolysis of water produces several species such as e_{aq}^{-}, OH•, H•, H_2, H_2O_2, H^+, and OH^-. Among these, the two reducing transient species are solvated electron (e_{aq}^{-}) and hydrogen atom (H•). Hydroxyl radical (OH•) is the major transient oxidizing radical.

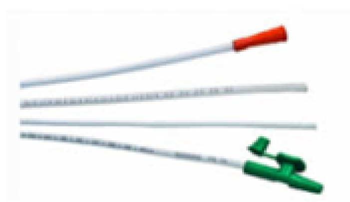
It is expected that the g-radiolysis of water may produce significant radiation damage at the surface in contact and water rich interior matrix.

g-Irradiations will be carried out using ^{60}Co g-source (dose rate: 7.8 kGy h^{-1} as obtained by Fricke dosimetry) in air at BARC Mumbai, India.

Catheters will be irradiated with electron beam (electron energy = 2 MeV; dose rate = 10 kGy/pass) in air at the electron accelerator facility, Bhabha Atomic Research Centre (BARC), Mumbai-85, India

C. Overall Program of work for the whole duration of the contract including proposed methods or techniques.

A Catheters to be Procured in first phase from the Hospitals

Manufacturer	**Images**	
ROMSON		

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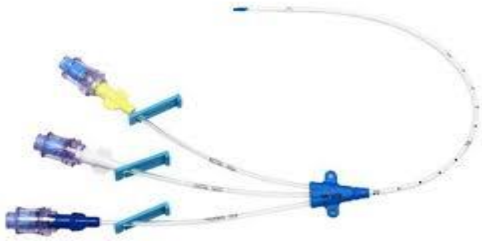
<tr><td>ARROW</td><td></td><td></td></tr>
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VYGON		
SURGIWEAR		

B Experimentation and Methodology

Gamma Irradiation to be done: 25, 50, 75, 100 kGy for 6x6 cm or 4x4 cm 7 samples of catheters for following experiments. These experiments will be carried out in the Bhabha Atomic Research Centre (BARC).

Before irradiation: Oxygen/air permeability, BET for pore-size and surface area measurements, Differential Scanning Calorimetry to investigate the response of polymers to heating, Xray Diffraction, AFM of surface, Growth of E. coli or suitable microbes or fungus, Optical properties (UV/Vis Spectra or Refractive Index) and Tensile strength.

Just after irradiation: Oxygen/air permeability, Xray Diffraction, BET for pore-size and surface area measurements, DSC for glass transitions, AFM of surface, Growth of E. coli or suitable microbes or fungus, Optical properties (UV/Vis Spectra or Refractive Index) and Tensile strength.

After 2 months of irradiation and keeping under ambient conditions: Oxygen/air permeability, XRD, BET for pore-size and surface area measurements, DSC for glass transitions, AFM of surface, Growth of E. coli or suitable microbes or fungus, Optical properties (UV/Vis Spectra or Refractive Index).

After 4 months of irradiation and keeping under ambient conditions: Oxygen/air permeability, XRD, BET for pore-size and surface area measurements, DSC for glass transitions, AFM of surface, Growth of E. coli or suitable microbes or fungus, Optical properties (UV/Vis Spectra or Refractive Index).

After 6 year of irradiation and keeping under ambient conditions: Oxygen/air permeability, XRD, BET for pore-size and surface area measurements, DSC for glass transitions, AFM of surface, Growth of E. coli or suitable microbes or fungus, Optical properties (UV/Vis Spectra or Refractive Index)

After 8 year of irradiation and keeping under ambient conditions: Oxygen/air permeability, XRD, BET for pore-size and surface area measurements, DSC for glass transitions, AFM of surface, Growth of E. coli or suitable microbes or fungus, Optical properties (UV/Vis Spectra or Refractive Index)

(The detail proposed project work is for five years. The year-wise specific work plan is give below:

- **1st Year:** the gamma-rays induced chemical changes in the selected polymeric catheters will be studied by Differential Scanning Calorimetry, Thermogravimetric Analysis /Differential Thermal Analysis, Fourier Transform Infra-Red analysis, Contact Angle etc.

- **2nd Year:** physical changes will be studied by Atomic Force Microscope, Field Emission-Scanning Electron Microscope, Tensile Strength, and Small Angle X-rays Study.

- **3rd Year:** Irradiation of polymeric catheters with electron beams and study on chemical changes

- **4th Year:** Study on physical changes in electron-beam irradiated polymeric cathters, documentations/publications.

- **5th Year:** Modellings and Simulations of obtained data in the previous years)

(In first year, the gamma-rays induced chemical changes in the selected polymeric catheters will be studied by Differential Scanning Calorimetry, Thermogravimetric Analysis /Differential Thermal Analysis, Fourier Transform Infra-Red analysis, Contact Angle etc. In second year, physical changes will be studied by Atomic Force Microscope, Field Emission-Scanning Electron Microscope, Tensile Strength, and Small Angle X-rays Study)

D. Related Work in Progress at Institute (Including work Started in connection with IAEA through technical connection with CRP projects)

In this institute, the radio-chemical study is being carried out including use of the polymeric materials in solid state nuclear track detectors. This Department of Nuclear & Radiochemistry from Kishinchand Chellaram College Mumbai is AERB Certified and well equipped with safe handling of radioactive materials. For this project, a collaboration with various Hospitals has also been initiated.

E. Instrumentation and Equipment

Gamma Chamber 5000

Gamma Chamber 5000 is a compact self-shielded cobalt-60 gamma irradiator providing an irradiation volume of approximately 5000cc. There are other variations of the Gamma Chambers which are also available. The material for irradiation is placed in an irradiation chamber located in the vertical drawer inside the lead flask. This drawer can be moved up and down with the help of a system of motorized drive which enables precise positioning of the irradiation chamber at the center of the radiation field. Radiation field is provided by a set of stationary cobalt-60 sources placed in a cylindrical cage. The sources are doubly encapsulated in corrosion resistant stainless steel pencils and are tested in accordance with international standards. Four access holes of 8 mm diameter are provided in the vertical drawer for introduction of service sleeves for gases, thermocouple, etc. A mechanism for rotating/stirring samples during irradiation is also incorporated. The lead shield provided around the source is adequate to keep the external radiation field well within permissible limits. The Gamma Chamber 5000 unit can be installed in a room measuring 4m X 4m X 4m.

Features of GC 5000:

- **Safe and self-shielded:** The shielding provided is adequate to limit the radiation field on the external surface of the unit, well within the permissible levels. No additional shielding is required for its installation and use.

- **Automatic control of irradiation time:** Built-in timer provides accurate control of irradiation time from 6 seconds onwards. The unit can also be operated manually. PLC based control system have been provided.

- **Manual control of irradiation temperature:** It is possible to irradiate samples at low or high temperature by circulating liquid nitrogen or hot air. These can be introduced through the service sleeves provided in the vertical drawer. The irradiation temperature is sensed by a thermocouple and displayed on the panel.

- **Dose uniformity:** Stationary source pencils, symmetrically placed in a cylindrical cage ensure good uniformity of radiation field in the sample chamber. In addition a mechanism is also provided for rotating/stirring samples during irradiation.

- **Easy loading and unloading of samples:** Sample chamber extends to a convenient height for easy loading and unloading of samples.

- **Safety assurance:** The design of Gamma Chamber conforms to American National Standards ANSI N433.1-1977 for safe design and use of self-contained dry source storage gamma irradiators (Category I). It also meets the requirements of type B(U) package for safety in transport of radioactive materials as per AERB code No.SC/TR-1, 1986 of Atomic Energy Regulatory Board of INDIA.

Applications:

Gamma Chamber is a versatile equipment for research studies in many fields such as:

- Radiobiology
- Preservation of tissue grafts
- Mutation breeding
- Food preservation
- Sterile male insect technique
- Biological and genetic effects of radiations
- Radiation chemistry
- Radiation effects on materials
- Radiation sterilization
- Modification of properties of materials

Specifications of Gamma Chamber 5000:

Maximum Co-60 source capacity	518 TBq (14000 Ci)
Dose rate at maximum capacity	~ 9 kGy/hr (0.9 Mega Rad/hr) at the center of sample chamber
Dose rate uniformity	+25% or better radially; -25% or better axially
Irradiation volume	5000cc approx.
Size of sample chamber	17.2cm (dia) X 20.5cm (ht)
Shielding material	Lead & stainless steel
Weight of the unit	5600 kg. approx.
Size of unit	125cm (l) X 106.5cm (w) X 150cm (ht)
Timer range	6 seconds onwards

Installation requirements:

Power requirement	220/230V, 50Hz, 10 Amps, single phase
Room	• size: 4M X 4M X 4M • door size: 1.2M clear width X 2M height • pit size :35cm dia X 70cm depth in the floor • floor loading capacity: 10MT per sq.M

Department of Nuclear & Radiochemistry, and other equipment listed above are collaborators at BARC, Mumbai and Nuclear and Radiochemistry Department K C College, HSNC University.

Equipment Required

- Oxygen Permeability Tester
- Bio-lab for microbe studies
- Spectrophotometry, Refractive Index.
- **Differential Scanning Calorimetry (DSC)**

Differential Scanning Calorimetry (DSC) is a technique used to investigate the response of polymers to heating. DSC can be used to study the melting of a crystalline polymer or the glass transition. The DSC set-up is composed of a measurement chamber and a computer. Two pans are heated in the measurement chamber. The sample pan contains the material being investigated. A second pan, which is typically empty, is used as a reference. The computer is used to monitor the temperature and regulate the rate at which the temperature of the pans changes. A typical heating rate is around 10°C/min.

DSC is capable of heating a given material at a controlled rate, such as 10°C per minute, and monitor the heat flow in an effort the characterize the thermal events of a sample as a function of increasing temperature. Most modern DSC instruments are equipped with the ability to measure absolute heat flow by dividing the signal by the measured heating rate, which thereby converts it into a heat capacity signal. The monitoring of this heat-capacity related signal is a function of the applied experimental conditions in an effort to determine how the heat capacity of the sample may change as it undergoes a phase change or chemical reaction. DSC is a useful tool for thermal analyses of thermosetting plastics using changes in heat capacity results due to exothermic or endothermic reactions. DSC can be used to identify the glass transition of thermosets.

- **Atomic Force Microscopy (AFM)**

The Atomic Force Microscope is a sophisticated instrument which helps delineate the characteristics of polymers by revealing physical properties and mechanical behavior at nanoscale, as well as providing images. The AFM allows the structure to be visualized via nanoscale topography of the surface, typically in tapping mode. This mode yields images with excellent spatial resolution, up to molecular and atomic structure. The small area in contact between the tip and the sample is responsible for the high resolution. This in turn is achieved by using ultrasharp tipped probes, in addition to the tapping mode which results in very gentle sideways and vertical forces between the tip and the sample.

- **Brunauer–Emmett–Teller (BET) Analysis**

Brunauer–Emmett–Teller (BET) theory **aims to explain the physical adsorption of gas molecules on a solid surface** and serves as the basis for an important analysis technique for the measurement of the specific surface area of materials. *BET Analyzers* for specific *surface area*& pore size, vapor adsorption & chemisorption. Innovative *BET Surface Area Analyzers* used in research, development, and quality control.

- **X-ray Diffraction Analysis (XRD)**

X-ray diffraction analysis (XRD) is one of the microstructural analysis methods used for the identification of crystallinity of polymers, recognition of crystalline phases (polymorphism), and orientation of polymers.

(After 2 years, detailed characterizations: FESEM of cross-section, TGA/DTA, Small angle X-ray scattering, Mechanical Properties (Tensile strength), GPC and FTIR.)

- **Field Emission Scanning Electron Microscopy (FESEM)**

Field emission scanning electron microscopy (FE-SEM) is an advanced technology used to capture the microstructure image of the materials. FE-SEM is typically performed in a high vacuum because gas molecules tend to disturb the electron beam and the emitted secondary and backscattered electrons used for imaging.

- **Thermogravimetric Analysis (TGA)**

Thermogravimetric analysis (TGA) of polymers is **conducted to measure weight changes as a function of temperature and time**. The weight changes of polymeric materials can be caused by decomposition and oxidation reactions as well as physical processes such as sublimation, vaporization, and desorption.

TGA measurements provide valuable information that can be used to select materials for

certain end-use applications, predict product performance and improve product quality.

The technique is particularly useful for the following types of measurements:

- ✓ Compositional analysis of multi-component materials or blends
- ✓ Thermal stabilities
- ✓ Oxidative stabilities
- ✓ Estimation of product lifetimes
- ✓ Decomposition kinetics
- ✓ Effects of reactive atmospheres on materials
- ✓ Filler content of materials
- ✓ Moisture and volatiles content

- **Differential Thermal Analysis (DTA)**

A technique in which the difference in temperature between the sample and a reference material is monitored against time or temperature while the temperature of the sample, in a specified atmosphere, is programmed. A DTA curve can be used only as a fingerprint for identification purposes but usually the applications of this method are the **determination of phase diagrams, heat change measurements and decomposition in various atmospheres**

- **Small Angle X-ray Scattering (SAX)**

SAXS is used for **the determination of the microscale or nanoscale structure of particle systems** in terms of such parameters as averaged particle sizes, shapes, distribution, and surface-to-volume ratio.

- **Mechanical Properties (Tensile strength)**

It is of great importance to be familiar with some basic mechanical properties of the material before its application in any field, such as how much it can be stretched, how much it can be bent, how hard or soft it is, how it behaves on the application of repeated load and so on. Strength, Factors Affecting the Strength of Polymers Molecular Weight, Cross-linking Crystallinity can be studied.

- **GPC**

Gel permeation chromatography (GPC) is a type of size-exclusion chromatography (SEC), that separates analytes on the basis of size, typically in organic solvents. The technique is often used for the analysis of polymers. **Gel Permeation Chromatography** (GPC) for measurement of polymer molecular weight, size and structure. Gel Permeation Chromatography (GPC) is an analytical technique that separates dissolved macromolecules by size based on their elution from columns filled with a porous gel.

- **FTIR**

FTIR spectrometers rely on the same basic principle as NDIR analyzers, i.e., the fact that many gases absorb IR radiation at species-specific frequencies. However, FTIR spectroscopy is a **disperse method**, which means that measurements are performed over a broad spectrum instead of a narrow band of frequencies.

Three different functional groups such as allyl group ($-CH_2 = CH-CH_2-$), ether group ($-CH_2-O-CH_2-$) and carbonyl group (C=O) present in the polymers can be studied by FTIR. Upon exposure to any kind of radiations these useful functional groups are liable for the alterations in their structural and physicochemical properties. Different structural changes take place in the polymer material when heavy charged particle pass through it and these changes are influenced by several factors such as structure of polymer, exposure condition, radiation type and energy, etc.

Equipment Needed for the project / Requested to IAEA

Item	**Estimated Project cost in Euros.**
	Requested contribution from the IAEA
Olympus Microscope (Transmission with option of inverted to view opaque surface)	40,000
Sub Total	**40,000** **(3,494,591.37 INR/-)**

Budget Estimate of the Project by Year (In EUROS €)

Project Year	Staff Cost	Equipment	Miscellaneous	Project Total	Contribution by Institute	Requested Contribution from the IAEA
1st Year	4763	40,000	1200	45963	1963	44000
2nd Year	4763		1500	6263	2263	4000
3rdYear	4763		1500	6263	2263	4000
4th Year	5580		1500	7080	3080	4000
5th Year	5580		2000	7580	3580	4000
Total	**25449**	**40000**	**7700**	**73149**	**13149**	**60,000**

F. Expected Outcome

This study will lead to safer utilization of ionizing radiation on polymeric catheters, and selection of appropriate polymer for the specific application in the radiopharmaceutical and radiation-based sterilization.

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Indonesia

The Effect of Gamma Irradiation on the Performance of Ultra High Molecular Weight Polyethylene/chitosan/hydroxyapatite Implant

Abstract

High energy radiation, such as gamma ray and electron beam, has been mainly used for the sterilization of biomedical devices because it has high penetration ability and the products can be sterilized in their final packaging. Despite the fact that high energy radiation is very effective to sterilize the biomedical devices, high energy radiation may also affect the performances of the devices. Therefore, it is important to ensure that the characteristic of the biomedical devices remains similar after high energy radiation. In this study, we are going to investigate the effect of gamma irradiation on the performance of ultra-high molecular weight polyethylene (UHMWPE) implant in the presence of hydroxyapatite (HA) and chitosan. The study is focused on the investigation of the effect of HA and chitosan on the physico-chemical, mechanical properties, thermal stability, degradation, and biocompatibility of the irradiated UHMWPE implants. The effect of different concentration of chitosan and HA on the performances of gamma-irradiated UHMWPE will also be investigated. We hope, this study can provide comprehensive data on the effect of gamma irradiation on the performance of the gamma-irradiated UHMWPE implant in the presence of HA and chitosan.

Introduction

Biomedical devices must be sterilized prior to their use to prevent disease transmission [1,2]. High energy radiation, such as gamma rays and electron beam, has been mainly used for the sterilization of biomedical devices because of its effectiveness independent of temperature and pressure conditions [3,4,5]. In addition, gamma radiation offered several advantages over other sterilization methods, such as the products can be sterilized in their final packaging [3,4,5].

Ultra-high molecular weight polyethylene (UHMWPE), silicone rubber, polymethyl methacrylate, polypropylene, and polyvinyl chloride are polymers which commonly used in the fabrication of biomedical devices [5]. However, these polymers are radio-sensitive and the sterilization treatment of these polymers by standard dose of gamma irradiation i.e. 25 kGy can induce irreversible structural changes in these polymers [5-8]. The polymer structures altered by gamma irradiation can affect their clinical use as a result of the auto-oxidation of the irradiated polymer [6].

UHMWPE is a semi-crystalline polymer that is commonly used as a material for fabricating implants for bone and orthopedic applications [10]. UHMWPE has a molecular weight of greater than 3.1 million and its properties is largely dependent on their microstructure [10]. Previous reports showed that gamma irradiation generates free radicals in UHMPWE leading to the decrease in mechanical properties and performance of the UHMWPE based materials affecting their clinical use [8,9].

HA, $Ca_{10}(PO_4)_6(OH)_2$, has been widely used in bone regeneration because of its biocompatibility and osteoconductivity. Previous reports showed that combination of HAP and implant improved biological fixation, biocompatibility, and bioactivity of the implants [11]. We hypothesized that the presence HA can enhance the osteoconductivity of the implant and it can be used for bone tissue regeneration application.

Chitosan, a *N*-deacetylated derivative of chitin, and its derivatives have gained considerable interest because of its biological activities. Chitosan has been known also for its free radical scavenging activity based on the ability of the amine and hydroxyl group of the chitosan to scavenge the free radical [12,13]. We assume that the chitosan may help the UHMWPE to remains its excellent properties after gamma irradiation.

Objectives

In this study, we are going to investigate the physico-chemical, mechanical, and biological performances of the gamma-irradiated UHMWPE implant in the presence of HA and chitosan. The study will be focused on physico-chemical, mechanical, and thermal stability, ageing and degradation, and biocompatibility of the irradiated UHMWPE implant.

Workplan

Year 1

a. Optimization of fabrication of UHMWPE based implant in the presence of chitosan and/ HA at different concentration. Optimization will be conducted by optimize the concentration of the materials and hot press condition such as temperature, pressure, and pressing time.

b. Characterization of UHMWPE/chitosan, UHMWPE/HA, and UHMWPE/chitosan/HA implants by mechanical properties using universal testing machine (UTM), functional groups using fourier transform infrared spectrophotometer (FTIR), thermal behavior using differential scanning calorimetry (DSC) and differential thermal analysis (DTA), structure using X-ray diffraction (XRD), and morphology using scanning electron microscope (SEM).

c. Irradiation of the UHMWPE based implant using Cobalt-60 at a irradiation dose of 25 kGy. The irradiation was carried out in Gamma Cell 220 upgraded (doses rate 3.4 kGy/hour).

Methods

Materials

UHMWPE (surface modified, powder, 125 μ average particle size, Sigma), chitosan low molecular weight (deacetylation degree ≥ 75%, Sigma) and HA (Sigma).

Fabrication of UHMWPE based Implants

The UHMWPE/chitosan implant prepared by mixing UHMWPE and chitosan at different concentration (0.1 - 1 % w/w). The mixture of UHMWPE and chitosan is then mechanically mixing using a force mill. The homogeneous mixture is then molded using a hot press apparatus at 190 °C and 50 Mpa for 15 min. The thickness of the UHMWPE/chitosan implant after hot pressing is about 1 mm. UHMWPE/HA and UHMPWE/chitosan/HA implants are prepared using the same procedure as mention above. The schematic diagram for the fabrication of the UHMWPE based implants is shown in Figure 1.

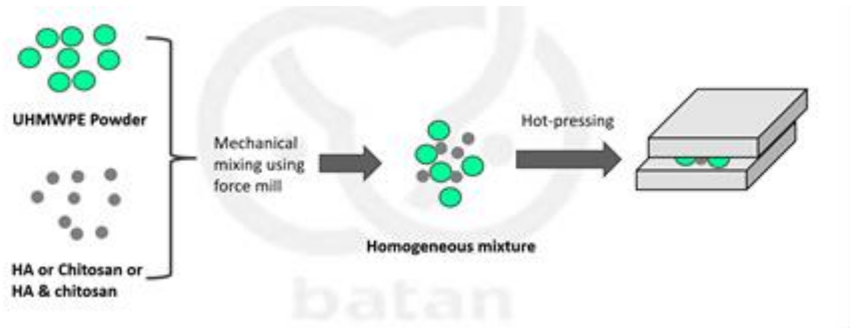

Figure 1. The schematic diagram for the fabrication of the UHMWPE based implants

Irradiation of The UHMWPE based Implants

Characterization of The UHMWPE based Implants

The UHMWPE based implants were then analyzed by FTIR, XRD, SEM, and DSC to analyze the functional group, morphological structure and thermal properties of the UHMWPE, UHMWPE-Chi, UHMWPE-HA, and UHMWPE-Chi-HA. The mechanical properties of the implant will also be performed using UTM.

DSC analysis (TA 60; Shimadzu, Tokyo, Japan) was used to study the thermal characteristics of UHMWPE based implant before and after 25 kGy of gamma-irradiation (dose rate 3.4 kGy/h). All DSC measurements were carried out with a crimped empty pan (alumunium pan, Shimadzu, Tokyo, Japan) as a reference. The reference and crimped pans containing samples were measured at the heating rate of 10 °C/min under a nitrogen atmosphere at a temperature range of 30 – 250 °C.

The mechanical properties of the UHMWPE based implant before and after 25 kGy of gamma-irradiation were conducted at room temperature using universal testing machine (Zwick role, Z005, German) equipped with 2.5 kN load cell. The test speed of the measurement was 50 mm/min. The specimen thickness was about 1 mm.

Preliminary Results

The DSC profiles of the UHMWPE/HA at different concentration of HA are shown in Figure 2. The DSC profiles showed that the addition of HA tends to decrease the melting temperature of the UHMWPE based implant.

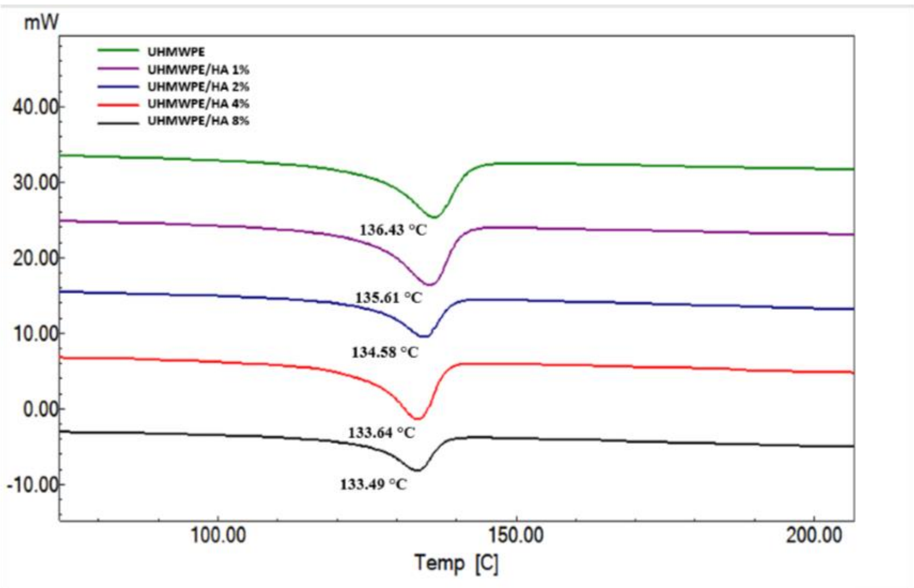

Figure 2. DSC profiles of UHMWPE/HA at different concentration of HA.

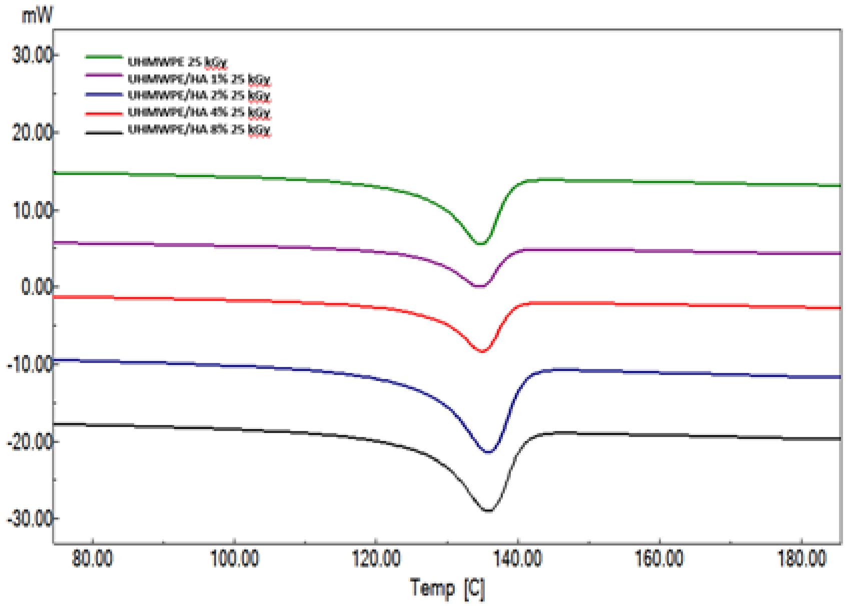

Figure 3. DSC profiles of gamma-irradiated UHMWPE/HA at different concentration of HA

The mechanical properties of the unirradiated and gamma-irradiated UHMWPE based implants containing HA and chitosan are presented in Figure 4 and 5.

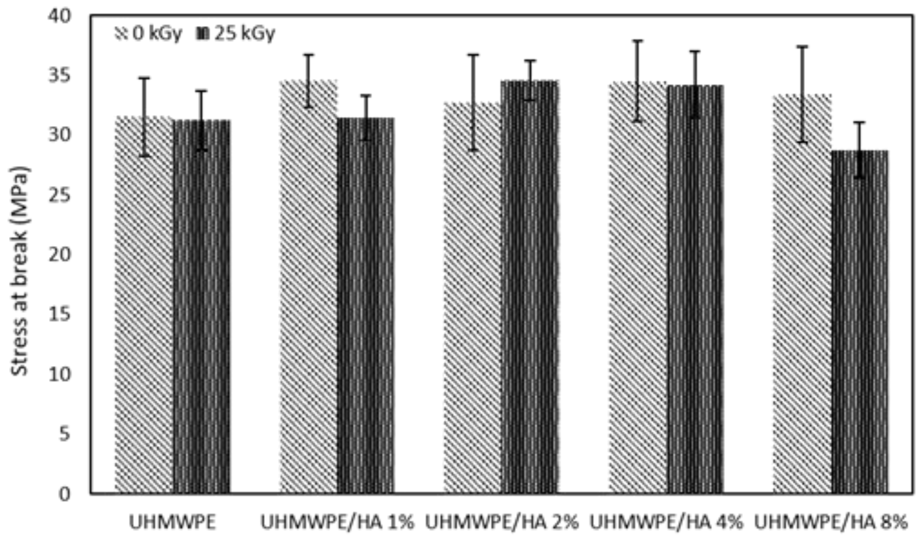

Figure 4. Stress at break of un-irradiated and irradiated UHMWPE/HA at different concentration of HA

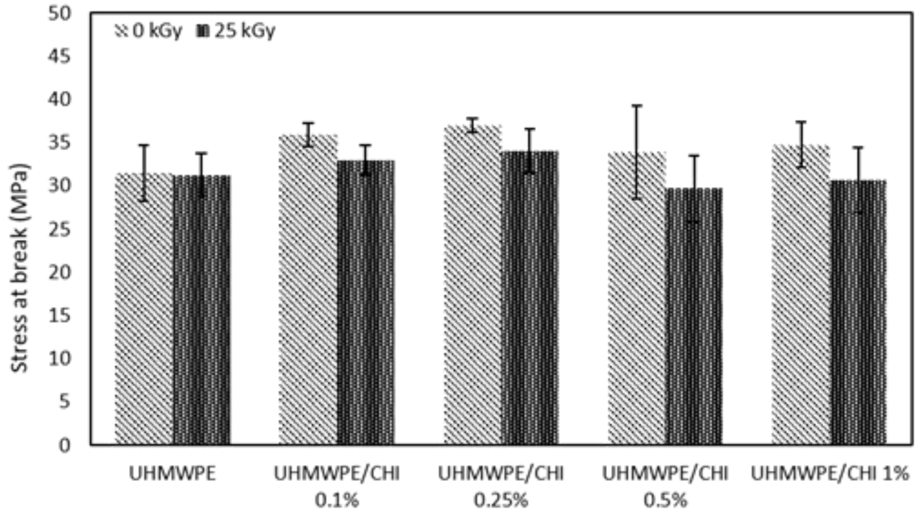

Figure 5. Stress at break of un-irradiated and irradiated UHMWPE/chitosan at different concentration of chitosan

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Philippines

Direct Comparison of Gamma and Electron Beam Irradiation Effects on Raw Polymer Materials Used and Final Products of Single-Use Catheter Devices: Workplan and Related Studies

C. Tranquilan-Aranilla, B. J. D. Barba, A. K. R. Gallardo, and L. S. Relleve

Chemistry Research Section, Atomic Research Division

Philippine Nuclear Research Institute, Department of Science and Technology

Quezon City 1101, Philippines

Abstract

Radiation sterilization offers an efficient way to eliminate microorganisms in medical devices. It is the preferred method for complex materials that cannot withstand heat or steam sterilization and direct chemical disinfection. Moreover, it has a cleaner footprint than gas sterilization technique such as ethylene oxide treatment. While gamma sterilization has been predominantly used for the past 50 years, there has recently been a shift towards non-radiological sources of radiation years. In this light, electron beam accelerators have shown promising potential in various industries offering higher throughput and overall efficiency. Despite the many advantages of both radiation modalities, their applicability towards the sterilization of polymeric products remains limited due to induced chemical effects that can alter polymer structure and properties. In this project, catheters will be evaluated as they remain one of the most in-demand single-use medical devices in the Philippines and in the global healthcare sector. These products and their most common polymer bases will be characterized for their parametric response to gamma and electron beam irradiation in order to establish the suitability of ionizing radiation as a sterilization technique.

1. INTRODUCTION

Sterilization is a major processing step within the overall healthcare product manufacturing process. A wide range of single-use, disposable medical devices are supplied to the final user as sterile products. Approximately, the distribution of sterilization modalities used by the medical industry is 45% radiation (gamma, e-beam, x-ray), 50% ethylene oxide gas, and 5% pressurized steam (GIPA & IAA, 2017). These data show that radiation technology constitutes a significant share in the sterilization arena and largely contribute to the reliability and viability of the global healthcare system by providing sterile and fit-for-purpose products.

Gamma sterilization still dominates radiation-based sterilization methods. A high percentage of polymeric medical devices are sterilizable by gamma. A dose of 25 kGy has been used as the reference dose that guarantees a sterility assurance level (SAL) of 10^{-6} (USP30-NF25). Recently, advancements in medical device technologies drive for a shift to accelerator-based sterilization such as e-beam and x-ray. However, there exists a knowledge gap in the radiation effects of e-beam and x-ray on common medical device materials (Kroc, 2017). Hence, there is a need to study and document materials response to all three methods (gamma, e-beam and x-ray) to expand understanding of radiation effects on material property, functionality and biocompatibility and establish the suitability of e-beam and x-ray as alternative methods to gamma radiation. In a recent publication, results of the extensive comparison of gamma, e-beam and x-ray effects on single-use blood collection devices with plastic components such as PET, LDPE, CIIR, POE, PPH and PVC showed that both e-beam and x-rays are potential irradiation sterilization options for other medical devices fabricated from similar polymers (Fifield et al., 2021).

Figure 1. PNRI Irradiation Facilities: (top) Multi-purpose Gamma Irradiation Facility with the semi-automated tote box loading system and (bottom) Mid-Energy Electron Beam Irradiation Facility with cart conveyor system.

In the Philippines, there are two irradiation facilities that operate on a semi-commercial scale located in the Philippine Nuclear Research Institute - the Multipurpose Gamma Irradiation Facility and the 2.5 MeV Electron Beam. In the past, medical products that have been processed in the Multipurpose Gamma Facility include orthopedic implants, bone grafts, surgical gloves, aluminum tubes, gelatin capsules, sutures, and surgical kits. Currently, bone grafts remain to be processed by gamma sterilization. Terumo Philippines, a private manufacturer of syringes, catheter ship syringes, and urinary bag, has three in-house 10 MeV electron beam facilities for sterilization of their products. In 2022, another private company will put up a 10 MeV Electron Beam irradiation facility located in Metro Manila. This facility will cater to sterilization of medical products and food processing.

Catheters are medical grade tubes made of polymeric materials that can be used for various cardiovascular, neurovascular, urological, gastrointestinal, and ophthalmic applications. Catheters are one of the most in-demand single-use medical devices, and the estimated number of catheters used worldwide reach 1 billion per year (Ratner, 2016). Rising prevalence of chronic diseases which require hospital intervention has led to the increasing demand for catheters in the global market, valuing at USD 37.3 billion in 2018. Commonly used polymers in catheter manufacture include thermoplastics such as polytetrafluoroethylene (PTFE), polyolefins such as high-density polyethylene (HDPE), polyamides (PA), polyurethane (PU), polyvinyl chloride (PVC), and polyether ether ketone (PEEK), thermosets such as polyimides, and elastomers such as silicone rubber and latex rubber (Maitz, 2015). Catheters may also contain polymer coatings such as polyethylene glycol (PEG), polydimethylsiloxane (PDMS) and polyethylene oxide (PEO) for enhanced hydrophilicity and antifouling (Campoccia et al., 2013). Among these polymers, HDPE, PTFE, PVC, silicone rubber and latex rubber can be radio-sensitive. Sufficiently high doses can cause their unwanted physical or chemical transformation as well as irreversible reduction of thermomechanical properties (Harrell et al., 2018). Often, these materials are modified or blended with more resistant polymers like polyamides or polymers with aromatic side groups, to be more resilient from radiation degradation effects. This highlights the importance of the simultaneous study of the dose-property relationship of polymeric products and their effective sterilization dose.

Although many countries are already using radiation sterilization methods for catheters (Dziedzic-Goclawska, 2008), existing local manufacturers of catheters carry out their product sterilization via non-radiation modes. Hence, this study is also motivated to introduce radiation sterilization to local manufacturers and increase radiation sterilization activities in the country. In this research, the effects of gamma and electron beam radiation on locally manufactured catheters will be conducted. The direct comparison is purposed not only to widen the understanding of radiation effects in common polymeric materials used in medical devices but also to give evidence-based recommendations to the manufacturers in considering radiation methods of sterilization, either by gamma or e-beam.

2. OBJECTIVES

This study covers the effects of gamma and e-beam irradiation on base-polymers materials used in catheter devices, as well as actual products. Non-sterile catheter products samples will be sourced from local manufacturers.

Overall Objective: To directly compare the effects of gamma and e-beam irradiation modalities on polymer materials used in and catheter devices sourced from local manufacturers.

2.1 Specific Objectives:

(1) To assess the physical, chemical, and mechanical properties of polymer materials used in catheter devices irradiated at doses 25, 35, 50 and 80 kGy.

(2) To determine suitability of gamma and e-beam irradiation as a sterilization technique to locally produced catheter devices and optimize effective sterilization dose.

(3) To assess the functionality and biocompatibility of irradiated catheter devices.

(4) To conduct real-time and accelerated ageing of irradiated catheter devices and assess functionality.

3. WORKPLAN

3.1 Workplan for Year 1

- Sourcing of locally manufactured urological and/or vascular catheter devices.
- Gamma and electron beam irradiation of raw polymer materials used in catheter manufacture at doses 25, 35, 50 and 80 kGy.
- Assessment of physical, chemical, and mechanical properties using FTIR, TGA, DSC, SEM and UTM.
- Conduct real-time and accelerated ageing of irradiated polymers.

3.2 Workplan for Year 2

- Gamma and electron beam irradiation of non-sterile urological and vascular catheter products at doses 25, 35, 50 and 80 kGy.
- Assessment of functionalities based on industrial standards specific for catheters (ASTM F623 or ISO10555).
- Conduct of real-time (1 year) and accelerated ageing of gamma and e-beam irradiated catheter devices.

3.3 Workplan for Year 3

- In vitro assessments of biocompatibility of gamma and e-beam irradiated devices: cytotoxicity, genotoxicity, hemocompatibility

3.4 Workplan for Year 4

- Determine suitability of gamma or e-beam radiation sterilization for the studied catheter devices.
- Optimization of effective radiation dose for studied catheter devices.

3. CONCEPT DESIGN

The general concept design of the study is summarized in Figure 2. The work is divided into three general work packages involving the (1) observance of basic principles and formulation of the technology concept using model polymer compounds, (2) proof of concept experiments and (3) technical feasibility validated in the laboratory environment. Technology readiness levels are used as markers for project milestones.

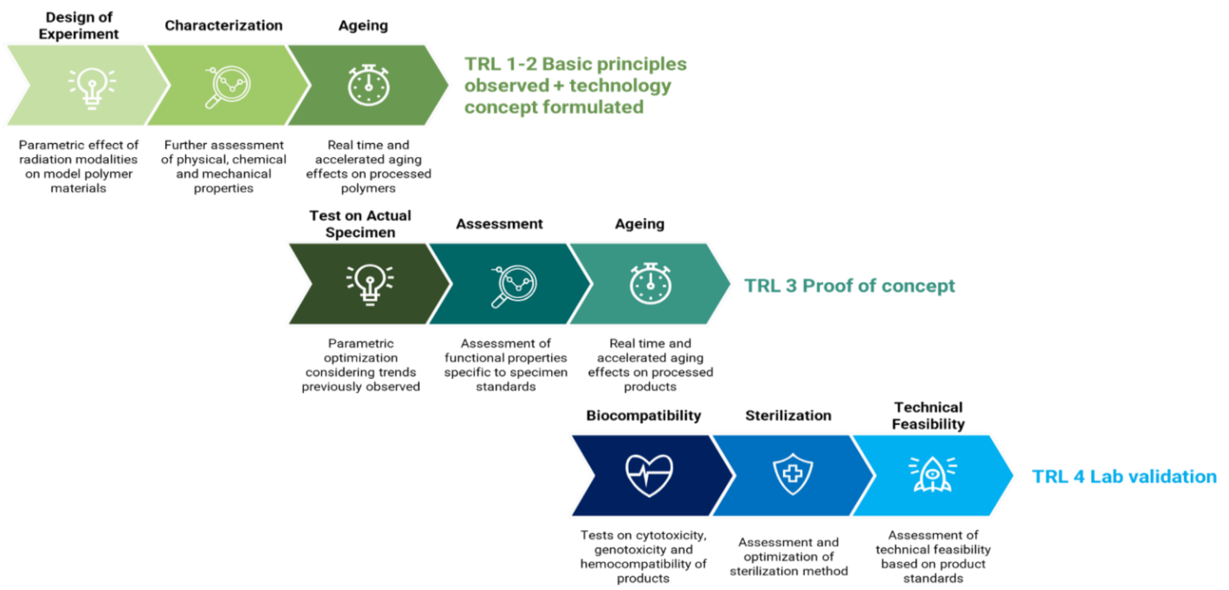

Figure 2. Concept design for the direct comparison of gamma and electron beam irradiation effects on single-use catheter devices.

3. METHODOLOGY

The following are the detailed methodologies to be carried out in the project:

Materials. The polymers of interest for the study are thermoplastic polyurethane (TPU), silicone rubber, and polypropylene. These polymers are among commonly used base-material for catheter devices. Medical grade polymers in sheet form will be utilized and the procurement is being processed.

Different batches of non-sterile catheter devices will be obtained from Indoplas Philippines, Inc., a local manufacturer of medical devices.

Radiation processing. Gamma processing will be performed at the Multipurpose Gamma Irradiation Facility of DOST-PNRI. The polymer sheets (4" x 4") vacuum-sealed in foil pouches and packed in boxes will be irradiated at ambient temperature and subjected to doses 25, 35, 50, 80 kGy at a dose rate of 2 kGy/hr. Electron beam processing will be performed in the 2 MeV irradiation facility of DOST-PNRI. The polymer sheets (4" x 4") vacuum-sealed in foil pouches will be arranged in the conveyor cart and irradiated at doses 25, 35, 50, 80 kGy with an applied 5 kGy per pass to achieve the desired doses. Dosimetry for both irradiation modalities will be conducted.

Characterization. After radiation processing, samples will be stored out of direct light at ambient temperature for at least one week prior to testing to control post-irradiation time variability and effects.

Polymer sheets will be characterized for effects in the physical, chemical, and mechanical properties as a function of dose. Discoloration will be assessed using Yellowness Index (ASTM E313), if applicable. Chemical properties will be determined using FTIR, TGA, DSC and SEM analyses. Effect on the tensile strength and modulus will be measured using a Universal testing Machine, in accordance with ASTM D638 and ASTM D412.

Irradiated catheter devices will be subjected to functionality tests such as corrosion resistance, leakage under pressure, and peak tensile force, in accordance with ISO 10555.

Design of Experiment (DOE). Experiment runs were determined using randomized response surface methodology as optimized by Design-Expert v11 (StatEase Inc.). The runs are summarized below:

Table 1. Randomized runs determined through response surface methodology

Run	Dose (kGy)	Mode	Representative dose rate
1	25	gamma	low
2	50	gamma	low
3	50	gamma	high
4	80	EB	low
5	80	EB	high
6	80	gamma	high
7	80	EB	low
8	80	gamma	low
9	25	gamma	high
10	50	EB	high
11	35	gamma	low
12	80	gamma	high
13	25	gamma	high
14	25	EB	high
15	35	EB	low
16	25	EB	high
17	25	EB	low
18	80	EB	high
19	80	gamma	low
20	50	EB	low

Response to be noted per run include gel fraction, tensile strength and modulus, yellowness index and thermal properties.

Ageing Studies. Accelerated and real-time stability tests will be conducted for both the polymers and catheters devices. Accelerated stability testing parameters will be formulated following ASTM F1980-07 standards, where temperature will be used as the stress factor as its effect on degradation can be easily characterized by the Arrhenius equation. Using the Q rule for statistical projection, the following simplified equation will be used:

$$Time_{accelerated} = Time_{real} \div Q_{10}^{\frac{T_{test}-T_{ambient}}{10}}$$

Example, using 55±2ºC as the test temperature (T_{test}) (with Q_{10}=2 and $T_{ambient}$=27 °C), accelerated aging may commence at 79 days for an equivalent of 18 months in real time. Sampling will be done after 3, 6, 12, 15 and 18 months. Real-time aging will be done simultaneously with sampling done quarterly (4 months). Product gel fraction, tensile strength and modulus, yellowness index and thermal properties will be measured per sampling cycle.

Cytotoxicity Studies. Cellular response of sample extracts will be evaluated using the MTT cytotoxicity assay based on ISO 10993-5 using L-929 mouse fibroblast cells, ATCC CCL1, NCTC 929, Strain L in MEM completed medium. Irradiated samples will be extracted using the same media at 37±1ºC for 24 h with a mass-to-volume extraction ratio of 0.3 g/mL. Polyurethane film containing 0.1% Zinc diethyldithiocarbamate (ZDEC): RM-A will be used as positive control while Thermonox (Nunc) coverslip will be used as the negative control. The medium without test specimen will be used as the blank.

Genotoxicity Studies. Product genotoxicity will be measured using the Bacterial Reverse Mutation Test (Ames Test). Tester strains TA98, TA100, TA1535 and TA1537 will be grown overnight in a nutrient broth. Standard plate incorporation will be done to expose the tester strain to the specimens directly on a minimal glucose agar plate in the absence of a metabolic activation system. The positive control to be used includes 4-nitro-o-phenylenediamene, sodium azide and 9-aminoacrudube hydrochloride monohydrate. The specimens will be added to 2 mL molten top agar supplemented with trace amounts of histidine-biotin solution, which will then be mixed and poured on GM agar plates. After hardening, the plates will be inverted and incubated at 37 ºC for 120 h, after which the number of revertant colonies per plate will then be measured.

Hemocompatibility. Human whole blood will be drawn from healthy volunteers after obtaining written informed consent and stored in an ACD Solution A blood collection tubes (BD). The testing solution will be prepared by diluting 4 ml of ACD-blood in 5 mL 0.9% saline solution. The specimens (100 mm^2) will be equilibrated in saline for 30 mins. To the specimens, 0.2 ml of testing solution will be added followed by incubation at 37 ºC for 60 min. Hemolysis will be halted by the addition of 4 ml saline. Controls are taken as 0.2 ml testing solution in either 4 ml saline (0% hemolysis) or water (100% hemolysis). The solutions will be centrifuged at 100 x g for 5 min and the supernatant will be measured at 545 nm using a Spectro STAR Nano Microplate Reader (BMG LABTECH). Hemolysis will be calculated from the absorbance of the sample (Ax), positive (Apos), and negative control (Aneg) as follows: Hemolysis (%) = 100 x (Ax – Aneg) / (Apos – Aneg) (Dey & Ray, 2003).

Bioburden. Bioburden will be carried prior to the sterilization process using 10 replicates per sample. Using aseptic techniques, the samples will be placed in an appropriate amount of diluent containing buffered peptone water and sodium chloride. The initial solution (10^{-1}) will be diluted by a magnitude of ten (10^{-2}, 10^{-3}, 10^{-4}) by serial dilution. These will be plated into Aerobic Count Plates and incubated for 48 h at 35±2 ºC. The bioburden in terms of number of colony-forming units (CFU) per gram of sample will be calculated as follows:

Sterility Tests. Tryptic Soy Broth or Soybean Casein Digest Medium will be prepared according to manufacturer's specification. Using aseptic techniques, ten replicates of the samples will be placed in sterile bottles with enough medium to cover them and then incubated for 14 days at 30±2 ºC. Microbial growth is indicated when the clear, transparent medium becomes turbid in appearance.

5. RELATED STUDIES

Study 1. In collaboration with our research group at the Chemistry Research Section and the Irradiation Services Section, the Industrial Technology Development Institute of the Department of Science and Technology conducted an initial study on the effect of gamma irradiation on the physicochemical, structural, and mechanical properties of 3D printed Form Labs grey resin (Sy et al., 2020). The objective was to determine the suitability of gamma sterilization on SLA printed medical parts. The photopolymer resin used in this study was a 'Standard Grey Photoreactive Resin' obtained from Form labs. Two sets of tensile test specimens were printed and assigned as 'control' and 'irradiated' specimens. The irradiated 3D printed specimens were exposed to 50 kGy gamma radiation. The effect of the gamma irradiation was evaluated based on the results of the mechanical, chemical, thermal and morphological analyses. Results showed no significant difference in the chemical, microstructure, and thermal properties of the material after subjecting to gamma irradiation. The irradiated samples were observed to have lower surface roughness due to the extended crosslinking/curing upon irradiation which arranged the polymer chain in less random manner. In effect, irradiation increased the tensile strength and modulus of elasticity of the material by 12.2% and 12.4% respectively.

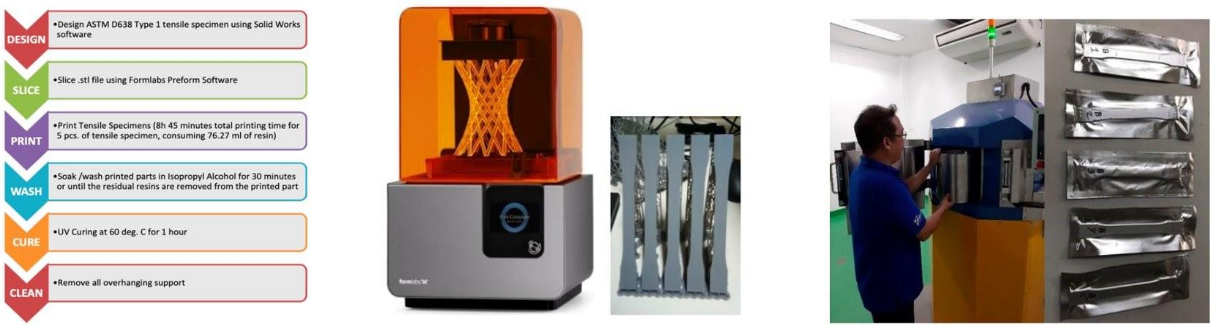

Figure 3. Sample preparation and irradiation at the PNRI Ob-Servo Sanguis self-shielded gamma irradiator (50kGy, 2.5 kGy/hr).

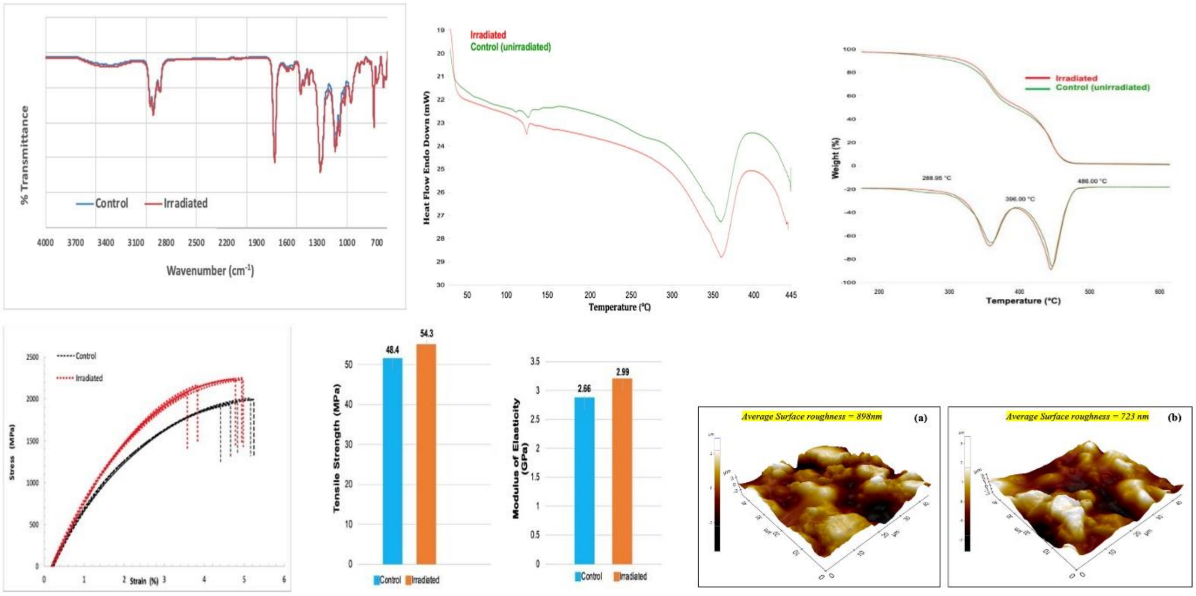

Figure 4. Results of (a) FTIR, (b)DSC, (c)TGA, (d)Tensile, (e)Modulus, and (f) Surface roughness.

Study 2. The suitability of radiation sterilization on wound care dressings based on bacterial cellulose will also be studied in collaboration with PatchMed Trading Company, who developed the wound dressing products. With the goal of expanding their biomedical products repertoire, the company intends to explore the use of ionizing radiation for sterilization. Our group will also conduct a comparative study on the suitability of gamma and e-beam sterilization for their products.

Figure 5. Wound dressing products for study.

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POLAND (Hanna Lewandowska)

Warsaw, November 11, 2021

Technical report

Comparison of gamma and e-beam radiation effects on polymer materials commonly used in medical devices

CRP IAEA: Radiation Effects on Polymer Materials Commonly Used in Medical Devices, **IAEA Research** Contract No: 24388

Hanna Lewandowska, Magdalena Rzepna, Jarosław Sadło

Centre for Radiation Research and Technology Institute of Nuclear Chemistry and Technology 16 Dorodna St., 03-195 Warsaw, Poland;

Introduction

The demand for sterile containers for collecting samples from patients remains high, particularly in the era of the pandemic. Two types of ionizing radiation sources are used in the process of radiation sterilization of medical devices: electron accelerators (with conversion to X-ray) and radioactive isotopes. Currently, over 90% of industrial radiation sterilization plants are isotope devices operating on the basis of the radioactive isotope of cobalt Co-60 (mostly) or cesium Cs-137 (approx. 10%). The drawback of this type of device is the power drop caused by the decay of a radioactive element and the resulting need for periodic replenishment of the isotope. It is a technically difficult and costly operation. Worldwide, there are over 200 gamma installations in 55 countries with a total activity of 220 MCi, and in addition, nearly 60 electron accelerators are used for radiation sterilization. The number of accelerators used for radiation sterilization, increasing every year, includes the result of the intensive development of accelerator technology (high power and high-reliability accelerators) and the fact that their prices are not rising as fast as Co-60 prices. Lack of the knowledge of radiation effects on polymers for e-beam and X-ray is one of the reasons to impede the spreading use of these technologies.

In addition, electron radiation sterilization has many advantages over gamma sterilization, including:

- high intensity of the electron beam enabling the administration of a dose,

- sterilization in a short time and allowing to minimize the effect of radiation degradation of the material,

- the ability to maintain a constant radiation power is constantly controlled by electronic parameters,

- directivity of the electron beam and limited range of electrons (this increases the degree of beam energy use),

- small beam area, limited to a few packs, facilitating quick changes of the radiation treatment process,

- the ability to quickly change the parameters of the accelerator, which allows a flexible transition between sterilization regimes suitable for various types of products,

- the device approval process need not to be repeated after routine accelerator maintenance [1],

- the accelerator can be turned off at any time, which reduces costs of consumables and simplifies the inspection, after the device is turned off, the emission of radiation ceases, which means that accelerators are perceived safer than gamma radioactive sources.

The choice of the type of sterilization requires two issues to be resolved:

1) finding a method that will be appropriate for a given product (shape and material),

2) determining the influence of the selected type of radiation on the functional properties of a medical device.

3) conducting a financial analysis (costs of the sterilization process, transport costs, validity period).

Before choosing the radiation method as a method of sterilizing medical equipment, it is necessary to consider the influence of radiation on the stability of the materials from which the products are made [2]. These materials exhibit different changes in physical properties resulting from the effects radiation has on the chemical structure of the polymer. Radiation can cause some polymers to cross-link, some to chain scission, while a few others are mostly unaffected. The polymers which are commonly used in the medical industry are low-density polyethylene, polypropylene, poly (ether-block-amide) thermoplastic elastomers, polytetrafluoroethylene and others.

General data on the resistance of plastics for medical applications are contained in the literature. Nevertheless, each time, i.e. for each specific product, a cycle of tests must be carried out to demonstrate the functional stability of the product during its useful life. The tests should check the specific properties of a given product, strictly related to its intended use, such as durability, transparency, color.

Due to the aforementioned advantages of e-beam over gamma radiation for sterilization purposes, transition to accelerator-based sterilization is observed. To meet the requirements of the knowledge of radiation effects on polymers for e-beam, in this project we plan to expand our understanding of radiation effects on the chosen polymer materials commonly used in medical devices by comparing gamma and e-beam irradiation. Especially, this impact may include:

• cross-linking, when the polymer radicals react with each other by joining a three-dimensional network,

• breaking the chain leading to the molecular weight deposits of macromolecules,

• oxidation, when radiation appears, active centers, reagents with correction molecules, junctions, superoxide radicals (oxidation and chain breaking often occur here),

• long-chain branching - the polymer chains are connected, but the three-dimensional network has not been formed,

• grafting - a new monomer is added to the base polymer chain.

The polymers that are most commonly used in the manufacture of disposable medical devices are low density polyethylene (LDPE), polypropylene (PP), poly (ether-block-amide) thermoplastic elastomers (PEBA), polytetrafluoroethylene (PTFE), and biopolymers (e.g., biodegradable polyesters like polylactic acid, polyglycolic acid).

The scope of the project

The scope of the project will be to determine the influence of the radiation modality (e-beam vs gamma) on the sterilized product material properties. The experimental design of the studies takes into account irradiation conditions, namely total dose, dose distribution, dose rate and irradiation environment (normal or oxygen-free).

The research will allow to assess whether the use of electron beam radiation to sterilize medical products gives effects comparable to those caused by gamma radiation in the sterilized materials. It will allow the assessment of early and late effects of e-beam on sterilized products and comparison of these effects with those caused by commonly used gamma radiation. The selection of polimeric materials from the European market was based on the data already collected as part of the work of the INCT Radiation Sterilization Plant.

Materials and methods:

A market analysis was carried out in terms of the selection of appropriate medical products for research. Two devices were selected from among those that are routinely sent for sterilization as part of the Radiation Sterilization Plant of Medical Devices And Allografts activities. Two types of medical devices were purchased: 60 ml MULTI stool/urine container with sticker, with a capacity of 60 ml (Producer: EL-COMPul. Warszawska 1182-300 Elbląg), and a PE-10 ml droplet dispenser bottle (Polfa Lublin S.A., Wojciechowska 42, 20-704 Lublin). The packaging consisted of the following parts: The multicontainer comprised of the translucent body of the container, a red-colored cap and a spatula for sample collection. The droplet dispenser comprised of three elements: the body of the bottle, the dispenser and the cap with a tear-off ring seal (Figure 1). The products were purchased directly from the manufacturer in collective packaging, before sterilization.

A B

Figure 1. The devices used in the tests. A, 60 ml MULTI stool/urine container, 60 ml B comprised of the translucent body of the container, a red-colored cap and a spatula for sample collection; B, the PE-10 ml droplet dispenser bottle comprised of: the body of the bottle, the dispenser and the cap with a tear-off ring seal.

The following specimens were chosen for testing:

The spatula (sample material denoted as specimen 1, polypropylene-based)

The container body of the multicontainer (specimen 2 polypropylene-based)

The container body of the droplet dispenser (specimen 3, polyethylene-based)

A portion of specimens (5 items per measurement point) of each type were packed in a in a thermoforming machine, into a barrier film under nitrogen. (Ulma Packaging, Kościelna 10, 05-124 Skrzeszew) An adequate portion was packed in air.

Then, the products were subjected to radiation sterilization using gamma radiation (^{60}Co gamma source, Interprofessional Investment Ltd, UK). The specimens were irradiated with 2 kGy/h dose rate, with doses of 25 kGy, 35 kGy and 100 kGy. The doses of 25 kGy and 35 kGy have been selected as the two commonly used for sterilization of medical devices. The 100 kGy dose was selected as a positive control - such a relatively high dose value will allow to confirm the correctness of the tests used.

Similarly, portions of the products in a protective atmosphere, and in air were sterilized by means of an electron beam. Irradiation was performed at ambient temperature with doses of of 25 kGy, 35 kGy and 100 kGy using 10 MeV electron beam generated in the linear electron accelerator Elektronika 10/10.

Non-irradiated specimens were used as a negative control.

An aging schedule was planned, and the measurements by each method (except EPR) are planned to be performed:

1. After a week (to allow the samples past very fast processes at the start of the measurement what might bring stochastic discrepancies)

2. after 4 months (16 weeks)

3. after 8 months (32 weeks)

4. after a year (November 2022)

5. after two years (November 2023)

6. after three years (November 2024)

The following tests were performed for the first aging period:

The tensile properties were examined with an Instron mechanical tester, model 5566 in accordance with PN-EN ISO 527-1:2012, at a crosshead speed of 50 mm min^{-1} at room temperature with head of maximum load of 100 N. The Young's modulus, tensile strength and elongation at break were measured. The measurements were repeated five times, for each material.

Thermogravimetric analysis (TGA) was performed on a TA Instruments TGA Q500 apparatus, in the range of 35 – 600 °C, ramp 10 °C min^{-1}. Balance gas N_2 40 ml/min., sample gas : air 60 ml/min.

Iso-TGA: Additionally, isothermal TGA analysis was performed: On the basis of the standard TGA curves in air (as described above) for the untreated samples, the two temperatures were chosen: the setpoint temperature for the decomposition process of samples, that equaled 280 °C for specimens 1 and 2 and 356 °C for specimen 3. The center-point decomposition temperatures: 315 °C for specimens 1 and 2 and 382 °C for specimen 3. The samples were heated in nitrogen to the setpoint or center-point temperatures, respectively at 10 °C/min. then the gas was changed to air and the process was performed at the set temperature for 60 min.

EPR Spectroscopy: The specimens were placed in EPR quartz tubes and immersed in liquid nitrogen, then irradiated with the gamma dose of 10 kGy. The EPR spectroscopy using an ESP 300 Bruker X-band spectrometer equipped with WinEPR software and ER 4131VT cryostat were used to measure spectra at various microwave power (0.1 and 10 mW) from 100 K every 30° to complete radicals decay. The following parameters were used: 0.1 mT modulation amplitude, 1.28 ms time constant and 10 ms conversion time. The simulation was carried out using the Simfonia-Bruker software.

Dose control was performed by graphite calorimeters for electron beam and by alanine dosimeter for gamma chamber sterilization.

UVVIS diffuse reflectance spectra (DRS): The JASCO V-670 spectrophotometer equipped with a reflection device was used to measure the diffuse reflection spectra. Samples irradiated with different doses were measured in the range 200–800 nm. The UV–vis absorbance of irradiated/aged samples are presented as the difference between the experimental spectra and the reference signal of non-irradiated material.

Surface wettability Surface properties of the samples before and after irradiation was tested by measuring the contact angle, using the tensometer Kruss K100C.

Determination of the dynamic contact angle in relation to water was carried out using the Wilhelmy plate method, consisting in immersion and emergence of the sample from the measuring liquid with the use of a rod mounted on the arm of the force measuring system. The tests were carried out with the use of a Krüss K100C strain gauge, equipped with a thermostated vessel for solutions, enabling measurements in the range of -10 °C - 100 °C. The position of the sample holder is adjusted by a high-precision motor. The balance is automatically calibrated with built-in weights. The measurement resolution is 0.01 mN / m. The tag is controlled by the LabDeskTM software. The contact angle of the polymer plaques of the specified dimensions was measured at 25 °C. The determined contact angle is the arithmetic mean of 10 measurements. The diagram describing the method of measuring the contact angle with the plate method is shown in Fig. 10.

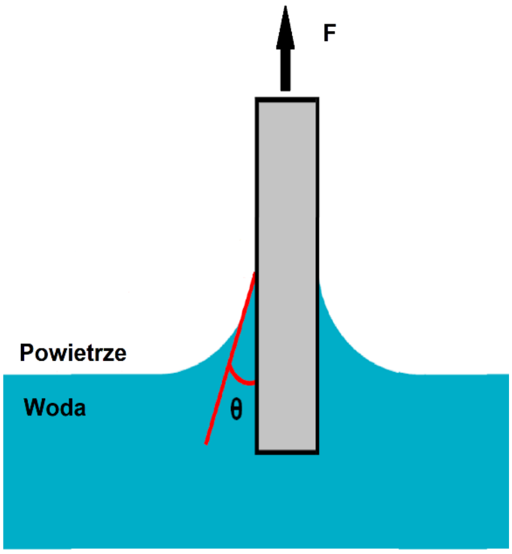

Fig. 2. Schematic drawing of the contact angle measurement with the plate method.

The following formula is used to determine the contact angle:

$$cos\theta = \frac{F}{L * \sigma}$$

Where:

θ - contact angle,

σ - surface tension of water at measurement temperature,

L - wetted circumference of the sample (L = twice the length of the sample + twice the thickness of the sample),

F - force acting on the weighing system.

The following parameters were applied: Immersion depth Max: 5 mm; Immersion Depth Min: 1 mm;

Measuring speed: 3 mm/min; Surface detection Speed : 6 mm/min.

The above tests are planned for each aging period. At the end of the aging cycle, an EPR test after probe-irradiation with the dose of 10 kGy at 77K will be performed in order to observe

the molecular structure changes as described in [3]. Also, a leak test will also be performed for specimens treated with the three above-mentioned doses, in both atmospheric conditions, 5 repetitions for a given measuring point. The test will be performed by pouring water into the body of the packages and checking for leaks.

Results

Thermogravimetric analysis

Thermogravimetric analysis results of the untreated specimens 1, 2, and 3 in air is shown in Figure 3. The values for the thermal decompositions were the same in the case of 1 and 2 specimens, defined by the manufacturer as made of polypropylene. The setpoint for degradation temperatures were 280 °C for specimens 1 and 2 and 356 °C for specimen 3. The center-point decomposition temperatures: 315 °C for specimens 1 and 2 and 382 °C for specimen 3. The thermograms of the radiatively-treated samples are given in Figure 4.

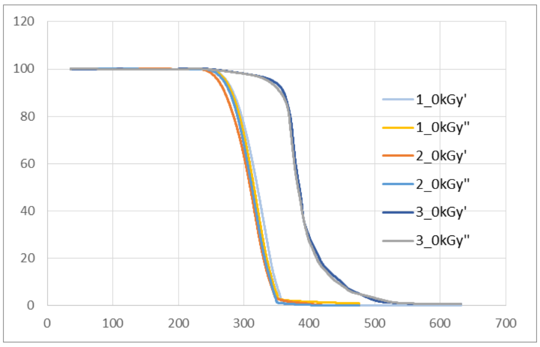

Figure 3. The thermograms for the untreated specimens. The measurements were performed in duplicate.

1 2 3

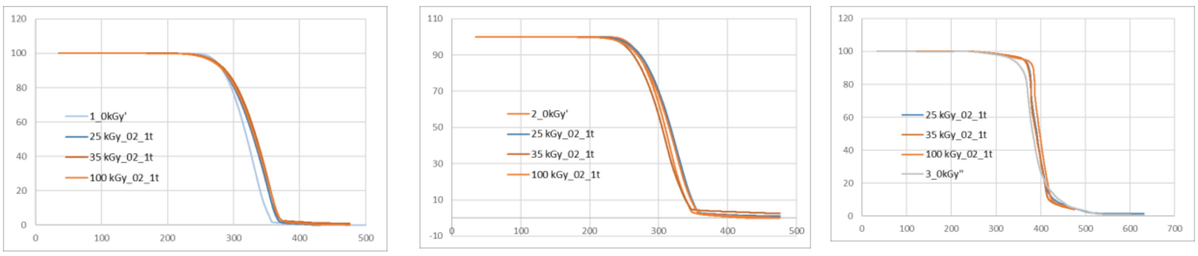

Figure 4. the thermograms for 1, 2, and 3 treated with the increasing doses of ionizing radiation (gamma source) measured one week after exposure.

The data for the e-beam treated samples were measured and are currently being processed.

Iso-TGA: On the basis of the obtained in standard TGA setpoint and middle-point values for the process of thermal decomposition, the isoTGA measurements for the both mentioned values of temperature were also performed. The results for the middle-point temperature of decomposition are given in Figure 5.

1 2 3

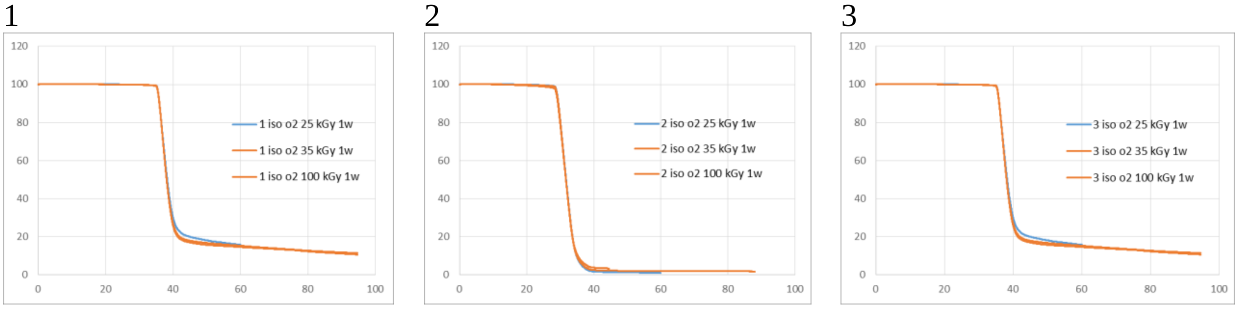

Figure 5. iso-TGA thermograms for specimens 1, 2, and 3 treated with different doses of gamma radiation measured one week after exposure, at their middle-point of decomposition temperature.

The results for the setpoint temperature of decomposition are given in Figure 6.

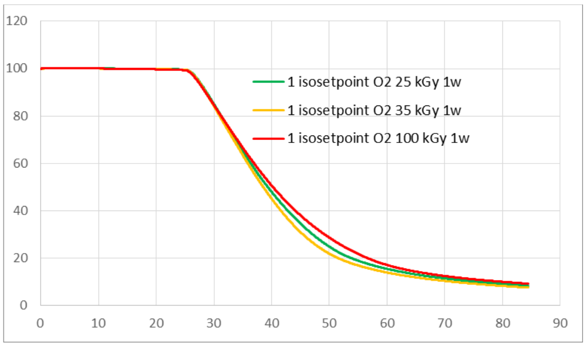

Figure 6. iso-TGA thermograms for specimen 1 treated with different doses of gamma radiation measured one week after exposure.

EPR Spectroscopy The specimens were probe- irradiated with the dose of 10 kGy gamma radiation in 77K (liquid nitrogen) in order to freeze the radicals formed in the sample upon irradiation. This method is used in our laboratory to analyze the structural changes during the degradation of polymers (see discussion) [3]. The EPR spectroscopy spectra at microwave powers 0.1 and 10 mW were measured in temperatures ranging from 100 K, with annealing, registered every 30°C to the temperature of complete radicals decay. This allowed observing radical interconversion and decay. The spectra for the three specimens in two different microwave powers and in different temperature are set aside in Figure 7.

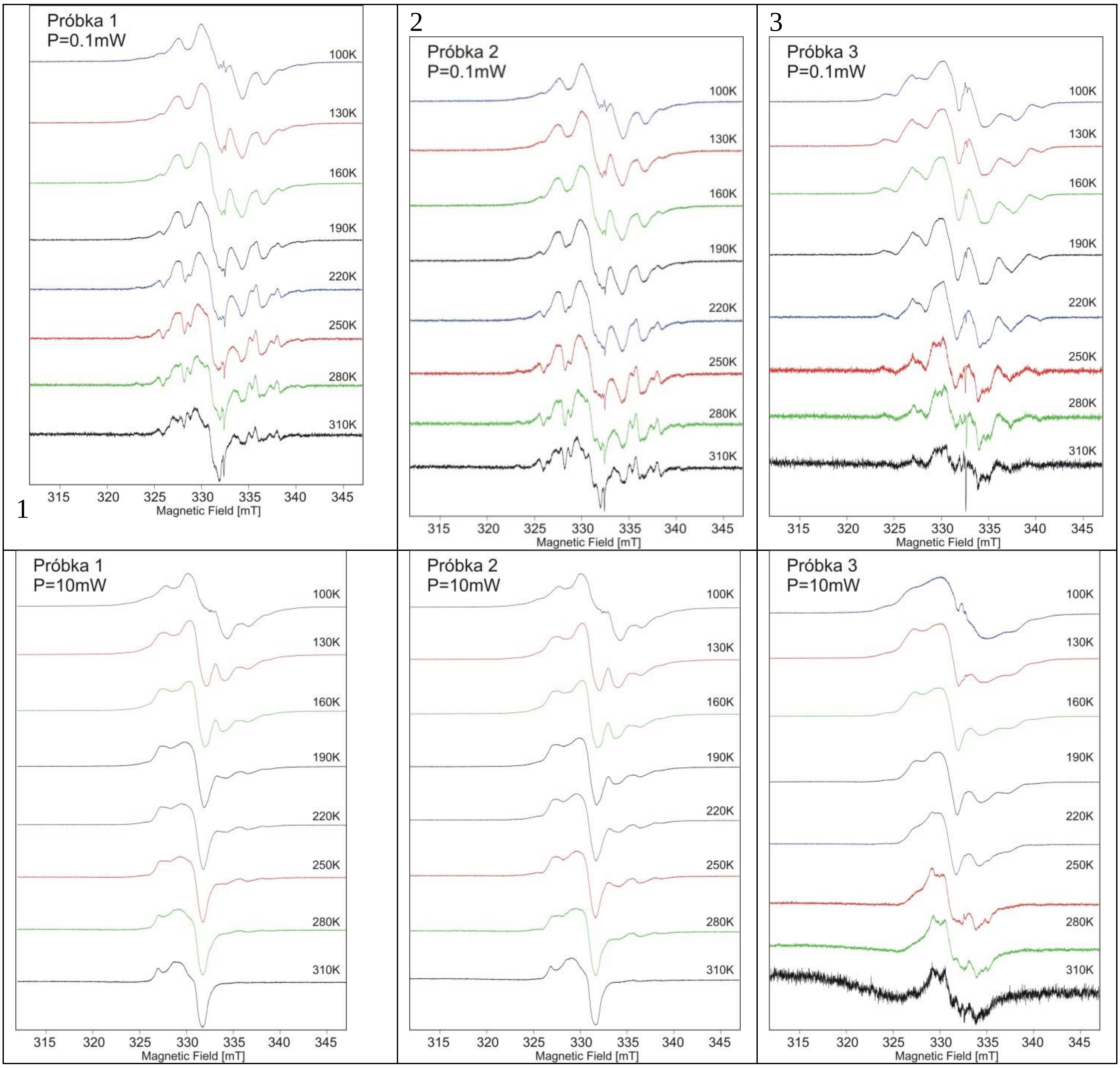

Figure 7. The spectra for the three specimens probe-irradiated with the dose of 10 kGy at 77 K. The spectra were recorded in two different microwave powers and in different temperatures.

The tensile properties were examined at a crosshead speed of 50 mm min^{-1} at room temperature with head of maximum load of 100 N. The Young's modulus, tensile strength and elongation at break were measured. The measurements were repeated five times, for each material. The mean values of the obtained parameters and their standard deviation values are given in Tables 1, 2 and 3.

Table 1. Mechanical test results for untreated samples

Specimen 1		strain at break [Mpa]	elongation at break [%]	Young modulus [Mpa]
	mean	19.71	611.80	631.43
	SD	4.61	39.93	62.51

Specimen 2		strain at break [Mpa]	elongation at break [%]	Young modulus [Mpa]
	mean	6.47	13.44	378.07
	SD	0.29	4.64	47.15

Specimen 3		strain at break [Mpa]	elongation at break [%]	Young modulus [Mpa]
	mean	12.79	576.56	66.99
	SD	2.04	63.78	8.81

Mean = mean value of 5 repetitions, SD = standard deviation

Table 2. Mechanical test results for specimen 1, 2 and 3, (1 week, gamma, air).

	ambiance	Irradiation type		SPECIMEN No 1 (RED)		
25 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	25.76	478.21	795.22
			SD	13.12	29.79	145.07
35 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	17.80	537.58	701.06
			SD	4.13	95.31	71.01
100 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	25.04	5.18	640.61
			SD	6.13	1.08	343.86

SPECIMEN No 2 (TRANSLUCENT)

25 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	11.77	12.07	598.49
			SD	6.08	14.68	147.72

35 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	11.05	2.55	651.46
			SD	5.04	0.84	230.27

100 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
				too brittle	too brittle	too brittle
				too brittle	too brittle	too brittle

SPECIMEN No 3 (WHITE)

25 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	12.1	494.79	94.64
			SD	2.01	105.07	20

35 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	15.06	582.01	94.71
			SD	2.39	32.53	16.82

100 kGy	air	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	17.42	621.95	103.15
			SD	1.63	28.07	14.04

Mean = mean value of 5 repetitions, SD = standard deviation, SAB = strain at break, EAB = elongation at break

Table 3. Mechanical test results for specimen 1, 2 and 3, (1 week, gamma, nitrogen).

	ambiance	Irradiation type		SPECIMEN No 1 (RED)		
25 kGy	N_2	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	16.69	592.95	658.16
			SD	3.81	90.08	80.87

35 kGy	N_2	gamma	SAB [Mpa]	EAB [%]	Young modulus [Mpa]
		mean	16.90	624.27	666.82
		SD	2.09	0.87	65.66

100 kGy	N_2	gamma	SAB [Mpa]	EAB [%]	Young modulus [Mpa]
		mean	20.31	348.83	736.02
		SD	3.15	91.90	71.41

SPECIMEN No 2 (TRANSLUCENT)

25 kGy	N_2	gamma	SAB [Mpa]	EAB [%]	Young modulus [Mpa]
		mean	19.57	10.34	720.87
		SD	2.05	3.34	41.80

35 kGy	N_2	gamma	SAB [Mpa]	EAB [%]	Young modulus [Mpa]
		mean	10.58	3.86	620.13
		SD	3.78	2.56	136.25

100 kGy	N_2	gamma	SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			16.90	5.49	556.75
			6.35	2.72	107.30

SPECIMEN No 3 (WHITE)

25 kGy	N_2	gamma	SAB [Mpa]	EAB [%]	Young modulus [Mpa]
		mean	15.84	558.6	101.33
		SD	0.8	35.66	5.89

35 kGy	N_2	gamma	SAB [Mpa]	EAB [%]	Young modulus [Mpa]

	mean	17.39	571.94	108.59
	SD	2.71	53.75	11.55

100 kGy	N_2	gamma		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	14.75	449.48	111.79
			SD	6.15	169.1	4.97

Mean = mean value of 5 repetitions, SD = standard deviation, SAB = strain at break, EAB = elongation at break

Table 3. Mechanical test results for specimen 1, 2 and 3, (1 week, e-beam, air).

	ambiance	Irradiation type	SPECIMEN No 1 (RED)			
25 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	18.93	603.31	720.72
			SD	5.44	77.03	125.29
35 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	24.51	443.89	777.00
			SD	9.04	12.70	87.96
100 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	19.80	202.45	697.15
			SD	5.37	122.68	97.24
			SPECIMEN No 2 (TRANSLUCENT)			
25 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	14.70	9.31	565.94
			SD	5.62	2.24	66.45
35 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	19.96	9.09	715.41
			SD	5.46	1.97	94.79
100 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	14.62	3.55	740.77
			SD	6.18	2.23	112.49
			SPECIMEN No 3 (WHITE)			

25 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	13.67	562.41	86.95
			SD	3.41	83.34	11.03

35 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	14.44	560.07	90.72
			SD	2.76	70.84	15.07

100 kGy	air	e-beam		SAB [Mpa]	EAB [%]	Young modulus [Mpa]
			mean	14.98	526.76	86.33
			SD	3.16	102.71	8.24

Mean = mean value of 5 repetitions, SD = standard deviation, SAB = strain at break, EAB = elongation at break

UVVIS diffuse reflectance spectra (DRS): The JASCO V-670 spectrophotometer equipped with a reflection device was used to measure the diffuse reflection spectra. Samples irradiated with different doses were measured in the range 200–800 nm. The UV–vis absorbance of irradiated/aged samples are presented in the comparison with the reference signal of non-irradiated material.

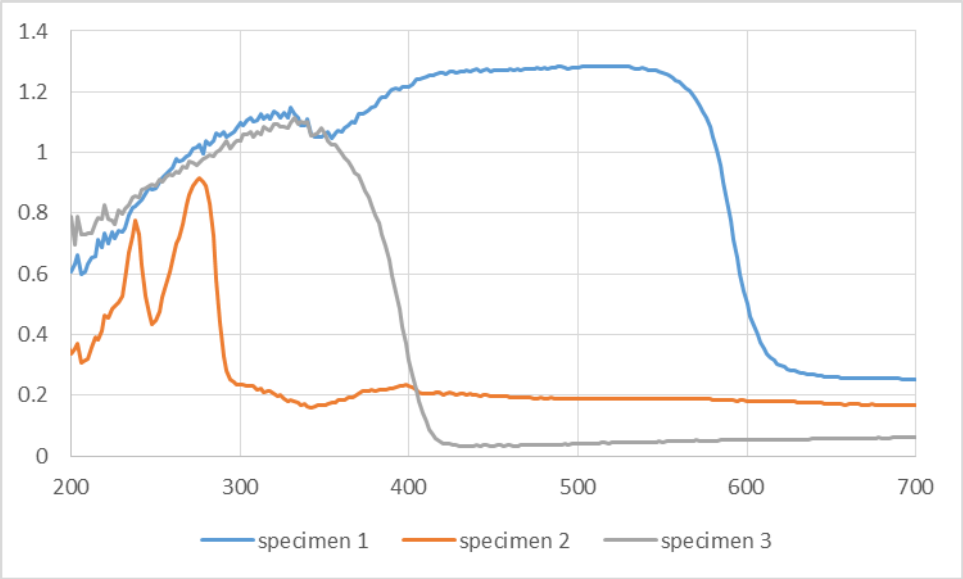

Figure 8. The UVVIS DRS spectra of the unirradiated specimens

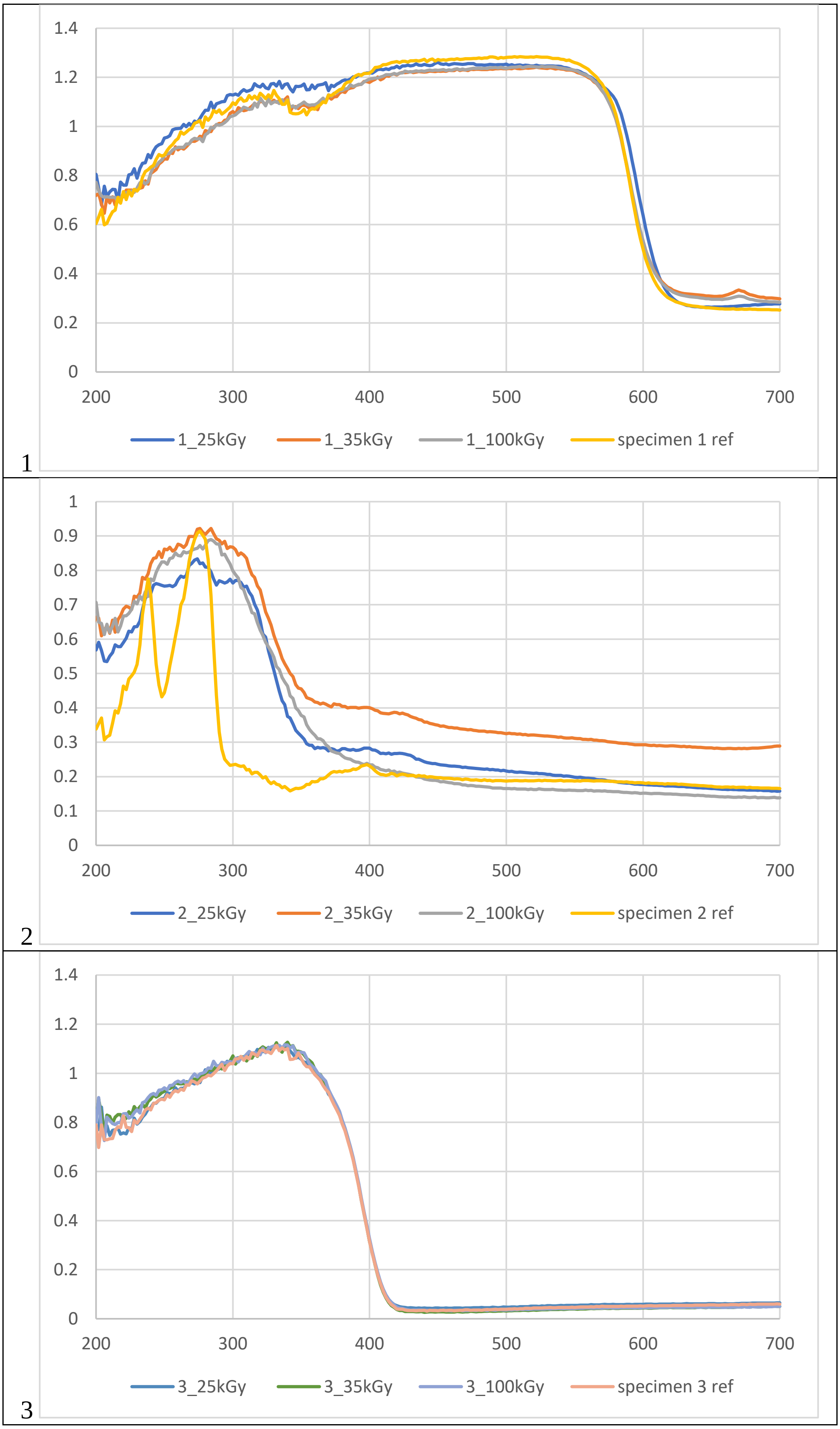

Figure 9. The UVVIS DRS spectra of the specimens irradiated with different dozes of gamma radiation in nitrogen atmosphere, versus the unirradiated specimens

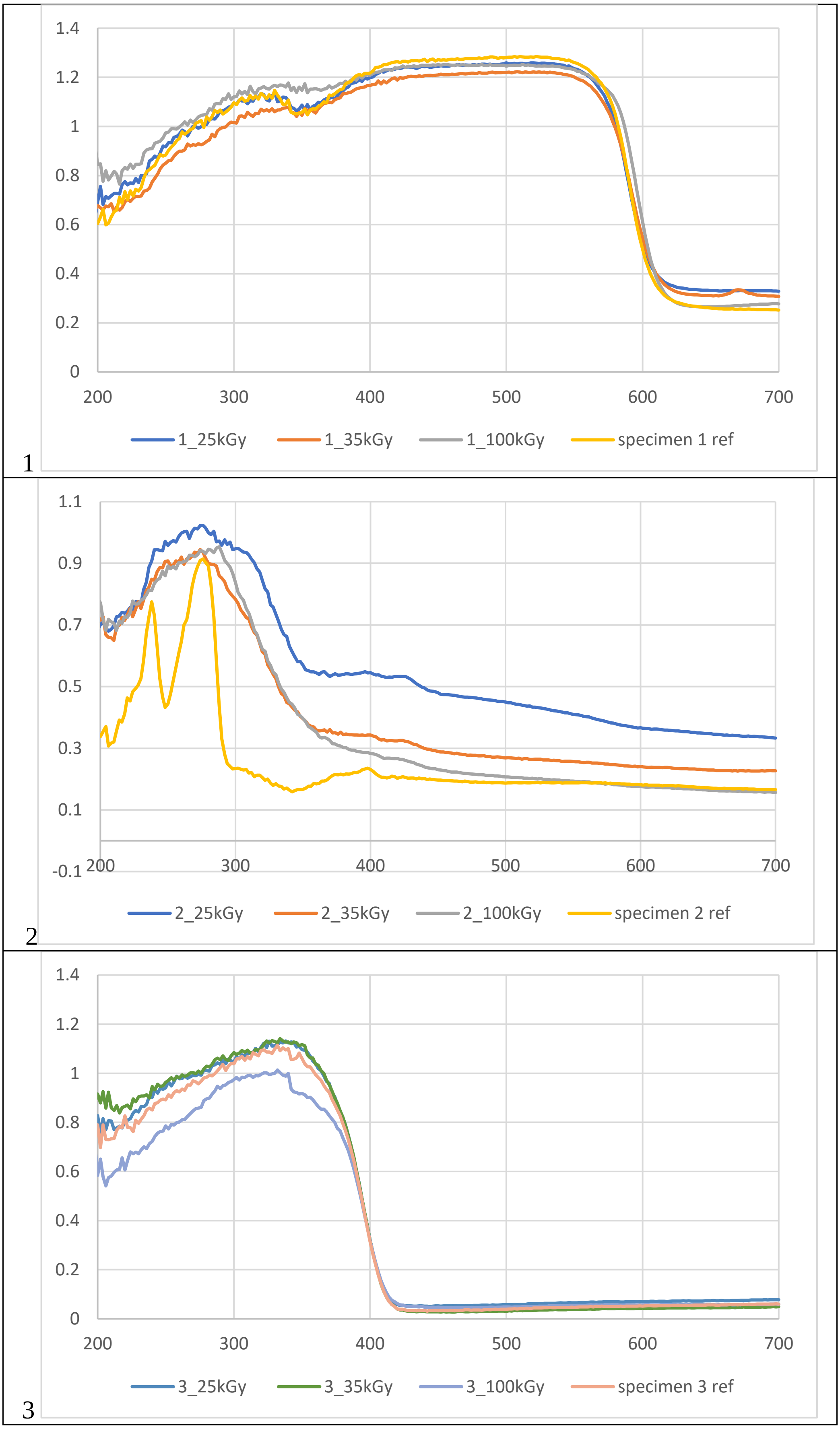

Figure 10. The UVVIS DRS spectra of the specimens irradiated with different dozes of gamma radiation in air, versus the unirradiated specimens

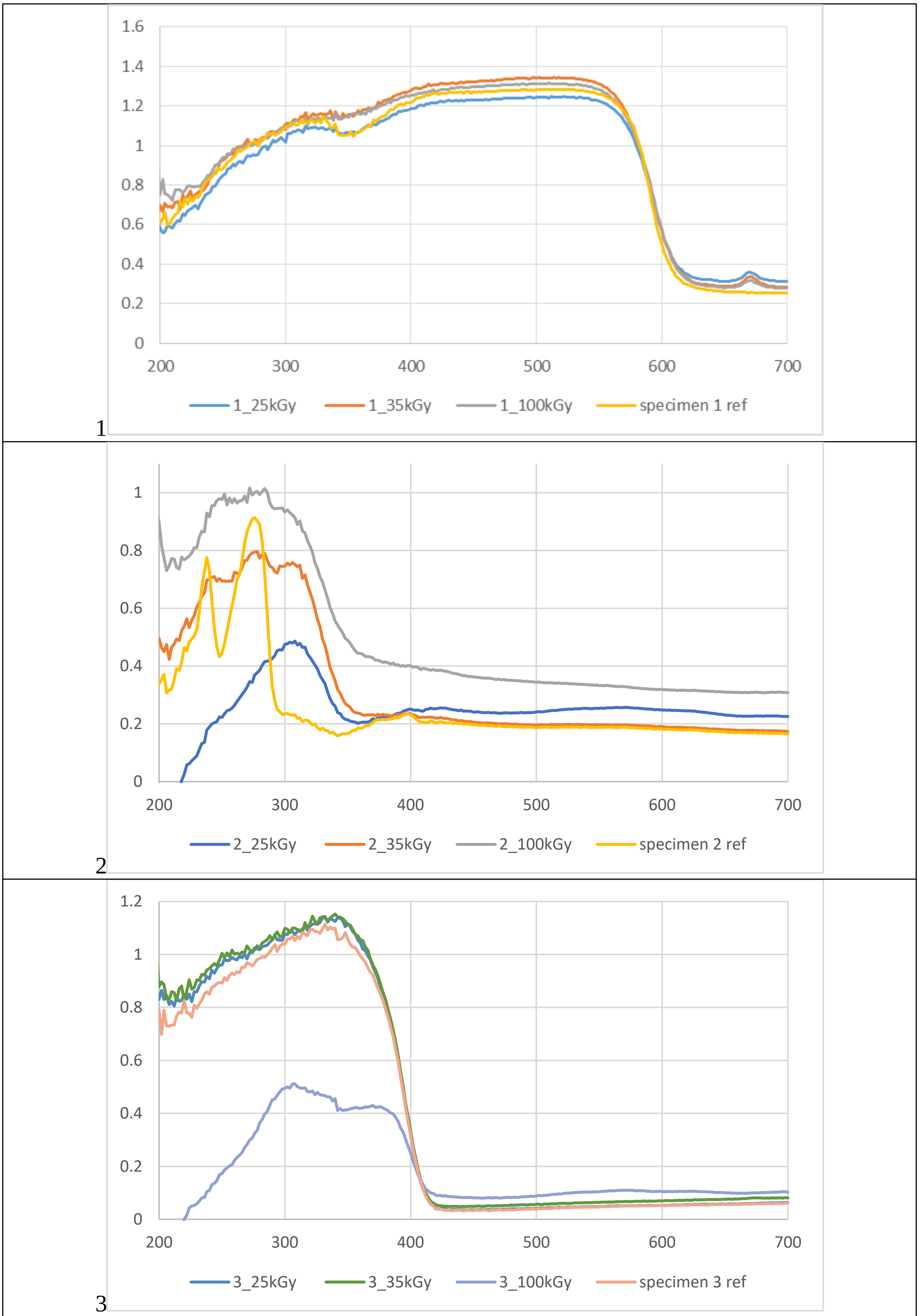

Figure 11. The UVVIS DRS spectra of the specimens irradiated with different dozes of e-beam radiation in nitrogen, versus the unirradiated specimens

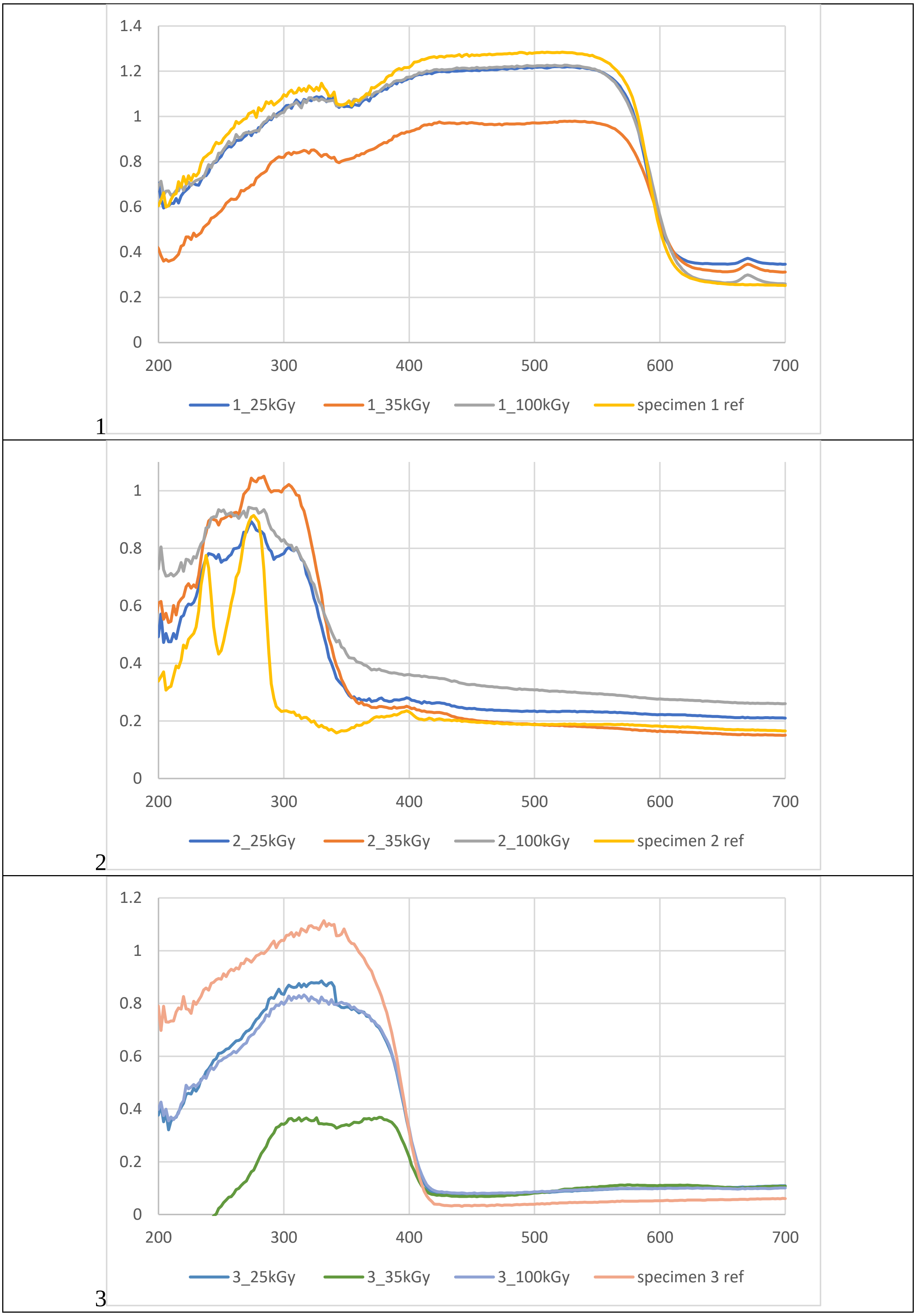

Figure 12. The UVVIS DRS spectra of the specimens irradiated with different dozes of e-beam radiation in air, versus the unirradiated specimens

Surface properties of the samples before and after irradiation were tested by measuring the contact angle, using the tensimeter Kruss K100C. Only specimen 2 and 3 were measured, due to difficulties with obtaining uniform samples from specimen 1 that would be sufficient for dynamic contact angle measurement. The data are presented in Tables 4, 5, 6, 7

Table 4. Wettability parameters for specimen 2 irradiated with different doses of gamma in nitrogen and air. SD – standard deviation

Specimen 2								
Dose	nitrogen				air			
	Ascending angle		Descending angle		Ascending angle		Descending angle	
	mean	SD	mean	SD	mean	SD	mean	SD
0 kGy	80.732	1.703	60.125	4.432	80.732	1.703	60.125	4.432
25 kGy	73.505	2.934	45.359	5.987	70.85	1.670	40.09	5.416
35 kGy	70.574	4.343	34.926	11.670	71.007	2.560	42.579	4.560
100 kGy	72.479	2.392	32.103	6.033	73.081	1.987	48.841	7.709

Table 5. Wettability parameters for specimen 3 irradiated with different doses of gamma in nitrogen and air. SD – standard deviation

Specimen 3								
Dose	nitrogen				air			
	Ascending angle		Descending angle		Ascending angle		Descending angle	
	mean	SD	mean	SD	mean	SD	mean	SD
0 kGy	87.676	1.571	55.64	4.325	87.676	1.571	55.64	4.325
25 kGy	69.598	2.909	41.741	3.750	69.039	1.750	48.655	3.450
35 kGy	67.316	1.992	39.965	5.489	67.088	14.00	42.579	4.560
100 kGy	69.908	3.347	26.577	7.208	62.687	4.127	35.014	6.933

Discussion and conclusions

EPR measurements allowed to define characteristic spectra of the polymers upon irradiation. Polypropylene and polyethylene–characteristic signals were found for samples 1,2, and 3, respectively. EPR for the radiation-treated samples was also performed, but the data have not been processed yet. However, the differences in the spectra for non-irradiated and irradiated specimens are not pronounced at this stage of the project (not shown). We expect to see some more significant changes along with the process of aging, and the occurring oxidation processes.

The TGA measurements gave the thermograms characteristic for each polymer type, but no clear differences can be seen at this stage of the project depending on the dose.

The EAB values for specimen 1, which is denoted by the manufacturer as polypropylene, and indeed gives an EPR signal characteristic for PP are surprisingly high for this plastomer [4–6] (see Tables 1, 2, 3). This can be explained by the presence of an additional plasticizer. The presence of the high amount of the plastifying additive can be also seen in isoTGA; where 10% of the sample mass at both temperatures (characteristic of PP decomposition) remains at the crucible. This justifies the choice of specimen 1 and 2, both based on PP but having different compositions, for the tests in the project.

The wettability test do not show any pronounced dependencies at this stage of the project.

The DRS-UVVIS results allow to observe pronounced changes in the electron transitions especially for the specimen 2.

The remaining gamma-treated samples in air, for which the data were not presented herein have been measured but the data were not processed yet. The specimens treated at ambient atmosphere have all been treated and are currently being measured. The remaining samples for e-beam will be processed when the gamma samples measurement ends. The shift in measurement timetable for some part of e-beam tests is because of the large number of samples to be tested. The specimens will be irradiated one week before the tests.

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POLAND (Slawomir Kadlubowski)

INFLUENCE OF IONIZING RADIATION ON POLYMERS AND MEDICAL DEVICES - A STUDY ON REACTION MECHANISMS AND CHANGES IN PRODUCT FUNCTIONALITY

S. KADŁUBOWSKI, A. OLEJNIK, B. ROKITA, P. ULAŃSKI

Institute of Applied Radiation Chemistry (IARC),
Lodz University of Technology,
Poland

Radiation is an effective and established tool to sterilize medical and healthcare products including a wide range of single-use medical products and devices. Sterilization is mostly done using gamma sources, however a transition to accelerator-based sterilization is being observed. Lack of the knowledge of radiation effects on polymers for electron beam is one of the reasons to impede the spreading use of these technologies.

Increasing need of the knowledge of sterilization or re-sterilization of medical devices, mostly respiratory masks and protective clothes used during COVID-19 pandemic is the other reason to start detailed research study on influence of ionizing radiation on polymer-based protective products used in medicine.

The purpose of the Project is to expand our understanding of radiation effects on selected polymers and polymeric materials commonly used in medical devices by comparing gamma and electron beam irradiation. The specific problems that we propose to address as CRP participant are described below.

TASK A. INFLUENCE OF TYPE OF IRRADIATION AND ITS DOSE RATE ON SELECTED POLYMERS

A number of studies has been devoted to analyzing the influence of ionizing radiation on different (synthetic, natural and modified) polymers. Based on that, a broad range of commercially available medical products is sterilized using ionizing radiation. Use of ionizing radiation is not only limited to production of that but also for its sterilization. Sometimes e.g. for hydrogel wound dressings processes of synthesis and sterilization proceeds simultaneously which significantly decreases production time and cost.

Polyethylene (PE), polypropylene (PP) and polystyrene (PS) are frequently used for production of basic medical devices or its components. Nowadays a number of modern materials used as a part of biomedical products (e.g. for tissue engineering, drug delivery) of required functionality (biodegradability, porosity, environment sensitivity, size (e.g. nanoscale)) is based on other, usually water-soluble, polymers (e.g. synthetic: poly(N-vinylpyrrolidone) (PVP), poly(acrylic acid) (PAA), poly(lactic acid) (PLA); natural: dextran (Dex); modified: chitosan (Chit), carboxymethylcellulose (CMC) etc.).

There is still considerable need for detailed analysis and comparison of influence of type of irradiation and its dose rate on changes in physico-chemical properties for mentioned above polymers. There is also a need for examination of influence of ionizing radiation on polymers in different state of matter. It is well known that in the case of irradiation of polymers in a dry (or molten) state a direct effect will be a dominating one, while irradiation of polymer in a solution will be connected with radiolysis of solvent and then reaction of the short-lived reactive species, namely OH radicals, H-atoms and hydrated electrons in case of aqueous solutions, with macromolecules. Mechanism of further reactions is connected with chemical nature of irradiated polymer (recombination vs. chain scission) and concentration of macromolecules and/or macroradicals in the solution (intramolecular vs. intermolecular crosslinking). One cannot forget significant effect of saturation (air vs. inert gas) on yield of degradation. That is why in a proposed study we will compare influence of two types of ionizing radiation (gamma and fast electrons) of different dose rates on number of different polymers both in a dry state and in solution. Irradiation will be conducted in air or inert gas and for solutions at different concentrations. Dose range applied within this project will correspond to doses used for sterilization of medical devices (25kGy) and higher (up to 100 kGy) connected with multiple re-sterilization. Mechanism of macroradicals reactions (degradation vs. inter- or intramolecular recombination) will be proposed in connection with chemical nature of irradiated polymer.

TASK B. INFLUENCE OF TYPE OF IRRADIATION AND ITS DOSE RATE ON COMMERCIALLY AVAILABLE PRODUCTS

COVID-19 pandemic reminded everyone on necessity of sterilization of medical devices or its possible re-sterilization. Radiation-induced sterilization is the method of choice as a cost- and time-effective process. Number of respiratory masks commonly worn by medical personnel as well as protective clothes are now gamma and electron beam sterilized, that is why it is important to compare effect of these two types of irradiation on mentioned above materials. Usually these devices are of composite nature, therefore we decided first to analyze changes in basic physico-chemical parameters of active compounds constituting their construction (see TASK A) and then to analyze possible changes in functionality of whole product. Irradiation can also influence on biocompatibility of sterilized (re-sterilized) devices. That is why we propose to analyze this important property of the products. Together with aging studies we will be able to monitor and define terms of use of irradiated materials.

Our team participated in a study organized by IAEA (April 2020) on sterilization of respiratory masks commonly worn by medical personnel and lately also by ordinary people. Our participation in this project has been focused specifically on analysis of chemical and physical changes in the structure of polypropylene-based membrane as a main part of analyzed devices.

The aim of this preliminary study is to find out if the melt-blown PP unwoven fabric, used as the filtration layer in the face masks, can withstand EB irradiation with the typical sterilization dose with no detrimental changes to its structure and basic properties. This information could help in finding out whether (re)sterilization of face masks is feasible.

We have irradiated commercial face masks, declared by the distributor to comply with ffp2 standard, by EB at the doses of 12.5, 25 and 50 kGy in two different conditions (air or vacuum, see below) and subsequently took SEM scans of the middle layer of the mask (made of melt-blown PP fabric). We have also made a visual inspection of the masks before and after irradiation. We have also studied an effect of storing the masks for 3 days after irradiation at various conditions. Preliminary data have been collected on the respiration resistance and aerosol penetration properties of the masks.

Face masks, size 20 x 16 cm, declared to comply with EN14683/N95/FFP2 standard, have been purchased from a Polish supplier. All 3 layers were composed of polypropylene, the middle layer being melt-blown PP (“Meltblown 25g/m2”), the outer layers being “Spunbond 15g/m2”and “Spunbond 20 g/m2”.

Masks have been divided into 3 series: to be irradiated with free access of air (A), to be vacuum-packed, irradiated and opened directly after irradiation (V) and to be vacuum-packed, irradiated, and kept unopened for 3 days (Q). Table 1 shows the data of all samples. Masks of the V and Q series have been vacuum-packed in PE foil, while masks of the A series were placed in open PE foil pouches.

Samples have been fixed in flat cardboard boxes and irradiated at RT on a semi-commercial setup consisting of a horizontal scanned-beam linear electron accelerator ELU-6 (Elektronika, Russia) and a vertical flat box conveyor. Electron energy was 6 MeV and the dose per single pass was 12.5 kGy as determined by calorimetry.

Masks have been subsequently cut open, the middle layer has been taken out, cut into small pieces, sputtered with gold and analyzed on a Hitachi TM-1000 tabletop scanning electron microscope, at various magnifications. Three different spots of each sample have been visualized. Masks of the series A and V have been analyzed within 4 hours after irradiation, while masks of the series Q have been kept in their vacuum packages for 3 days, subsequently opened and analyzed.

It can be seen that the starting material (blank samples) is not fully homogeneous. In some fragments the fibers seem to be partially molten (which might be the result of manufacturing process or of the procedure used to fix this layer to the outer layers). Exactly the same effect can be seen in the irradiated samples.

In general, EB irradiation in air and in vacuum with a dose up to 50 kGy, with SEM analysis immediately following irradiation (chapter 3.1. below) did not reveal any significant visible changes in the studied structure of the fabric or fibers.

At the highest magnification and highest dose (50 kGy), in some pictures there seem to be some mild irregularities at the otherwise smooth surface of some fibers (looking like small patches likely to peel off, or rare appearance of surface unevenness – probably spots from where some cracks can be formed, cf. A50 position 2, V50 position 3), but no fibers are actually broken, neither any cracks were observed.

The only picture with some broken fibers has been obtained for sample irradiated with dose 25 kGy (in air), but the breaking points are adjacent to some larger structural irregularity and it is difficult to assess if the breakage is linked to irradiation. Other positions of the same sample don't show broken fibers, so it doesn't seem to be a reproductible effect.

Moreover, we haven't noticed significant changes in the appearance and mechanical properties (no measurements; assessed just by hand) of the masks and of the melt-blown PP layer upon irradiation, at least in the samples analyzed immediately after irradiation. At double sterilization dose (50 kGy) leads to a barely perceptible change of color (slight darkening). The masks also haven't developed any perceptible malodor.

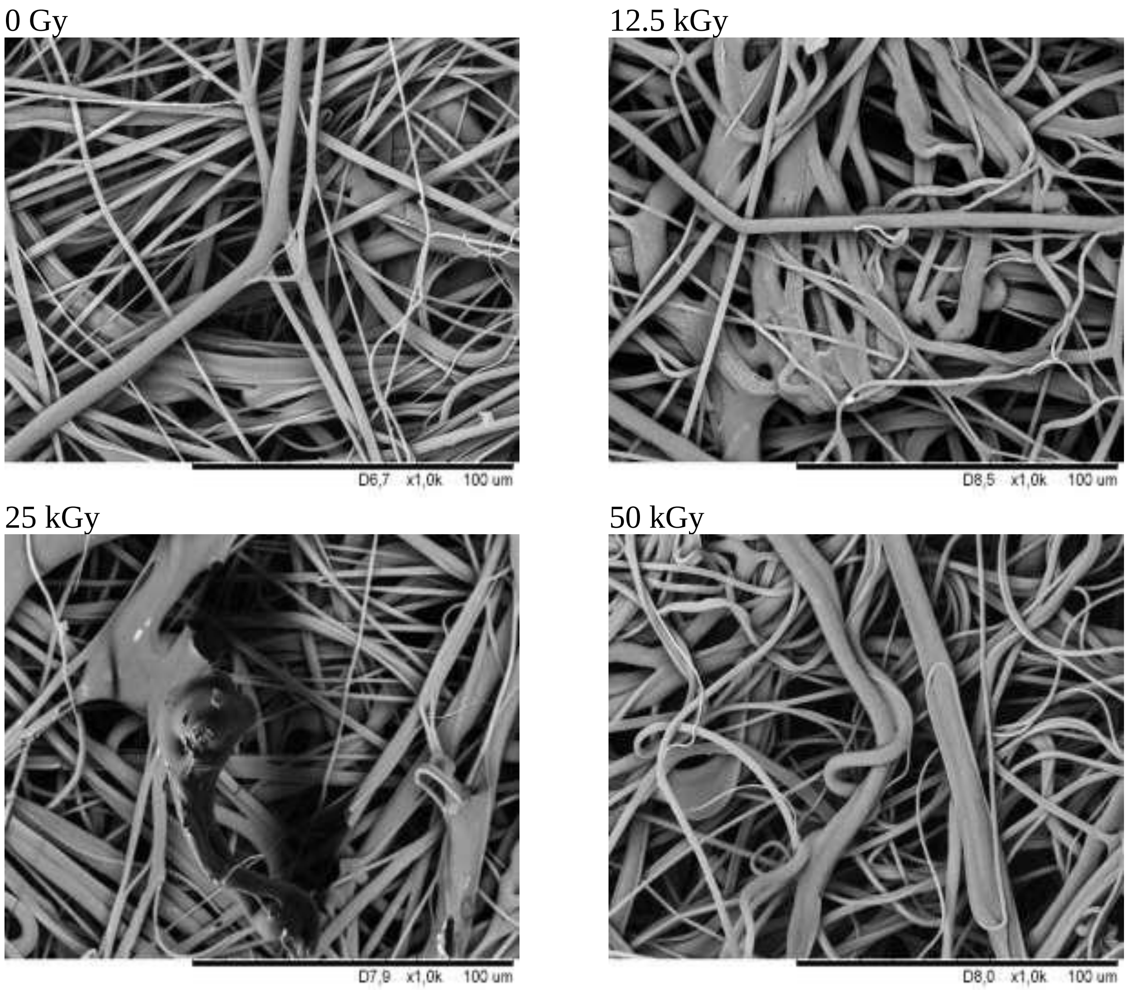

Figure 1. SEM pictures of masks irradiated in air

Two masks, A00 and Q25, have been analyzed for respiration resistance and permeation properties, according to the procedures described in the EN 149:2001 + A1:2009 standard.

Table 2. Preliminary results of respiration resistance test and paraffin oil mist penetration test for unirradiated and irradiated masks, marked A00 and Q25, respectively (irradiation in vacuum at 25 kGy, sample kept for 3 days in unopened package, then analyzed).

Sample	Inspiration resistance [mbar] (flow rate 30 l/min)	Inspiration resistance [mbar] (flow rate 95 l/min)	Exhalation resistance [mbar] (flow rate 160 l/min)	Paraffin oil mist penetration [%] (flow rate 95 l/min)
A00	0.203	0.617	1.016	48.3
Q25	0.231	0.687	1.109	46.9
Requirements according to EN 149:2001 + A1:2009	FFP1 ≤ 0,6 mbar FFP2 ≤ 0,7 mbar FFP3 ≤ 1 mbar	FFP1 ≤ 2,1 mbar FFP2 ≤ 2,4 mbar FFP3 ≤ 3 mbar	FFP1 ≤ 3 mbar FFP2 ≤ 3 mbar FFP3 ≤ 3 mbar	FFP1 ≤ 20% FFP2 ≤ 6% FFP3≤ 1%

The irradiated mask seem to have slightly higher respiration resistance than the control, but also slightly better resistance to paraffin oil mist penetration. Due to the preliminary character of this test, it is difficult to judge if the observed small changes were actually caused by irradiation or by the fact of keeping the irradiated mask in vacuum packaging (which might have resulted in somewhat more compacted structure of the materials forming the mask). It should be noticed that while the used masks had low respiration resistances (well within the standards for ffp1, ffp2 and ffp3 classes), they performed poorly in the penetration tests.

Summing up: preliminary results do not indicate any significant effect of irradiation with the dose of 25 kGy on the respiration resistance and penetration properties of the tested masks.

This work will be continued with the use of masks composed of biodegradable polymer to insure faster decomposition after usage.

TASK C. COOPERATION WITHIN PROJECT

Institute of Applied Radiation Chemistry possess two radiation facilities: linear electron accelerator (6 MeV) and radiation chamber with a panorama-type irradiator (ca. 30 kCi cobalt-60, to be extended to 55 kCi still in 2020) of different dose rates. Detailed dosimetry e.g. alanine will be performed to follow irradiations planned within points 1 and 2 (see above). Results of these measurements will be delivered to all Project Partners to serve as a potential source of irradiation. Moreover, based on more than 30 years of experience in analysis of physic-chemical changes in irradiated polymers and broad research facilities (light scattering, viscometry, chromatography etc.) will let as to help to analyze materials irradiated in other institutions. Cooperation established within this Project will lead to further collaboration with other Partners.

Portugal

The current COVID-19 pandemic highlights how crises can rapidly jeopardize traditional supply chains, depriving health institutions of indispensable medical supplies. In these circumstances, the resort to 3D printing technology allowed local production of various medical devices, using multiple materials. Additionally, this method of manufacture permits the production of complex geometries, tailored to fit individual patient's needs.

The goal of the present research is to assess the safety and efficacy of using common commercially available polymers to 3D print customized medical devices, to sterilize these devices with ionizing radiation (gamma radiation and e-beam), and to use these devices to repair different types of structures in several experimental models that simulate clinically common conditions. Hence, our multidisciplinary team will use some commonly polymers as polylactic acid (PLA), polyvinyl alcohol (PVA), polycaprolactone (PCL), and polyamide (PA), to 3D print 4 different medical devices to be implanted with therapeutic intention: i) Hollow cylinder designed to be used as an alloplastic vascular conduit; ii) Rectangular mesh used to be used as an alloplastic myofascial reinforcement or repair; iii) Hollow cylinder used as an alloplastic nerve conduit; and iv) Hollow parallelepiped used as an alloplastic replacement of the rat's first lumbar vertebra body.

The data generated by this research project will be of great scientific, medical and economical value. It may help change the way many medical devices are produced, reducing costs and increasing availability even in remote areas.

Work Plan

1. Prepare 3D printed samples from PLA, PVA, PCL, PA (Ultimaker®).

2. Irradiate these samples up to 100 kGy using both gamma radiation and e-beam.

3. Analyze the samples including physical, chemical and biological *(in vitro* and *in vivo*) properties.

DEDICATE - RADIATION EFFECT ON 3D PRINTED MEDICAL IMPLANTS FOR CUSTOMIZED TISSUE REPAIR

M.H. CASIMIRO[1], G. RODRIGUES[2], D. CASAL[3,4], P.M. SANTOS[1], J.P. LEAL[1], L.M. FERREIRA[1]

[1] C²TN, Instituto Superior Técnico, Universidade de Lisboa, Lisboa, Portugal

[2] cE3c, Faculdade de Ciências, Universidade de Lisboa, Lisboa, Portugal

[3] Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisboa, Portugal

[4] Centro Hospitalar de Lisboa Central, Lisboa, Portugal

Abstract

During the COVID-19 pandemic the resort to 3D printing technology allowed local production of medical devices of simple and complex geometries. Nevertheless, the 3D printed medical devices were mainly limited to protective equipment and parts of essential medical machinery, since sound data regarding printed materials features, devices sterilization protocols, and biological safety and efficacy of these devices is clearly lacking. In this way, the goal of the present research is to assess the safety and efficacy of using common commercially available polymers to 3D print customized medical devices, to sterilize these devices with ionizing radiation (gamma radiation and e-beam), and to use these devices to repair different types of structures in several experimental models that simulate clinically common conditions. Hence, our multidisciplinary team will use some commonly polymers as polylactic acid (PLA), polyvinyl alcohol (PVA), polycaprolactone (PCL), and polyamide (PA), to 3D print 4 different medical devices to be implanted with therapeutic intention: i) Hollow cylinder designed to be used as an alloplastic vascular conduit; ii) Rectangular mesh used to be used as an alloplastic myofascial reinforcement or repair; iii) Hollow cylinder used as an alloplastic nerve conduit; and iv) Hollow parallelepiped used as an alloplastic replacement of the rat's first lumbar vertebra body.

1. INTRODUCTION

3D printing, an increasingly popular method of manufacturing medical devices allows an unprecedented customization to patients' anatomy and needs. This alternative method opens the possibility to complex geometries optimizing the topological distribution of materials and thus promoting bio integration and facilitating local tissue growth and survival. Additionally, 3D printing can manufacture devices where and when they are needed, using multiple materials, many of which derived from common and renewable sources, available in most places, decreasing economic and environmental costs. Finally, 3D printing may the only option for obtaining critically essential equipment in situations where conventional supply chains maybe compromised or exhausted. This is precisely the case of the current COVID-19 pandemic, where 3D printing has been used all over the world, including by our group, to produce face shields, ventilator parts, orthoses, and various other pieces of medical equipment.

However, the main limitation to the more widespread use of 3D printing in Medicine is the lack of sound data regarding several parameters required to ensure the safety and efficacy of 3D printed materials, in order to meet the stringent requirements needed for medical advices certification.

One of the most common methods of sterilization of medical devices is gamma irradiation. Radiation processing can be used for preparation/modification of polymers at room ambient temperature, in absence of harmful initiators or solvents and with high penetration through the bulk materials, with the unique advantage of allowing to obtain the desired material and its sterilization at the same time. The implementing institution has ample experience in sterilizing medical equipment, providing this service for hospitals and industry. The team itself has a vast experience on the use of gamma radiation for research purposes, namely on the structural and chemical functionalization of polymer-based materials through radiation technologies and the effects of sterilization doses on materials [1-9], and has being developed a preparation methodology of polydimethylsiloxane-hetraethylorthosilicate (PDMS-TEOS) hybrid materials using e-beam as alternative. However, there are insufficient data regarding the potential changes in structural properties of materials commonly used in 3D printing after being subject to different dosages of ionizing radiation. Another important drawback of 3D printing is the void formation between adjacent layers of material, which predisposes objects to anisotropic mechanical properties and to a proclivity to delamination.

Therefore, the goal of our work will be to assess the safety and efficacy of using common commercially available polymers to 3D print customized medical devices, to sterilize these devices with ionizing radiation (gamma radiation and e-beam) up to 100 kGy, and to use these devices to repair different types of structures in several experimental models that simulate clinically common conditions.

To achieve this goal, we gathered a multidisciplinary team composed of researchers from multiple backgrounds: chemists, radiation processing of materials, biologists, and medical doctors [1-13]. Our group has also already gathered some experience in 3D printing anatomical and preoperative models, as well as in external medical devices.

The host institution, Centro de Ciências e Tecnologias Nucleares (C^2TN), a research unit of Instituto Superior Técnico (IST), and the campus where it is inserted own an Ionizing Radiation Facility with an experimental source of cobalt-60 (ca. 1.7 kCi), a linear accelerator (10 MeV), and a Semi-industrial 60Co facility (unique in the country; 142 kCi, Mar-2019), as well as other laboratories that are vital to carry out the project. This is fully inserted in the C^2TN scientific/research strategy, in its Advanced Materials/Materials Science and Engineering thematic strand.

2. OVERALL PROGRAMME

The team will capitalize its experience to model and print medical devices that are paradigmatic of a variety of situations in which medical devices are implanted with therapeutic intention. Hence, different medical devices will be 3D printed using the commonly used materials polylactic acid (PLA), polyvinyl alcohol (PVA), polycaprolactone (PCL), and polyamide (PA):

<u>Device 1</u>- Hollow cylinder designed to be used as an alloplastic vascular conduit;

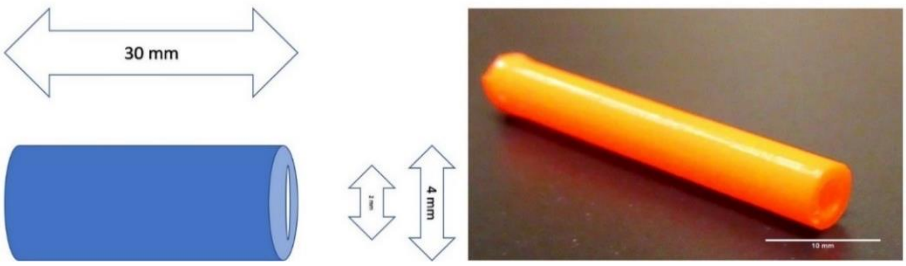

Figure 1: Prototype of medical device 1. This device is intended to reconstruct a segment of the abdominal aorta of the rat.

<u>Device 2</u>- Rectangular mesh used to be used as an alloplastic myofascial reinforcement or repair;

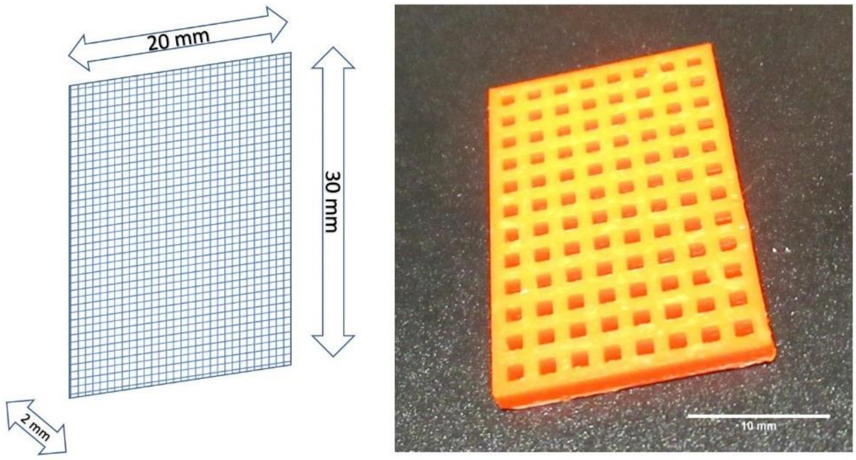

Figure 2: Prototype of medical device 2. This device is a mesh intended to reconstruct a myofascial segment of the ventrolateral aspect of the abdomen of the rat.

Device 3- Hollow cylinder used as an alloplastic nerve conduit. The inner surface of this cylinder will have a grooved to provide physical clues to promote axonal elongation (medical device 3).

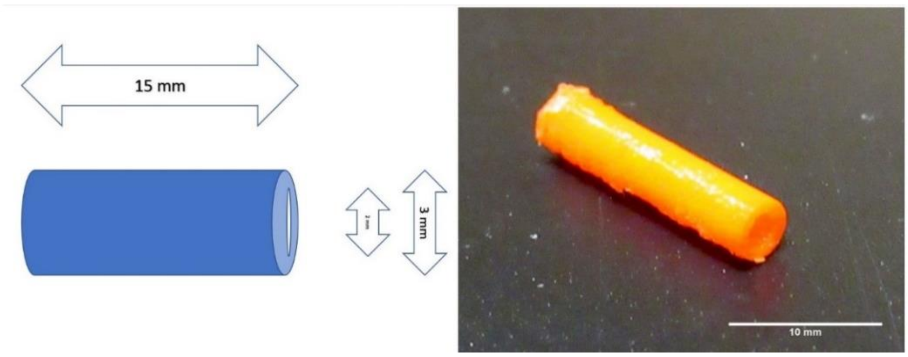

Figure 3: Prototype of medical device 3. This device is intended to reconstruct a segment of median nerve of the rat.

Device 4- Hollow parallelepiped used as an alloplastic replacement of the rat's first lumbar vertebra body (medical device 4).

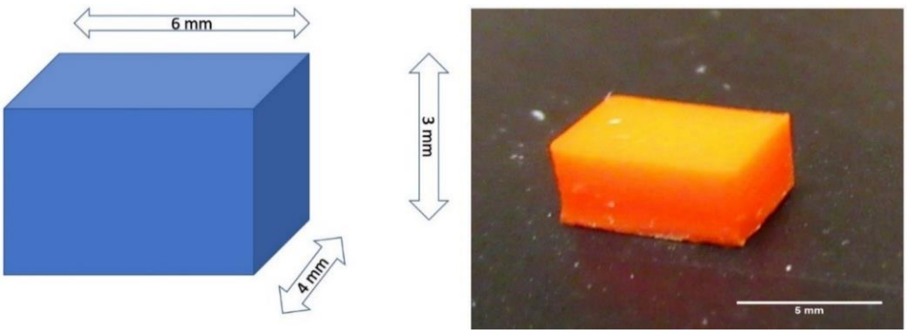

Figure 4: Prototype of medical device 3. This device is intended to reconstruct the body of the first lumbar vertebra of the rat.

After evaluating the relevant baseline structural features of each of these devices, it will be established an irradiation protocol (type of ionizing radiation: gamma radiation versus e-beam; dose; dose rate) to obtain adequate sterilization of the devices following the stringent standard regulations for medical devices. To avoid oxidation irradiation will be done in inert atmosphere. Next, the irradiated devices will be subjected to physical, chemical and structural evaluation. Techniques like FTIR; DSC/TGA; SEM and PALS (Positron Annihilation Lifetime Spectroscopy) will be used. Hydrophilicity measurements, uniaxial tensile tests; and degradation behavior will also be evaluated.

We anticipate that the doses of ionizing radiation needed will be relatively diminutive, as the 3D printers we will use depend on high temperatures for filament and powder melting. These temperatures are not compatible with the survival of most pathogens, decreasing the materials' bioburden. Nevertheless, a complete study will be done considering doses until 100 kGy. This knowledge will be of main importance not only for these particularly medical devices, but also for others devices that may be obtained by these printing techniques and materials even though for different purposes. For instance, these data will be of utmost importance and utility in the case of re-sterilization of medical devices with already long storage times.

The team will then conduct biocompatibility evaluation of the medical devices, sterilized by the different sterilization protocols, using cell cytotoxicity, cellular viability, attachment, morphology, and proliferation, resorting to different cell cultures. Namely, for vascular reconstruction, endothelial cells will be used to grow on the 3D vascular device; for the muscle reconstruction model, myoblast cell lines, such as C2C12 cells, can be used; for the peripheral nerve regeneration model, Schwann cells and neuroblastoma cell lines can be used; and finally regarding the bone substitute device, osteoblasts can be cultivated, or, alternatively, mesenchymal stem cells can be tested as well. All the protocols for growing the cells in these different model studies will be adjusted properly according to reference protocols for the growth of these cell types.

We expect that the implants produced will not show significant signs of cell toxicity, as all the materials used in their manufacturing are known to be biocompatible. This task will allow to study and correlate the biological behavior of the cells growing on the devices with the devices composition, properties and irradiation conditions.

However, we can only be certain of biological compatibility after placing the medical devices inside rodent models. To confirm biological safety and efficacy, we will conduct 4 experiments in Wistar rats of both genders to reconstruct vascular, myofascial, peripheral nerve, and bone defects. Clinical, physiological, and histological evaluations will be performed.

Efforts will be done also aiming to establish a radio sterilization protocol feasible to be executed in hospitals' small gamma irradiation chambers in order to improve the hospitals autonomy in the sterilization of the personalized 3D printed medical devices. This could be of paramount importance in surgical urgencies and in crisis periods, just like with the current COVID 19 pandemic, when it can be difficult to obtain a fast response from industrial irradiation facilities.

3- EXPECTED OUTPUTS

By the end of the project, based on a detailed comparative study of physical, chemical, structural and biological properties with the modelling/printing and irradiation conditions, the team will have identified the best materials and designs for each type of medical device, as well as an optimized irradiation protocol. The knowledge acquired will be of main importance not only for the particularly medical devices in study, but also for others devices that may be obtained by similar printing techniques and materials even though for different purposes. These data will be of great scientific, medical and economical interest. It may help change the way many medical devices are produced, reducing costs and increasing availability even in remote areas.

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RUSSIA

The effects of sterilization irradiation on properties of commercially available polymeric materials used in the production of medical appliances

Valentina Sharapova, Vladimir Ivanov

Ural Federal University, 620002 Yekateinburg, Mira st., 19
v.a.sharapova@urfu.ru

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Irradiation with accelerated electrons (energy 8.5 MeV, dose 5 kGy) of medical devices (vacuum tubes for blood sampling) made of polyethylene terephthalate (PET) was carried out. The study of changes in the physical properties of the material of the test tubes by methods of infrared (IR) spectroscopy has been carried out. Scientific article No. 19068 is being prepared for publication in the journal Technical Physics Letters. The revealed post-radiation changes in the IR spectra can be used to justify the choice of the dose of irradiation of PET products with electrons during the radiation sterilization procedure.

Introduction

Today, high requirements are imposed on the collection of blood from a vein. The difficulties associated with the process of delivering a test tube with blood to the laboratory should be separately noted. In the case of glass test tubes, they are faced with the fact that the test tube breaks, the blood spills, or some of the blood is absorbed into the cotton swab that covers the tube. These problems are easily solved by using PET vacuum blood collection systems. Such a system consists of three components: a tube, a needle and a holder. All system components are disposable (Fig. 1). Such test tubes are lighter than glass ones and are much less traumatic. However, due to its thermal sensitivity, PET medical products require so-called “cold” sterilization methods, one of which is radiation.

a

b

Figure 1. Items selected to study the effect of sterilization irradiation: a - irradiated tubes, b - a complete system consisting of three components: a test tube, a needle and a holder

 Processing with accelerated electrons with energies below the threshold for the occurrence of nuclear reactions (usually up to 10 MeV) is used for industrial sterilization of medical devices. State standard ISO 11137-1-2011, which regulates the procedure for radiation sterilization in the Russian Federation, defines a sterilization dose range of 15-25 kGy. The choice of a dose from the standardized range is primarily performed on the basis of the conditions for ensuring the established requirements for sterility. On the other hand, the radiation sterilization procedure should not significantly impair the consumer properties of the products, because the walls of any polymer container are accessible to the penetration of gases and liquids. In this regard, the search for sensitive methods for assessing post-radiation changes in the physicochemical properties of PET medical devices seems to be relevant.

Material and research technique

 The material for the study was samples of medical PET tubes for blood sampling produced by «Zdravmedtech-E» JSC. The assessment of changes in their properties was carried out by IR spectroscopy methods [1]. The samples were irradiated with accelerated electrons at the Innovation and Implementation Center for Radiation Sterilization of the Ural Federal University (UrFU) (Fig. 2). The radiation dose was 5 kGy at an electron energy of 8.5 MeV. The center has a modernized URT-1M electron accelerator with an accelerating voltage of up to 1 MV, an electron beam power of 1 kW, and a pulse duration of 100 nsec. Compared to the prototype, the URT-1 accelerator, the layout of the nodes has been changed, which allows it to be placed in rooms up to 2.5 m high, capacitors from Murata are used, a TPI1-10k/75 cold cathode thyratron is used for commutation. A system for automated monitoring of parameters has been created. To obtain an electron beam up to 400 mm wide, a cermet cathode of several elements with an uneven distribution of the electron beam current density on the output foil was used. This accelerator can be used in radiation technologies in layers up to 0.3 g/cm2 thick.

https://youtu.be/dpH0M6pSlIU?t=2

Figure. 2. Production line for sterilization of products, without the need to open the original packaging

The technology that was used for sterilization earlier involved the processing of products using ethylene oxide gas. This gas is toxic. The products were placed in a container, filled with gas, heated to 80-100 °C. The exposure was carried out for eight hours. After that, the gas was evacuated and the product was aired for several days. Radiation sterilization is "cleaner", faster, does not require opening the original packaging and even shipping containers. The electrons under the action of the potential difference are accelerated almost to the speed of light, and then they "rush" down and through a thin foil go to the conveyor, where there are products that need sterilization.

It is known [2] that the effect of ionizing radiation leads to a change in the physicochemical properties of polymeric materials.

Registration of IR spectra was carried out in the Laboratory of Comprehensive Research and Expert Evaluation of Organic Materials at the Center for Shared Use of the UrFU on a BrukerAlpha IR Fourier spectrometer (Fig. 3) in the frequency range from 4000 to 500 cm-1, resolution 1 cm-1, using a single horizontal external total internal reflection (Eco-ART) with ZnSe crystal (transparency range 0.5–20 µm, refractive index n = 2.42). Mathematical processing of the results was performed using the Fityk software [3].

Figure. 3. FT-IR spectrometer ALPHA. Bruker optics

Results

IR spectroscopy allows you to obtain information about the presence of certain functional groups, their number, the structure of the molecules that make up a substance, about the types of bonds between molecules. The essence of the method is to find the vibration frequencies of various atoms and atomic groups relative to each other.

In complex molecules, consisting of many atoms, all these types of vibrations are also found: symmetric and antisymmetric stretching, bending and torsional. Stretching vibrations usually give the most intense bands. The spectrum of any complex molecule contains the so-called "characteristic vibrations" of chemical groups. For example, stretching vibrations of carbon-hydrogen groups, the wave numbers of which are in the range of 2800-3100 cm-1. Another characteristic vibration - the stretching vibration of the group of atoms oxygen - carbon (carbonyl group) is in the range of wavenumbers 1640-1780 cm-1 [4].

In large polymer molecules, the number of atoms is very large, which leads to many vibrations. The spectra are complex, but their study can be greatly simplified, since the vibrations in a polymer molecule consisting of many simpler elements (monomers) are repeated. The vibrations change somewhat as a result of the interaction of bound neighboring units, but the influence of such interaction on the characteristic vibrations of chemical groups is quite small. In an n component molecule, each vibration turns out to be n times degenerate, i.e. each band is split into n components. The amount of cleavage depends on the degree of interaction between the monomers. In the observed spectrum, as a result of averaging, spectral bands lying close to each other are not resolved sufficiently well in many cases, so the spectrum acquires the characteristic form of a smooth curve enveloping the tops of individual peaks [4].

With FTIR spectroscopy, scanning over all wavelengths is not required - the inverse Fourier transform allows you to obtain the entire spectrum. The signal-to-noise ratio, which is proportional to the number of samples in the interferogram, can be improved by accumulating spectra [5].

Within the framework of the task of this work, IR spectra make it possible to determine the fact of the effect of radiation exposure on the structure and composition of PET. The spectra were obtained after normalization to the value of the integrated intensity of the 1410 cm-1 band - the “internal standard” [6].

Conclusion

The results of the work, which are in the process of being published in the journal Technical Physics Letters, indicate that the effect of accelerated electrons (energy 8.5 MeV, dose 5 kGy) on PET samples causes changes in their IR spectra. Thus, the analysis of PET IR spectra can be used for rapid assessment of post-radiation degradation of medical device parameters and selection of the optimal sterilization dose.

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SERBIA

COMPARATIVE STUDY OF E-BEAM AND GAMMA RADIATION EFFECTS IN POLYOLEFINS COMMONLY USED IN MEDICAL DEVICES

E. SULJOVRUJIC [1], G. STAMBOLIEV [2], D. MILICEVIC [1]

[1]Vinca Institute of Nuclear Sciences-National Institute of the Republic of Serbia,

University of Belgrade, Belgrade, Serbia

[2]Promethan, Thessaloniki, Greece

Abstract:

The proposed research project addresses detailed examination and comparison of e-beam and gamma radiation-induced effects, as well as post-irradiation oxidative degradation, in POs to provide a better understanding of medical device sterilization by proper use of ionizing radiation, aligned with enhanced product characteristics and increase in exploitation (service life and storage). In the case of gamma irradiation, the typical dose rate is of the order of kGy per hour and thus the long residence time enables the unceasing diffusion of oxygen into the polymer. The G(X) values are at a lower level and a decline in material properties can be expected. Namely, at this dose rate, oxygen can readily diffuse into a polymer and react with radicals leading to degradation. Contrary, with EB, the dose rate is higher than kGy per second and the oxygen cannot diffuse into the material at a rate equal to the radiation-induced reactions (although the oxygen participating processes are not totally eliminated).

Four different PEs (LDPE, LLDPE, HDPE and UHMWPE) and iPP, widely used in medical devices, will be the focus of the proposed research project. It is generally accepted that after exposure to ionizing radiation, PE is prone to cross-linking, while PP is susceptible to scission due to the existence of pendant -CH_3 groups in the macromolecular chains. The influence of initial preparation conditions (quenching and slow cooling of the samples following compression molding) and the consequential differences in the response of each PO to different types of ionizing radiation due to diverse initial crystallinities, will be investigated. For this reason gamma and EB irradiation of POs samples at room temperature, in air, within the sterilization dose range (up to 100 kGy) is going to be performed.

The proposed research will include an investigation of microstructure, crystallinity, gel content, oxidative degradation, thermal, mechanical and dielectric properties. The obtained results will be of interest in the practical application of ionizing radiation in polymer-based technologies which involve PO medical devices, as well as cable,

automotive, packaging, textile and other industrial uses. At the end of the project, a comparison of e-beam and gamma radiation-induced effects in POs will be summarized and presented.

1. BACKGROUND

Among the various sterilization techniques, e.g. heat/autoclave/steam, gas technologies (ethylene oxide, EO), and ionizing irradiation, the latter is most attractive due to its safety aspects, versatility, and simple application procedures in fields such as medical devices, biopharmaceuticals and food industries. Global constraints on sterilization capacities at present will push the demand for all sterilization technologies towards growth, while the shift in the use of sterilization technologies in the future is expected. In the case of EO, concerns raised about emissions, regulatory pressure, and residual toxicity are present. Gamma irradiation is the most common irradiation modality, used for sterilization of medical devices and biopharmaceutical products. Even though this well-established technology is limited by the availability of Co-60 (tightness in supply), it will remain the cornerstone of sterilization by irradiation in the future. Two other irradiation modalities, e-beam and X-ray, have a significantly smaller market share but will grow gradually due to restrictions of other sterilization technologies (Fig. 1a). Commercial irradiators that use X-rays are relatively new and very few are used for sterilization purposes, but this sterilization technology emerges as a more routine one [1].

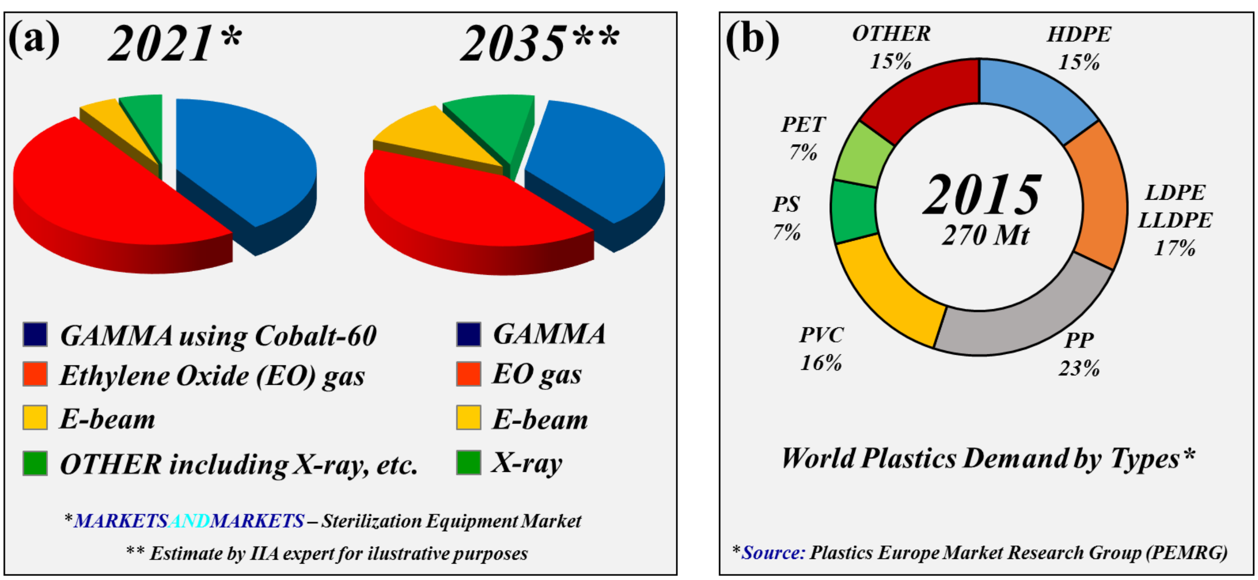

Fig. 1 (a) Expected trends in global medical device sterilization market; (b) World plastics demand by types

POs dominate global plastics production with market share of more than 55% (Fig. 1b), and they are used for medical devices and pharmaceutical packaging more than any other material. They generally include polyethylene (PE), such as low-density (LDPE), linear low-density (LLDPE), high-density (HDPE) and ultra-high molecular weight polyethylene (UHMWPE), as well as polypropylene (PP). Different PEs hold the largest market share by type, followed by PP. Whether moving from non-plastic materials, like glass or metal, or the iterative upgrade of materials as new generations of medical devices are being developed, POs are increasingly being used as an alternative material due to their combination of excellent property profiles and good value in exploitation [2]. The use of plastics in healthcare applications continues to increase, even against the backdrop of ever-increasing regulatory oversight, economic volatility and customer sensitivity.

Practical applications of radiation processing of polymers such as POs are many. They involve sterilization of medical devices, plastic containers and bottles, cross-linking of electric insulation, jacketing and polymeric pipes for water distribution, manufacturing heat shrinkable tubing and tapes, encapsulations for industrial products, polyolefin foams, etc. Regardless the used modality of ionizing radiation, two main effects result when POs are subjected to ionizing radiation: cross-linking and degradation. Both reactions occur simultaneously and primarily in the amorphous regions and the interface between the amorphous and crystalline regions, but one is usually dominant, depending upon the specific polymer and conditions involved. Thus, radiation-induced effects differ significantly on polymer peculiarities (structure, initial crystallinity, preparation condition, sample thickness, etc.), applied irradiation conditions (type of irradiation, atmosphere, radiation dose, dose rate, irradiation temperature, antioxidant and anti-radiation agent) and post-irradiation conditions (annealing, storage at ambient conditions and thermo-oxidative degradation) [3].

Due to the large diversity in PO types, different processing conditions during product fabrication, as well as irradiation conditions and applied type of irradiation (e-beam or gamma radiation), the final properties of medical plastics can differ significantly. This imposes the need for a comparative analysis of the influence of all of these factors to ensure optimal characteristics of sterilized PO medical products. A great number of articles have reported on the impact of gamma and e-beam irradiation on POs, while only a few reports have been focused on the comparison of the effects of these two irradiation modalities [4, 5]. For instance, the gamma irradiation of PP had a greater deterioration effect on its mechanical and thermal properties (i.e. decrease in load and extension at break and a smaller decrease in melting point for gamma irradiated samples) than electron beam irradiation [6, 7].

Since most medical devices are sterilized by radiation and stored until use at ambient conditions (in presence of air) oxidation chemistry typically dominates irradiation chemistry, and this factor significantly affects the characteristics of the final product. Varying irradiation dose rates, in presence of oxygen, one can favor cross-linking reactions or promote degradation through oxidation. Since the most important difference between gamma and e-beam irradiation is the dose rate, this factor significantly affects the characteristics of the final polymer product. For gamma rays, the typical dose rate is of the order of kGy/h and at this dose rate oxygen can readily diffuse into a PO and react with radicals, leading to degradation. Conversely with e-beam the typical dose rate is higher than kGy/s and oxygen cannot diffuse into the material at a rate equal to the radiation-induced reactions (although oxygen participating processes are not totally eliminated). Among POs, PP is prone to chain-scission and oxidative degradation to a much greater extent than PE, due to the existence of pendant -CH_3 groups in macromolecular chains.

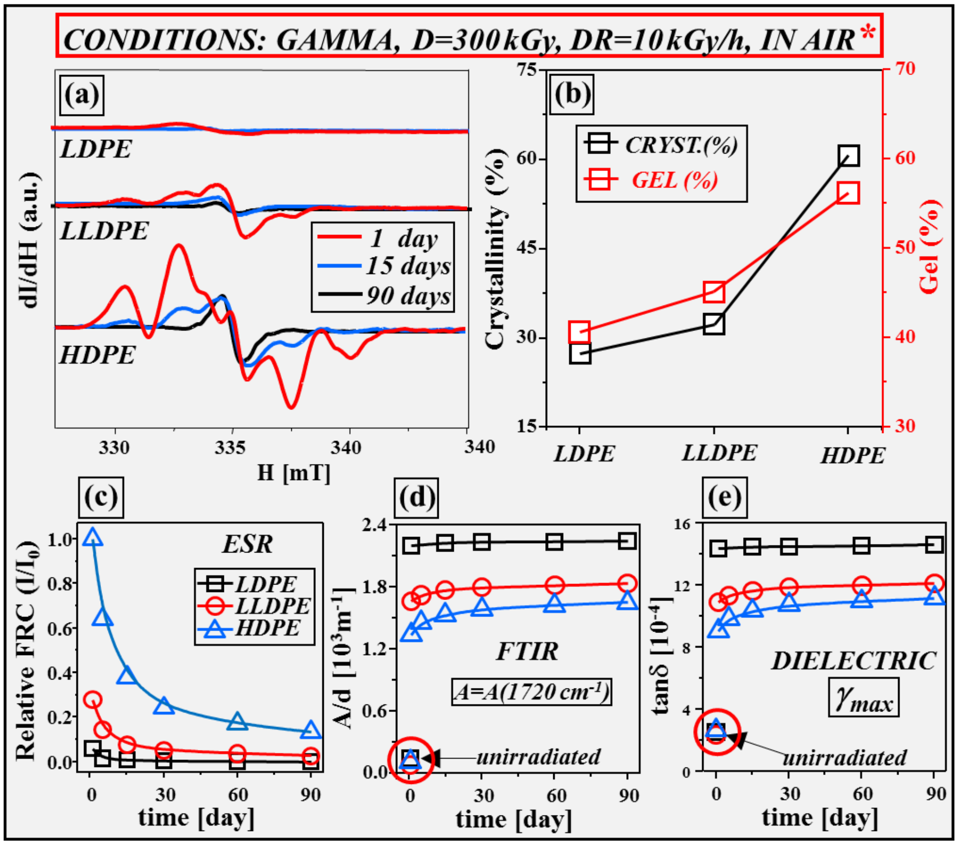

Fig. 2 (a) ESR spectra of different PEs after irradiation by gamma rays; (b) initial crystallinity and gel content of different PEs (c) relative free radical concentration (FRC) at room temperature, plotted as a function of storage time (d) IR normalized absorbance (A/d values; A=absorbance; d=sample thickness) at 1720 cm^{-1} and (e) dielectric γ relaxation maxima as a function of post-irradiation storage time for different PEs [10]

The effect of radiation on polymers can be seen in two ways. The first one is the direct action and the second one is the delayed action, as in the post-irradiation effects observed during storage. Oxidation initiates chain-scission reactions predominantly in the amorphous regions because oxygen is unable to penetrate the crystalline regions. The degradation of polymers due to post-irradiation effects results from reactions of residual radicals with oxygen. Long-lived free radicals, trapped in the crystalline regions, move to the boundary regions and to the amorphous phases where they undergo oxidative degradation reactions with available oxygen [8, 9].

It is found that the crystallinity and the size of the crystalline lamellae, in particular, play a major role in the post-irradiation effects. PEs with lower crystallinity show higher oxidation during irradiation, but post-irradiation oxidation occurs only to a small extent when irradiated and stored in air. On the other hand, lower oxidation during irradiation, followed by the development of significant post-irradiation oxidation, was observed in PE with higher crystallinity, such as HDPE (Fig. 2). We attribute these results to the different reactivity of the macro-alkyl radicals, formed upon irradiation in the amorphous or the crystalline phase. While the radicals formed in the amorphous phase decay in a short time, the share and perfection of the crystalline phase influence the number and migration time of the radicals trapped in the crystalline phase to the amorphous one as key factors, governing the post-irradiation oxidation [10, 11]. The level of post-irradiation deterioration in properties due to the presence of oxygen can significantly influence the service life of a polymer product, as is the case for iPP [9]. To avoid this, free radicals can be removed by thermal annealing which is not applicable in many cases. Also, oxidation can be inhibited by suitable additives which act as radical scavengers.

Even though e-beam and gamma irradiation modalities display similarities regarding the main mechanism of interaction of radiation with matter, they could induce significant differences in material properties when the radiation energy distribution, and especially the dose rate, vary. Our approach aims to be as close as possible to the industrial conditions of product fabrication and radiation sterilization. The influence of initial preparation (obtained by quenching and slow cooling following compression molding) and crystallinity on PO response to different types of ionizing radiation will be the focus of this investigation. For some other polymers such as poly-(L-lactide) (PLLA), it was shown that the initial preparation has a significant impact on the structure and crystallinity, and consequently on its response to ionizing radiation [12].

2. PROJECT OBJECTIVES AND WORKING PLAN

2.1 PROJECT OBJECTIVES

Comparison and a better understanding of:

- ***i.*** e-beam and gamma radiation-induced effects in POs
- ***ii.*** post-irradiation oxidative degradation effects in POs

to provide medical device sterilization by proper use of ionizing radiation, aligned with better product characteristics and increase in exploitation (service life and storage).

The project contains the following specific objectives:

i. to investigate and compare the impact of e-beam and gamma radiation on PO properties within the sterilization dose range (up to 100 kGy) in air

ii. to investigate and compare the influence of different structures, morphologies (obtained by different preparation conditions) and degrees of crystallinity on the polymer response to e-beam/gamma radiation

iii. to investigate the influence of post-irradiation oxidative degradation on POs (especially iPP) properties

iv. the focus of this research will be on four different PEs (LDPE, LLDPE, HDPE and UHMWPE) and iPP, widely used in medical devices

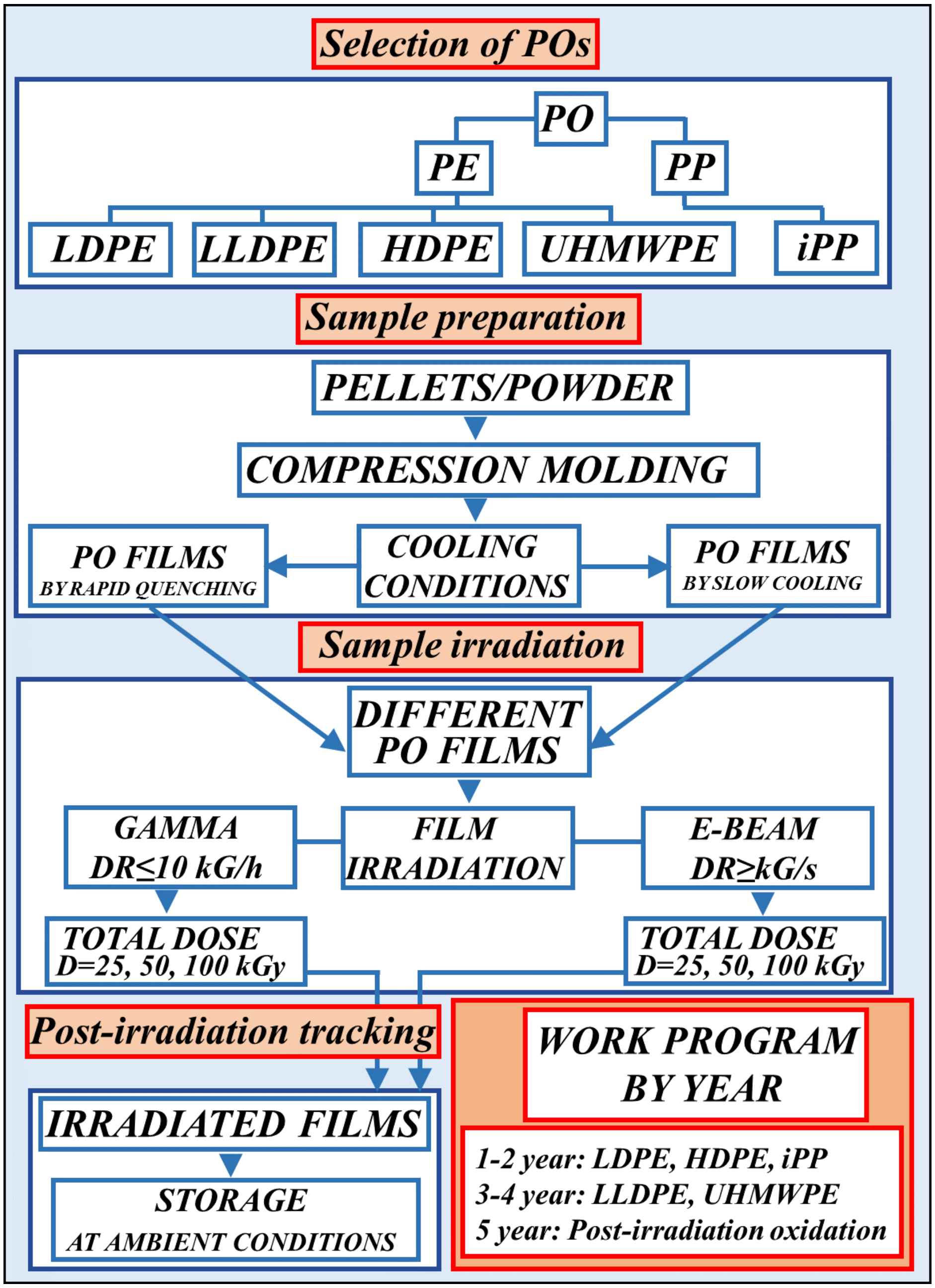

Fig. 3 Selection of POs, overall program of work and project work program by year

2.2 WORKING PLAN

Selection of POs, overall program of work and project work program by year is given in Fig. 3. The proposed program of work includes investigation of microstructure, crystallinity, gel production, oxidative degradation, thermal, mechanical and dielectric behavior.

Characterization tests:

Trapped radicals – ESR

Crystallite size/Crystallinity - XRD, DSC

Morphology - OM, SEM, AFM

Mechanical properties – MM

Dielectric properties - DRS

Thermal properties – DSC, PAM

Structure and oxidative degradation – FTIR, DRS

Cross-linking/net formation - Gel measurements

3. VISION TO FULFILL THE AIM OF THE CRP PROJECT

- ***i.*** To provide a comprehensive comparative study of e-beam and gamma radiation effects in LDPE, LLDPE, HDPE, UHMWPE and iPP plastics commonly used in medical devices
- ***ii.*** To provide new insight on radiation effects in different POs with diversity in initial structure, crystallinity and molecular weight
- ***iii.*** To provide valuable information for restraint of post-irradiation oxidative degradation
- ***iv.*** Publication of at least 3 scientific papers in international journals with project results, conference presentations, and other types of dissemination

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Tunisia

Effect of E-Beam radiation on physicochemical, mechanical and biological properties of polymers with low density used in medical devices

Haikel Jelassi[1], Amira Zaouak[1], Arbi Mejri[1] and Haitham Sghaier[1]

[1]Laboratory on Energy and Matter for Nuclear Sciences Development, Tunisia. National Center for Nuclear Sciences and Technologies, Sidi Thabet Technopark 2020 Ariana Tunisia.

I- Abstract

Around 50% of all single-use polymer-based medical devices manufactured worldwide are sterilized using ionizing radiation from sources, gamma irradiator or an electron accelerator, using either e-beams or, less commonly, X-rays. While all the above irradiation modalities are recognized in the applicable ISO standards, gamma irradiation dominates the radiation sterilization market and accelerator-based sterilization methods are only utilized for around 10% of products. However, the under-utilization of accelerator technologies for sterilization are due to various reasons. Part of them, the lack of knowledge about the radiation multi-effects on polymers using e-beam and X-ray. Thus, our contribution to this CRP is to study the effect of Tunisian gamma irradiator and electron beams facilities on different types of polymers, such as low-density polyethylene, polypropylene..., commonly used in the medical devices industry in order to better understand the mechanisms underlying radiation effects on these polymers.

II- Introduction

Based on the literature, many studies involving cobalt-60 irradiators have been discussed and reviewed the effects of such ionizing irradiation on polymeric materials frequently used in medical devices and their intrinsic properties [1-4]. However, studies including Electron beam and X ray irradiation are even more limited overwhelmingly, and cover a limited range of irradiation conditions, particularly regarding dose rate level [5]. Also, previous studies tested biocompatibility of irradiated polymers. Future progress in the capability to control the radiation effect of polymers is dependent on an understanding of the fundamental processes underlying degradation phenomena. Radiation degradation mechanisms are exceedingly complex, and constitute numerous chemical reaction sequences that result in changes to molecular structure leading to significant changes in material morphology [6-7].

Thus, this proposal will be addressed to study the effect of e-beam irradiations (in continuous and pulsed beams modes) on polymers with low density (PE, PP…). Our challenge is related to investigating the influence of dose rate effect, dose distributions (cartography of dose….) in different environmental conditions (the temperature range, cold temperatures, normal and oxygen-free atmosphere) in order to set-up a database that will allow the medical devices manufacturers from transitioning to accelerator-based sterilization. In addition, evaluation of our results will be examined by the investigation of the morphology, homogeneity, physicochemical, thermal and mechanical properties of irradiated samples using all analytical methods available in our centre. Based on the medical device category, pertinent biocompatibility tests will be also done.

III- Past relevant work: □-irradiated poly glycolic acid (PGA) as new solid state dosimetry system

The □-irradiated of Poly Glycolic Acid (PGA) Polymer has been investigated with ESR technique in order to evaluate this potential as radiation-sensitive material for dose measurements. The response curve was measured in the dose range 0.1 kGy - 200 kGy. Results demonstrated that the influence of post-irradiation storage on the ESR/PGA response might be very significant. The heating at 140°C for 35 minutes was found to be the most suitable procedure to stabilize the response of irradiated PGA dosimeter.

1) Materials and apparatus

a) Poly Glycolic Acid polymer (PGA)

The Poly Glycolic Acid was obtained from Boehringer Ingelheim of Germany. The characteristics of the materials, according to the supplier, are given in table 1.

Table 1: Physical and chemical proprieties of PGA.

	Fusion temperature (ºC)	**Glass-transition temperature (ºC)**	**Approximate Strength**	**Approximate Strength**	**Degradation product**
Poly Glycolic (PGA)	225-230	35-40	7.0 GPa (Modulus)	6 to 12	Glycolic acid

b) Irradiation methodology

The irradiations have been performed in air at the Tunisian semi-industrial ^{60}Co gamma-irradiation facility. Samples of PGA were irradiated by the Cobalt 60 gamma source installed, since 1999, in the National Centre for Nuclear Sciences and Technologies (CNSTN) at Sidi-Thabet, Tunisia [8]. Irradiation in the dose range 0.1 kGy - 200 kGy have been performed at room temperature in the inner zone of the gamma irradiator facility. The arrow of Figure.1 shows the selected γ-radiation position in the CNSTN source building. For precise control of the irradiation time, a specific determination of the dose rate is necessary. The dose rate was established with the alanine/EPR dosimetry system in term of absorbed dose traceable to the National Physical Laboratory, UK. Before the experiment the dose rate was verified by the standard Fricke dosimeter. Three dosimeters were irradiated for each point of measurement.

Fig. 1. The irradiation position in the source building.

c) ESR Measurement

EPR measurements at 9.837 GHz (X-band) were per-formed at 25°C using an EMX Bruker spectrometer. The microwave power used, 316 mW, were determined by considering the saturation properties of PGA EPR lines at 25°C. The Sample were accommodated in quartz sample tubes and kept up from the bottom. The different EPR spectra presented in this paper have been normalized to the same receiver gain (10^3) and sample weight (mg) in order to get quantitative comparison of the EPR lines intensities between the different samples. All dosimeters were fixed in the cavity center and flat ones were oriented to lie in the cavity nodal plane. In the present work, it is thus very difficult to compare theses spectra to determine the absolute number of radical spins.

2) Results

a) ESR Spectra of γ-Irradiated PGA

Before gamma-irradiation, the PGA used in this study has small signal at about 348 mT which can be related to impurity in PGA matrix. The X-Band ESR spectra were subsequently recorded at Room Temperature (25°C). The resulting ESR spectrum of PGA sample after exposure to 25 kGy is shown in Figure .2. All PGA samples, regardless of radiation dose produced similar EPR spectra varying only in the intensity of the observed signals. The radiolytic degradation mechanism of PGA and its copolymers due to samples irradiation has been investigated previously [9] and it's well known that chain scission processes dominate at low temperature. This results in a wide range of relative primary and secondary radical species which are visible by ESR. However, at elevated temperatures, as in ambient conditions studied here, hydrogen abstraction reaction by the primary radicals occurs extensively at secondary C-H bonds on the polymer backbone. This produces a narrower range of relatively stable radicals, such as -CH°-COO- which is visible at ambient temperature (25°C) [9].

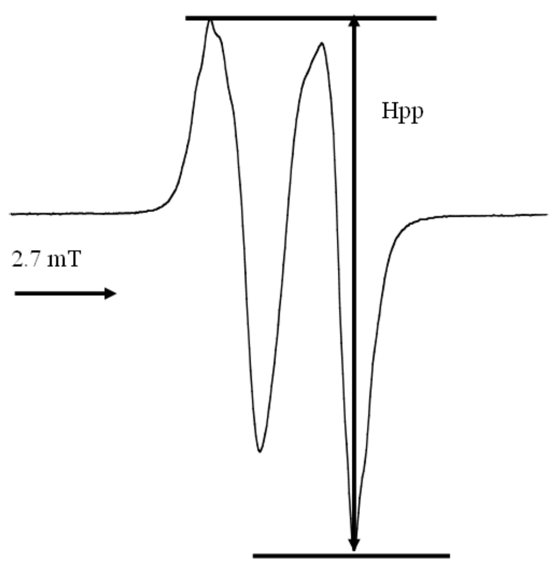

Fig. 2. Peak to Peak higher (Hpp) of ESR spectra related to PGA irradiated at a dose of 25 kGy.

b) Dose response curve

In order to find out the useful dose range for this polymer, the response curve (specific higher Peak to Peak (Hpp) versus dose) was measured in the dose range 0.1–200 kGy (Figure.3). All data for the dose response curve were immediately acquired after irradiation. As expected in (Figure.3) the radical concentration increase linearly as function applied dose in the dose range 0.1–200 kGy with the linear regression coefficient better than 0.99 (Figure 3). At higher doses the specific Hpp continued to grow slowly up to 200 kGy which was the upper dose level of the present experiments. The PGA response had not yet reached saturation at this dose level. There was linear growth of the Hpp as function of the dose because at room temperature only one radical contributes to the ESR spectrum which is formed by hydrogen abstraction (Figure. 1.) RI -CH°-COO$^-$. In the dose range 0.1 to 10kGy there was also linear growth of the Hpp as function of the dose see (Inset Curve).

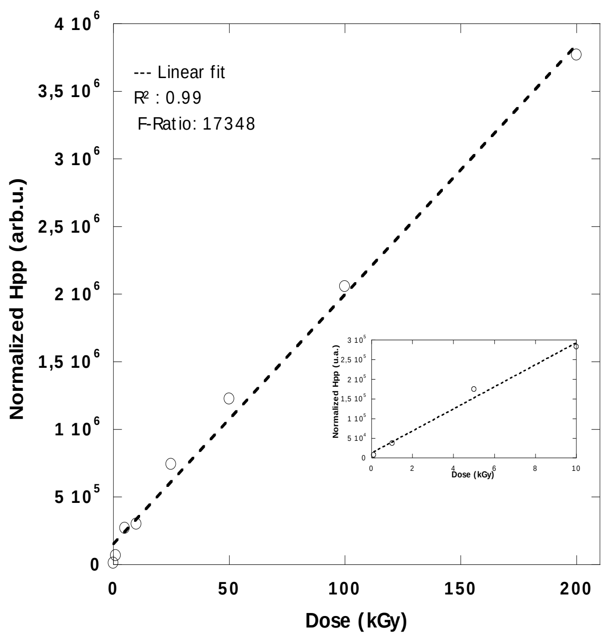

Fig. 3. Dose response curve of PGA dosimeter in the dose range of 0.1–200 kGy, experimental (°) and calculated by a linear function (dashed line).

IV- Future Work: Effect of E-Beam radiation on physicochemical, mechanical and biological properties of polymers with low density used in medical devices

1) Main idea

The main idea of this proposal is motivated by our previous studies related to □-irradiated poly glycolic acid (PGA) as solid state dosimetry system [10]. Thus, we propose through this CRP to combine our knowledge on polymer chemistry, microbiology, dosimetry and radiations technologies in order to study the irradiation effects on polymers (with low densities) such as polypropylene, polyethylene...) using the electron beam accelerator of the CNSTN. This study will be performed using both continuous and pulsed beams modes by variation in the repetition rate, the pulse duration and the scan width of our Electron beam facility. The dose rate and the dose distribution effects are part of major parameters and its effects that will be deeply studied. To do that, a dose mapping (cartography) will be performed with variation in different environmental conditions (the temperature range, cold temperatures, normal and oxygen-free atmosphere).

2) Materials and Apparatus

We propose through this CRP to study the effect of electron beams and gamma irradiation on different types of polymers, such as low-density polyethylene, polypropylene..., commonly used in the medical industry. The EB facility is the electron beam accelerator of the CNSTN which is a CIRCE III facility, with three energy points 5, 7.5 and 10 MeV energies. Gamma rays will be produced by the Cobalt 60 source installed, since 1999, in the National Centre for Nuclear Sciences and Technologies (CNSTN) at Sidi-Thabet, Tunisia. Irradiation process will be effected in the inner zone of the gamma irradiator chamber at room temperature.

Evaluation of the irradiated samples will be performed using many physical and chemical analysis such as (tensile strength, elongation at break, hardness and shock tests to check retention of mechanical properties; decolourization and degradation if relevant; Infrared spectrophotometry (FTIR) and NMR to detect by-products, and EPR for detecting peroxides and free radicals…). Another evaluation regarding biocompatibility, aging (post-irradiation) and functionality of the product will be studied. Cytotoxicity evaluation will be done using the MTT Cytotoxicity Test, the Colony Formation Cytotoxicity Test, etc. Thermal Gravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC) will be used to characterize irradiated polymers. However, for other analysis techniques not available, we hope to establish collaborations with other institutions engaged in this Coordination Research Program.

3) Proposed methodology

During the next period research agreement, the main objective project is to find a solution as well as a better understanding of radiation effects on polymer-containing medical devices such as degradation, crosslinking or chemical changes after gamma and electron beam irradiations.

The project is organized in 4 main tasks:

Task 1: Irradiation of polymers such as polypropylene, polyethylene, polytetrafluoroethylene using the electron beam accelerator (CIRCE III facility energy points 5, 7.5 and 10 MeV) and Colbat 60 source.

Task 2: Establishing protocols and optimum conditions of irradiation: irradiation dose, dose rate, repetition rate, the pulse duration and the scan width.

Task 3: Dose mapping (cartography) will be performed with variation in different environmental conditions such as the temperature range, cold temperatures, normal and oxygen-free atmosphere.

Task 4: Evaluation of the irradiated samples will be performed using many mechanical physical and chemical analysis such as:

4.1 Tensile strength, elongation at break, hardness and shock tests to check retention of mechanical properties

4.2 Decolourization and degradation if relevant; Infrared spectrophotometry (FTIR) and NMR to detect by-products, and EPR for detecting peroxides and free radicals…).

4.3 Evaluation regarding biocompatibility, aging (post-irradiation) and functionality of the product will be studied. Cytotoxicity evaluation will be done using the MTT Cytotoxicity Test, the Coirha

lony Formation Cytotoxicity Test, etc.

V- Conclusion

Our previous and the proposed next work comes under the progress and efforts conducted to find a solution as well as a better understanding of radiation effects on polymer-containing medical devices such as degradation, cross-linking or chemical changes after gamma rays and electron beam irradiations. We will try to combine our knowledge in polymer chemistry, dosimetry and radiations technologies advantages compared to conventional technologies in order to contribute to improve the existing database on publication covering the radiation effect on polymers used in medical devices.

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Turkey

Effect of Radiation on the Commonly Used Natural Rubber and Silicone Rubber in Medical Applications and Devices

T. Özdemir, C. Kurtuluş, İK Akbay, A. Güngör
Mersin University Chemical Engineering Department, Mersin TURKEY

ABSTRACT

Polymeric materials are indispensable materials for medical applications. Development of the polymeric materials over the recent decades provided valuable commodity materials to be used in different medical uses. Thermoset, thermoplastics rubbery materials, foam materials are used for the medical single/multi use medical accessories/apparatus. Single use materials increased the need for the sterilization of high volume of materials and ionizing radiation provided a cutting-edge solution. The combination of radiation technology and polymer technology helped to the medical industry and provided a vital input for the human health.

In this project, the effect of irradiation on commonly used rubbers will be studied. Rubbery materials are widely used in medical applications due to their unique physical and mechanical properties. Among rubber type materials, natural rubber and silicone rubber are the main types of rubbers frequently used in the medical applications. Since these polymeric materials are inevitably used in the medical devices and applications, these materials are needed to be sterilized and the convenient methods for the sterilization is achieved via employment of radiation that could be either gamma, e-beam or X-rays.

The research study will mainly concentrate on the gamma and e-beam irradiations and comparison of their corresponding changes in the commonly used rubber materials' properties. The planned total dose of irradiation is 40 kGy. After the irradiations the change in the mechanical, dynamic mechanical, thermal and morphological properties of the materials will be investigated and the irradiation results from e-beam and gamma irradiation would be compared to determine the degradation and modification pathways and the differences between the gamma irradiation and e-beam irradiation.

Gamma irradiation facilities have inherent drawbacks regarding to the safety and security dimensions a throughout shift to the e-beam or X ray sterilization could help to eliminate this drawback regarding to safety and security. The outcome of the overall CRP might have an important role for the future shift to e-beam and X-ray sterilization against gamma irradiation sterilization.

On the other hand, anti-rads are useful for the protection of materials from the effects of irradiation. In this project work, rheological tests for natural rubber and silicone rubber recipe would be developed, the change in the rheological properties (ts2, t90, MH, ML) via addition of different amounts of anti-rads would be determined. Moving Die Rheometer (MDR 2000 would be used for these analysis.

INTRODUCTION

As per the definition stated by the Food and Drug Administration (FDA), a medical device (MD) is “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: (i) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; (ii) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or (iii) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes" (Ref: https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device)

Number of devices within the medical industry rely on rubber and they would be unable to operate effectively without rubber material. Unique properties make rubbers ideal for tubing - used on a widespread level as a sanitary means of transferring fluids, including blood. Rubber's flexibility also makes it the number one choice for key hospital products. Crucial for the manufacture of the rubber gloves used by medical staff in all facilities, it is used to make components for needles used for injections. Rubber is also used for tubes, caps, stoppers and as components in many medical devices.

The other products that include rubbery materials include tubing, rubber rollers, blood pressure cuffs, catheters, cardiac pacemaker leads, rubber cords, diaphragms and latex products are used in the battle against AIDS and other sexually transmitted diseases.

It is a standard practice to sterilize final products to remove any microbial contamination. The commonly-used sterilization methods for medical devices include dry heat, ethylene oxide, steam autoclaving, electron beams and gamma radiation. Vulcanized rubber can withstand the many different methods of sterilisation (Ref. https://www.coruba.co.uk/blog/how-important-is-rubber-in-the-medical-industry). The basic approach for the irradiation sterilization of the medical devices by irradiation could be formulated as follows;

Medical Device (involving polymer) + e-beam/gamma/X-ray irradiation ======>Sterilized polymeric material/Medical Device.

As stated before, silicone rubber is a widely used polymeric material in medical devices and applications, the application areas include: respiratory care product, inhalers, infusion therapy, drug delivery systems, peristaltic pump sets, diabetes care, dental care devices, medical devices, diagnostic equipment, blood dialysis, catheters, disposable fluid transfer manifolds and closure assemblies, and breastfeeding.

Natural rubber and silicone rubbers are considered as two important biomaterials due to their biocompatibility, biodurability, sterilisability, processibility, as well as mechanical properties, such as flexibility and resilience. These properties make these rubbers appropriate materials of choice for medical applications. Medical devices based on natural and silicone rubbers include cardiac pacemaker leads, mammary prostheses, artificial skin, catheters, denture liners, diaphragms, blood pressure cuff coil, tubes and seals. These types of rubbers are commonly used in controlled drug delivery systems as a carrier for pharmaceutical agents and in the fabrication of other medical devices [1].

Natural Rubber:

Although natural rubber (NR) can be produced by more than 2000 plant species, it is an isoprene polymer prepared by coagulating latex from the Hevea brasiliensis tree [3]. Natural rubber consists of C5H8 units (isoprene), mostly in cis configuration, with a double bond in each repeating unit. Polyisoprene, especially in the form of natural rubber latex, is widely used in prophylactic medical disposables, such as gloves, and found to be an effective barrier [4]. Because of its unsaturation, natural rubber and many other elastomers will slightly crosslink when exposed to radiation sterilization conditions. Such crosslinking will not detract from the overall extensibility or elongation of these rubber devices. Natural rubber formulations, as well as formulations based on other elastomers, can also be used as gasketing materials in devices, as stated before.

Medical applications of Natural Rubber:

Applications of natural rubber include membranes, diaphragms, blood pressure cuff coils, gaskets, caps, tubes, gloves, condoms, balloons, pacifiers / bottle teats and different parts of medical and dental equipment [5]–[8]. One of the most interesting properties of NR is its ability to stimulate angiogenesis, cellular adhesion and extracellular matrix formation, which promotes tissue replacement and regeneration. A new biomembrane is made from natural latex for the manufacture of gloves, ducts, rubbers, urinary or tracheal tubes and other devices. Natural rubber male condoms are widely used in many countries to prevent human immunodeficiency virus infection. Natural rubber latex (NRL) has been used to make medical gloves for many years to provide a barrier to prevent the transmission of microorganism to and from patients [9].

Silicone rubbers:

One of the most important classes of organosilicon materials are silicones or more scientifically polysiloxanes. The molecular backbone in these synthetic material consists of silicon and oxygen atoms alternately. Silicone rubber can be used to provide soft, supple components for medical devices. It can be used as gasketing material or to form tubing, and when properly formulated it has US Food and Drug Administration (FDA) Class IV status for temporary implants. Silicone rubber supposedly has superior biocompatibility [10]. Gum silicone rubber itself can radiation cross-link and thus tolerate sterilization exposure. The moisture permeability of the silicone polymer facilitates wound healing, since some exudate from the wound helps prevent scar formation.

Medical applications of silicone rubbers:

In recent years, different applications of silicones in healthcare and medical fields have been reported. In 1964, Folkman and Long suggested using silicone rubber to deliver low molecular weight drugs such as digoxin by implanting the device into the myocardium of dogs for therapeutic purposes [11], [12].

It has been almost four decades since elastomers based on PDMS have been used in a wide range of biomedical applications because of their physiological inertness, good blood compatibility, low toxicity, good thermal and oxidative stability, low modulus and antiadhesive properties [13].

PDMS owing to its mechanical properties and inertness in biologic systems, is also a suitable material for substitution of stiffer tissues such as the ear, nose and chin, though its application as a breast implant is controversial [14]. Polydimethylsiloxane has also been used in heart pacemakers, blood pumps, mammary prostheses, drainage implants in glaucoma, artificial skin, replacement oesophagus, contact lenses, finger joints, coating for cochlear implants, catheters, denture liners and drug delivery devices, and the construction of cerebrospinal fluid shunts [15], [16].

Irradiation effects on different polymer types:

The influence of e-beam radiation on the mechanical, thermomechanical and structural properties of the commodity polymers, technical polymers, glass fibers, and high performance polymers were studied [17]. The polymers were selected across the whole area of thermoplastics – which includes commodity polymers (LDPE,HDPE), technical polymers (PP with 30% glass fibers (GF), PBT, PA6, PA6 with 30% GF) and high performance polymers (Polyamide 9T (PA9T). The main reason for the selection of these materials from these groups was their easy modification by beta irradiation and their frequent application in technical practice. The samples were made by using injection molding. The irradiation of the tested polymers was performed using accelerated electrons (a Rhodotron e-beam accelerator). The range of doses was 33 to 198 kGy. Gel tests, X-ray diffraction, Raman Spectroscopy, thermo-mechanical analysis and visual observations were carried out in order to characterize the samples. The thermo-mechanical analysis confirmed the influence of radiation doses on the structure of the polymers that were studied. When the dose of radiation increased, the thermal resistance of the studied polymers above the melting temperature of a basic polymer also increased. Polymers changed their behaviour from thermoplastic to thermo-elastic after radiation crosslinking. From the measurements, it was observed that the highest change was achieved by all materials examined at higher doses of radiation. Irradiation acted on each polymer differently but when the optimum dose was found the mechanical properties increased by up to 36% [17].

The impact of commonly used irradiation sterilization methods such as electron beam, gamma and X-ray irradiation on PCL was investigated [18]. PCL has a low melting temperature which is 60 ^{o}C. Sterilization techniques like steam processing and autoclaving techniques are not applicable for PCL, since these methods could damage the material or implant structure. That study [18] compared low temperature sterilization techniques (e-beam, gamma radiation and X-rays) on PCL scaffolds. Two radiation doses were used including the commonly used dose for medical devices sterilization of 25 kGy and the other irradiation dose was 33 kGy to investigate the possible dose effect. In order to determine the impact on the fiber mats, mechanical, chemical, thermal properties and crystallinity were investigated. Fiber mats (scaffolds) were produced by electrospinning of PCL. For mechanical characterization, PCL scaffolds were tested to determine ultimate tensile strength and elongation at break. It was reported that the ultimate tensile strength decreased slightly for non-aligned scaffolds upon sterilization, while elongation at break remained unchanged. For aligned scaffolds the ultimate tensile strength did not change significantly, while elongation at break values have slightly higher values. Mechanical properties did not change significantly upon irradiation, because effects of lower molecular weight were balanced with a high degree of crystallinity. No significant effects of the dose or type of irradiation on the mechanical properties were reported. The results indicated that a lower molecular weight after sterilization due to irradiation induced chain scission. Gamma radiation with 33 kGy had the highest degree of impact and led to a significant molecular weight reduction. DSC measurements were used to determine degree of crystallization and changes in thermal properties. Crystallinity of the fiber mats increased significantly. Human body temperature can reach up to 42ºC, so lowering of the melting point could lead to failure of the implant. None of the sterilization doses and techniques had a big impact on melting temperature of the samples and Tg was not affected significantly. Change in heat capacity and entalphy of fusion were reported to be affected significantly. It was reported that low dose of irradiation should be favorable to minimize changes in thermal properties and crystallinity of PCL. Molecular weight decreased significantly with irradiation. Also, crystallinity of fiber mats increased significantly. Normally, one can expect a change in the mechanical properties upon radiation. However, the mechanical properties did not change significantly, most likely because the effects of a lower molecular weight were balanced with the higher degree of crystallinity. It was shown that use of e-beam radiation is preferable since it has less effect on the scaffolds compared to gamma irradiation [18].

EB irradiation could be applied for the sterilization of all polyesters [19]. When compared to gamma irradiation, EB is promising due to its close flexibility and much higher dosing rate. One drawback is EB has a limited penetration range. High absorbed dose is required for thick products since machine-accelerated electrons has less penetration ability. EB irradiation is also used for the crosslinking of the polymers besides sterilization purpose. For the sterilization, the physicochemical or mechanical property changes after irradiation is expected to be ignored. The effect of EB irradiation dose ranging 25-100 kGy on the properties of PLA, PBAT and PLA/PBAT blends were studied [19]. The changes in molecular weight, yellowness index, thermal and mechanical properties were evaluated. 0.5 mm thick flat sheets of samples were prepared by compression molding from the melt [19]. The dumbbell shaped samples were obtained for mechanical testing. The samples were irradiated by an electron accelerator to absorbed doses of 25, 50, 75 and 100 kGy. For PLA, the dominant mechanism under irradiation is reported as chain scission which led to the reduction of the molecular weight. A severe decrease in normalized molecular weight was observed as a function of absorbed dose. In the case of PBAT, the crosslinking of all the irradiated samples was not detected which was reported from the evidence of their complete dissolving in DMF solvent. It was reported that the effect of EB irradiation on the molecular weight of PBAT and PLA/PBAT blends was ignorable. Thermal analysis results showed that, for PLA, both Tg and Tm decreased with increasing absorbed dose, which was ascribed to irradiation induced decrease in Mw [19]. For PBAT, the effect of irradiation on its Tm was reported as ignorable [19], while its molecular weight stated to remain almost constant. The yellowness index of PLA and PBAT increased with the increase of irradiation dose, while the trend was less significant for PLA/PBAT blend. A severe reduction in the mechanical properties of PLA occurred when subjected to higher doses of EB irradiation which was ascribed to irradiation induced decrease in molecular weight (chain scission). The effect of EB irradiation on the mechanical properties of PBAT and PLA/PBAT blends was ignorable.

Irradiation is one of the most widely used technology for sterilization of medical products [20]. For polymers like PP, high energy radiation leads to yellowing and embrittlement due to dominant degradation mechanism. After the interaction of PP electrons and high energy irradiation, macroradicals are generated and in the presence of oxygen, this can lead to oxidation mechanisms in PP matrix which is known as auto oxidation. In auto oxidation, oxygen immediately reacts with radiation-induced macroradicals and forms hydroperoxides by capturing another hydrogen proton from the polymer chain[20]. After initial sterilization, the hydroperoxides decompose and lead to main chain cleavage. As a result, discoloration and embrittlement of the polymeric products occurs. The impact of gamma and e-beam sterilizations at a dose of 45 kGy of a commercially available, radiation-resistant PP accompanied by accelerated aging studies were compared. Mechanical, optical and molecular characteristics (molar mass characterization, crystallinity analyses) were investigated [20]. Oxygen concentration has a major role in the degradation of polymers, atmosphere, geometry and dose rate have an impact on degradation mechanism. Because of the limited oxygen diffusion during sterilization, e-beam is thought to be less damaging for PP compared to gamma sterilization. A specially formulated commercially available PP was used in that study [20]. E-beam and gamma irradiations were carried out. For accelerated aging studies, Environmental Stress Chamber was used and samples were exposed to varying temperature and humidity conditions. Each group was analysed before and after one, two, and four accelerated aging cycles (AACs). For the evaluation of the influence of aging and irradiation, tensile tests were performed immediately after manufacturing in order to get initial values as control group. From the tensile test results, it was reported that storage time at room temperature alone has a strong influence on mechanical properties [20]. Elongation at break is known to be the most sensitive mechanical parameter to observe effects of degradation and aging. For non-irradiated, e-beam and gamma irradiation groups, it was reported that there was a decrease during accelerated aging. This was because of auto oxidation process that led to further degradation resulted with embrittlement. SEC was carried out in order to detect degradation during aging and to compare irradiated samples with the non-irradiated ones. It was shown that radiation sterilization has large effects on molar mass and e-beam irradiation shows less damaging effects compared to gamma irradiation [20]. Gamma irradiation indicated much more impact regarding yellowing, embrittlement and molar mass degradation than e-beam does. After irradiation, yellowness index increased during aging, while yellowness index of non-irradiated samples remained at constant level [20].

Other Possible Usage of Rubber Materials (Literature Review):

Doğan et al [21] studied poly(imide) siloxane copolymers for usage in biomedical products. The addition of copolymer to the rubber matrix increased the creep recovery of the samples. The testing results of poly(imide) siloxane presented the importance for creep-recovery for several application areas covering biological molecules (proteins, carbohydrates, RNA, DNA), biomedical applications, flexible organic electronics devices, nanostructures, micro and nano-fabrication. The addition of BTDA anhydride (Benzophenone-3,3’,4,4’- tetracarboxylic dianhydride) to the PDMS (polydimethyl siloxane) has increased the flexibility of the samples and they were also suitable for pelletizing. Biocompatible property of the final material is high because of its hydrophobic nature, against chemical interaction and oxidation. Therefore, it was concluded that the siloxane copolymers can be used within any soft microelectronic devices which are in contact with the body without causing any adverse reactions in the body [21].

Ansar et al [22] studied silicone rubber and glycerine composite for soft tissue phantom applications. The prepared composite is aimed to replace human soft tissue for CT simulator. The addition of glycerine was done to fill the air bubbles in the neat sample. Moreover, 10% and 20% glycerine addition show similar results with the range of human soft tissue. The HVL value of the phantom with glycerine 20% confirmed the suitability of this sample as the replacement of the human liver in measuring radiation doses for radiotherapy studies and educational purposes.

Irdawati et al [23] studied silicone rubber with lead-acid composite for a novel radiation filter in digital radiography. They prepared radiation filters made from silicone rubber and lead acid composite with a lead amount of 0 to 5%. The image quality of the prepared phantoms analyzed within range to readable range. The results showed that the prepared composite can be used in the bone examination. The increase in tube voltage affected the doses received by the patient. The higher tube voltage used, the greater the dose will be received by the patient. However, the dose could be minimized by using SR-Pb radiation filters because the amount of radiation absorbed by the SR-Pb filter will make a percentage of X-ray transmission to decrease. The dose reduction using the SR-Pb radiation filter up to 50% for all tube voltage variation.

Wang et al [25] studied pneumatic-actuator soft robot made of silicone/W-based composites used in the nuclear environment. The gamma ray shielding, and the tensile elongation properties of the silicone/W-based composites were evaluated. They studied the gamma transmittance of the silicone/W-based composite and it reached up to 0.64 with the tensile elongation of 171.8%. Moreover, the gamma ray shielding was experimentally assessed by using a Co-60 radioisotope. Wang et al [25] have also showed that that the gamma transmittance of the silicone/W-based composite decreased approximately 30.0% when compared to neat silicone.

SCIENTIFIC SCOPE OF PROJECT:

The polymeric materials and especially rubber materials (as a part of polymeric material class) are inevitably used in the medical devices and applications, these materials are needed to be sterilized and the convenient methods for the sterilization is achieved via employment of radiation that could be either gamma, e-beam or X-rays.

Recalling the gamma irradiation facilities for sterilization purposes that employ very high amount of radioactivity impose inherent drawbacks regarding to the safety and security dimensions. A throughout shift to the e-beam or X-ray sterilization facilities could help to eliminate these inherent drawbacks regarding to safety and security. The outcome of the overall CRP might have an important role for the future shift to e-beam and X-ray sterilization methods against gamma irradiation sterilization method.

The scope of the project includes the irradiation (gamma and e-beam) of the natural rubber and silicone rubber, that are widely used in medical applications, with the doses of sterilization to understand the change in the mechanical, dynamic mechanical, thermal and morphological characteristics of the materials. The rubbery materials are widely used for the medical applications and they are vital for many of the medical applications due to the easiness of the radiation sterilization the rubbery materials are subjected to irradiation, in this study the change in the mechanical, thermal, structural, morphological characteristics of the natural rubber and silicone rubbers are to be investigated. Gamma irradiation would be used for the irradiations, additionally e-beam irradiation is also planned. The changes in the properties of the materials irradiated would be compared in details.

The materials (mostly used rubber materials in medical applications, silicone rubber and natural rubber) will be irradiated with 3 different doses and 2 different dose rates. The doses of irradiation would be 10, 20 and 40 kGy. Upon the degree of changes in material properties with irradiation, further increase in irradiation (gamma and e-beam) dose would be considered. The gamma irradiation dose rates to be applied are 15 Gy/h and 270 Gy/h, as planned. The same total doses would be applied both for gamma and e-beam irradiations. For gamma irradiations, Gamma cell 220 model irradiator would be used. Additionally, an e-beam irradiator is to be used, upon agreement with a center within the scope of CRP or e-beam facility of Turkish Atomic Energy Agency might be used.

After irradiations, change in mechanical, dynamic mechanical, thermal (DSC, TGA), characteristics would be investigated. Glass transition temperature would be determined from both DSC and DMA analysis and the change in the glass transition temperature would be investigated. Soxhlet extraction would be carried out to understand the degree of crosslinking. Flory-Rehner equation will be used to calculate the crosslink density. The morphological investigations would be carried out to understand the surface characteristics and their corresponding changes via irradiations. Additionally, the samples irradiated and non-irradiated samples would be investigated through X-ray radiography and computer tomography imaging techniques. By using the dynamic mechanical analyzer, the loss modulus (G'') and storage modulus (G') and tan (delta) thermograms would be obtained, the change in the loss modulus (G'') and storage modulus (G') and tan (delta) thermograms would be investigated. Within the mechanical properties the tensile tests would be carried out, namely elongation, tensile strength, Young's Modulus, toughness would be determined and their respective changes via e beam and gamma irradiation would be compared. Scanning electron microscopy imaging and XPS analysis would be carried out to understand the morphological characteristic of the materials and the changes via gamma and e-beam irradiations would be compared by using the SEM imaging. In addition, thermal stability and their respective changes/modifications via gamma and e-beam irradiations would be investigated and compared. Additionally, the non-irradiated and (gamma and e-beam) irradiated samples would be investigated tghrough X-ray radiography and computer tomography (CT) imaging techniques.

Anti-rad additives are used for the protection of polymeric materials from the effect of ionizing radiation. The amount of additive is important and this might interfere with the processibility of the material. In general, anti-rad additives can be categorized into two groups depending on the mechanism of their protective action. The first group ensure the energy transfer from the polymer to the additive without any chemical change in the polymer main chain. In the process, the additive either dissipates the energy or undergoes transformations or decomposition. Anti-rad additives of the second groups can heal the radiation damaged site.

In this regard, the change in rheological properties with the anti-rad additive is worth to be investigated. Within this project work, the rheological tests for a natural rubber and silicone rubber recipe would be carried out, the change in the rheological properties (ts1, ts2, t90, MH, ML) via addition of different amounts of anti-rads would be determined. Moving Die Rheometer (MDR 3000) available in our laboratory would be used for these analysis. MDR 3000 Rheometer is most cost-effective way to determine viscoelastic properties of polymers and rubber compounds before, during and after cure. The acquired data would give information about processability, cure characteristics, cure speed and the behavior of the compound after-cure with the addition of anti-rad additive.

PROJECT WORK PROGRAM:

The materials will be procured the materials would be tested prior to irradiation. The mechanical and thermal tests would be carried out. Additionally, the degree of polymerization would be determined. the irradiations would be carried out with different doses of 10, 20, 40 kGy. The change in the mechanical thermal and morphological properties would be determined.

After irradiations, the tensile tests would be carried out. The irradiations might change the degree of crosslinking within the rubbery matrix and this issue could be determined by using the Soxhlet extraction and by calculating the crosslink density. Soxhlet extractions before and after irradiations would be carried out. Flory-Rehner equation would be used to calculate crosslink density. TGA, DMA, DSC tests would be carried out to investigate the changes of the thermal and dynamic mechanical properties. Derivative of the weight loss of the materials would be calculated and the results would be compared for both gamma and e-beam irradiations. SEM imaging and XPS analysis would be conducted to understand the morphological changes and degree of changes.

The change in rheological properties with the anti-rad additive is worth to be investigated. The rheological tests for a natural rubber recipe would be carried out, the change in the rheological properties (ts1, ts2, t90, MH, ML) via addition of different amounts of anti-rads would be determined. Moving Die Rheometer (MDR 3000) available in our laboratory would be used for these analysis. MDR 3000 Rheometer is most cost-effective way to determine viscoelastic properties of polymers and rubber compounds before, during and after cure. The acquired data would give information about processability, cure characteristics, cure speed and the behavior of the compound after-cure with the addition of anti-rad additive.

EXPECTED OUTPUTS:

The expected outputs from the CRP project could be listed as outlined below:

- the modification and degradation mechanism of the natural rubber with irradiation (gamma and e-beam) and comparison of the different radiation types (gamma and e-beam)

- the modification and degradation mechanism of the silicone rubber with irradiation (gamma and e-beam) and comparison of the different radiation types (gamma and e-beam)

- the change in the mechanical, thermal, dynamic mechanical properties of the natural rubber and silicone rubber (gamma and e-beam) and comparison of the different radiation types (gamma and e-beam)

- the difference and comparison of the thermal, dynamic mechanical, morphological characteristics of the natural rubber and silicone rubber via gamma irradiation and e-beam irradiation.

- the change in the rheological properties of rubber (natural and silicone rubber) with addition of anti-rad chemical agents.

CONCLUSIONS

The polymeric materials and rubber materials as a part of polymeric materials are inevitably used in the medical devices and applications, these materials are needed to be sterilised and the convenient methods for the sterilization is achieved via employment of radiation that could be either gamma, e-beam or X-ray. Gamma irradiation facilities have inherent drawbacks regarding to the safety and security dimensions a through shift to the e-beam or X-ray sterilization could help to eliminate this drawbacks regarding to safety and security considerations.

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Direct Comparison of Gamma-ray, Electron Beam and X-rays Effect on Materials Property of Medical Device Polymers

Min Huang, Md Kamrul Hasan, David Staack, Matt Pharr

Department of Mechanical Engineering, Texas A&M University, 3123 Spence St, College Station, TX 77840, USA

Abstract

Gamma-ray treatment predominates among current medical device radiative sterilization methods. However, there are potential nuclear security concerns associated with Cobalt-60 gamma radiation; E-beam and X-ray methods may serve as safe future sterilization alternatives. Doses ranging from 0kGy to 100kGy have been applied on 5 medical devices (vacutainer (VT), push button (PB), two bone cement mixing systems, and interpulse pulsed lavage system), 6 polymer dog bones (polyvinyl chloride (PVC), polypropylene homopolymer (PPH), polyethylene terephthalate (PET), low-density polyethylene (LDPE), polyolefin elastomer (POE) and chlorinated isobutylene isoprene rubber (CIIR)), and 8 pieces provided by Becton, Dickinson and Company (BD) and Stryker. The functionality of the control and treated medical devices were tested, and raw material tensile strength and hardness were measured. Results from both BD and Stryker's devices indicate no significant dependence on irradiation sources in terms of yellowness index, functionality testing, and raw materials mechanical testing, while there is an obvious dependence on the irradiation dose. Three raw polymer materials (LDPE, POE, PP) are selected and discussed in detail in this report with a comparison to the literature results. Overall, the investigated relationship between the type of radiation source and observed chemical and physical changes show that e-beam and X-ray are viable alternatives to gamma-ray for sterilization of the polymers tested.

1. Introduction

Since the word "polymer" was first introduced in 1833 by a Swedish chemist, Jöns Jakob Berzelius, it has been widely used in the medical devices field. Polymers used in medical devices are critical to life and health (such as catheters, drug-delivery components, blood oxygenators, et al), so it is of vital importance to ensure properties are not compromised by sterilization using ionizing irradiation [1].

In the current market, the most common methods used for medical device sterilization are ethylene oxide (EtO) and gamma-ray radiation, with market occupancy of 50% and 40.5%, respectively. However, governments and the public, are aiming to reduce the dependence on EtO due to environmental quality issues and health risks (e.g., elevated-cancer risks outside a Chicago EtO facility in 2019 have been reported [2]). Likewise, gamma-ray sterilization is expected to be reduced, while e-beam and X-ray sterilization are expected to be increased due to the nuclear security issues associated with gamma-ray. Currently, e-beam radiation takes around 4.5% of the global sterilization market, and less than 1% is covered by X-ray irradiation[3]. The existence of different radiation technologies can be explained by knowing that no single technology is ideal for the diversity of medical devices.

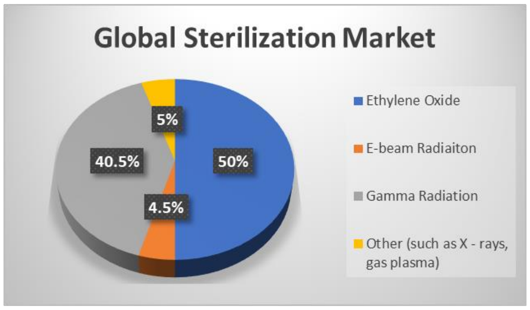

Figure 1. Global sterilization market share in 2016

Although some researchers have compared the effects of these irradiation modalities on polymers, they are scattered throughout different applications and most of them only focus on two modalities. From this perspective, more systematic work that compares the differences among irradiation modalities on effects in selected polymers is needed, which is the goal of our NABLO project.

1.1 Comparison of three irradiation methods: electron beam, X-rays, and gamma

An electron beam can be produced by energizing and accelerating a stream of electrons through an electromagnetic or electrostatic field. Unlike gamma-ray and X-ray which have the same speed as light, since e-beam is comprised of accelerated electrons, it has a speed less than that of light. X-rays can be converted by an e-beam facility when high-energy electrons impinge with metallic targets. The energy of an electron is absorbed by metallic materials generating X-rays in the form of bremsstrahlung radiation, which is related to several factors, including atomic number, the thickness of the target, and energy of the injected photon and current of the incident electron beam [4]. Due to low conversion efficiency (7%-12%), a more powerful beam is required to convert into X-rays. As high-energy electromagnetic radiation, gamma-rays generated by radioactive decay interact with the molecules of the matter they irradiate through secondary electrons. It is a form of a photon emitted by Cobalt-60 (1.173MeV and 1.332MeV) or Cesium-137 (0.662MeV). During the ionization process, Compton scattering dominates and gives rise to secondary photons and scattered electrons.

Although all three modalities are considered as low ionization density radiation and have similar irradiated-induced behavior on polymers based on previous research [5], they can still be distinguished in several ways, including penetration depth, dose rate, injected particles, and applied source, thereby potentially resulting in varied processing results on different polymers. To choose the appropriate method for sterilization applications, the differences among these three methods should be elucidated. The two most significant differences are in terms of the dose rate and the depth of penetration. The dose rate is around $0.168\ \frac{kGy}{min}\left(\sim 10\frac{kGy}{h}\right)$ for gamma-ray and $1.62\ \frac{kGy}{min}\left(\sim 100\frac{kGy}{h}\right)$ for X-ray, which are four to five orders of magnitude lower than e-beam. E-beam has a high dose rate of around $60\sim 6000\frac{kGy}{min}$ [6]. In terms of the depth of penetration, X-ray and gamma-ray have excellent penetration profiles, while e-beam has a limited penetration profile. **Figure 2** presents the penetration capability of the three irradiation modalities in water. The limited penetration of the e-beam stems from the kinetic energy of an electron being dissipated through impaction along the track. In industry applications, large loads can be processed by gamma-ray, bulky material is suitable for X-ray, and layers of pallets are normally treated by e-beam. Other differences also exist among these three ionizations methods, shown in Table 1.

Table 1. Comparison among three radiation modalities from IBA [3][7]

	E-beam	**X-ray**	**Gamma-ray**
Largest processing unit	Box	Pallet	Layer pallet
Label requirement	Label intensive	Label efficiency	Label efficiency
Source energy	Electricity	Electricity	Radioisotopes
Equipment	Complicated to control and maintain	Easy to control and maintain	
Penetration	Low	Very high	High
Dose uniformity ratio	Average	Excellent	Good
Dose rate (kGy/min)	60-6000	1.62	0.168
Treatment time	Seconds	Hours	More hours
Heat development	~0.5°C/kGy	Smallest	About max 20°C
Oxidation sensitivity	Small	Small	More than e-beam and X-ray
Medical device product requirements	Compatible with radiation, penetrate full box with bulky density up to 0.25g/cm^3	Compatible with radiation, penetrate full pallet with density up to 0.5g/cm^3	Compatible with radiation, penetrate full pallet with bulky density up to 0.4g/cm^3
Material compatibility	A wider range of polymer compatibility compared to gamma-ray		Limitation on PTFE and PVC due to oxidation effects

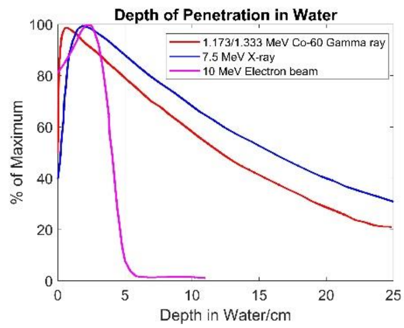

Figure 2. The depth of penetration of three irradiation modalities in water, data from reference [8]

1.2 Radiation chemistry and dominant chemical responses induced by irradiation

There are three major processes of interest during the interaction between high-energy particles and treated chemical materials (primary reactions, secondary reactions, and monomer polymerization), over which the ionization process predominates. Both excitation and ionization can give rise to free radicals and stable molecules [6].

Primary interactions start with ionization and excitation, achieved via passing high energy from injected particles or photons to electrons ejected from molecules. It can also be described as transferring injected energy to thermal energy and chemical reactions. As a result of these primary reactions, secondary processes such as crosslinking, chain scission, oxidation, long-chain, and grafting will occur. A metric known as G-value has been introduced to determine the radiation efficiency of observed reactions, defined as the number of molecules of a given chemical species produced in the medium induced by the absorption of 100eV of energy. The ratio G(S)/G(X) indicates a different reaction tendency. For example, G(S)/G(X) < 1 represents predominately crosslinking reactions, while G(S)/G(X) > 1 represents predominately chain scission reactions. The G-value (either G(S) or G(X)) is dependent on the specific structure and property of the polymer, total absorbed dose, and reaction environment, with lower G-values signifying resistance to radiation [4].

In summary, highly energetic irradiations result in bond cleavages and free radicals, allowing the occurrence of chemical rearrangements, oxidation, crosslinking, and further chain scission reactions in irradiated polymers. The prevalence of chemical responses induced by irradiation depends on factors intrinsic and extrinsic to the polymer. Discoloration is also a common resultant phenomenon due to the oxidized functional groups. While intrinsic factors have been extensively researched and reported, research focusing on extrinsic factors is still in midst of expanding awareness, such as irradiation condition (temperature, ambient environment, dose rate), irradiation source (electron, photon, proton, and ion), and the geometry of treated sample (uniformity and thickness), among others.

Oxidation

Oxidation can occur during and after irradiation, regardless of whether irradiation happens in the air or in vacuum. Additionally, oxidation effects depend on the diffusion rate of oxygen from the surrounding environment into the materials, the distribution of oxygen in materials, the consumption rate of oxygen, the formation rate of oxidation products, and the thickness of samples (thickness is related to the number of reaction sites, but it is independent of the number of reaction site per unit area). Absorbed energy will influence the reaction site per unit. Generally, the actual distribution of oxygen appears to depend upon at least two factors: 1) the availability of reaction sites with which oxygen may combine, and 2) the kinetics of oxygen diffusion and carbonyl formation rate [9]. If polymers are irradiated in air, the free radicals produced by ionizing radiation can yield oxidized functional groups (carbonyl, peroxides, hydro-peroxides, hydroxyl, carboxyl). Generally, un-crosslinked polymers tend to have higher diffusivity of oxygen, leading to deeper oxidation. Observation also shows that the concentration of oxidation products decreases with increasing distance to the surface, while the gel content increases toward the bulk since crosslinking is prone to happen in bulk. Higher crystallinity leads to lower oxygen diffusivity, resulting in less interior oxidation. Considering the irradiation condition, a high dose rate generates a proportionally higher concentration of oxidizing radicals; however, the time of exposure of the process is proportionally less. The oxidative effects thus depend in part on whether diffusion or reactive oxygen species into the solid is rate limiting or diffusion through the gas; typically the former is rate limiting. The process is diffusion rate limited and not concentration limited and lower dose rates will lead to more oxidation farther into the solid. Higher dose absorbance contributes to the higher concentration of oxidative products with the same thickness. **Figure 3** shows this relationship in LDPE. The dose rates plotted here are comparable to gamma radiation (~10 kGy/h), while are much smaller compared with e-beam (~100,000 kGy/h) and X-ray (~100 kGy/h). Therefore, ebeam and X-ray will have much thinner carbonyl.

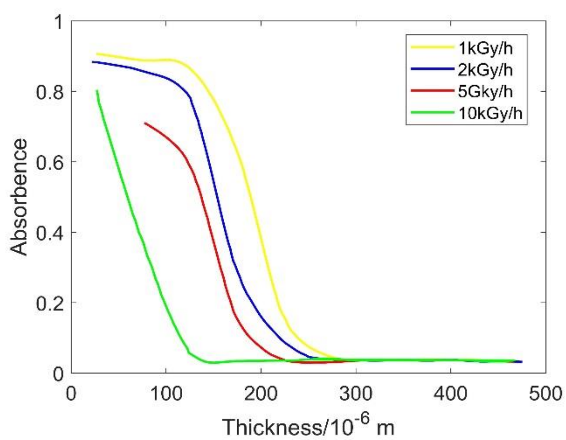

Figure 3. Carbonyl concentration profiles for samples of LDPE irradiated in air at a total absorbed dose of 675kGy and different dose rates, data from reference[10].

Chain scission and crosslinking

Oxidized macromolecules can undergo chain scission, causing a decrease in molecular weight. Accompanied with adverse effects induced by chain scission, it is commonly referred to as degradation reaction. Chain scission can be separated as main-chain and side-chain scission depending on the position where cleavage occurs, and the prevalence of the two scissions mainly relies on the structure of the polymer and the absorbed energy and even irradiation condition (temperature, atmosphere). Normally, the bond energy required for cleavage varies even within the same bond linked in different C. A polymer containing methyl groups ($-CH_3$) functions to suppress crosslinking, instead of enhancing chain scission. Halogen atoms linking to main-chain C atoms appear to make polymers more cross-linkable, while uniformly distributed halogen atoms tends to enhance chain scission. Phenyl groups are favorable for resisting crosslinking and chain scission, however, the replacement of hydrogen atoms in the main chain causes the predominance of chain scission even with the phenyl group attached to the main chain.

Cleavage of chains results in different forms of radicals, which encounter other radicals and induce a combination reaction, causing an increase in molecular weight. The crosslinking process involves the formation of chemical bonds (cross-links) between adjacent molecular chains, resulting in the formation of a three-dimensional network. Alkyl radicals can crosslink with unsaturated groups, which are generated by the hydrogen abstraction of the alkyl radical. The structure of each polymer affects its extent to form crosslinks. A loosely bound hydrogen atom can undergo an abstraction reaction, which decreases the possibility of crosslinking.

Generally, increasing the crosslinking will improve mechanical performance, while degradation behaviors weaken mechanical performance. However, a high density of cross-links can often result in brittleness and stiffness. Different mechanical properties, which are the most sensitive to molecular modifications, magnify the effect of chemical responses induced by irradiation, especially cross-linking, chain scission, and oxidation, springing from the formation of free radical and cleavage of bonds. A flowchart based upon the work from Spadaro et al. was generated and is listed in **Figure 4** [10],

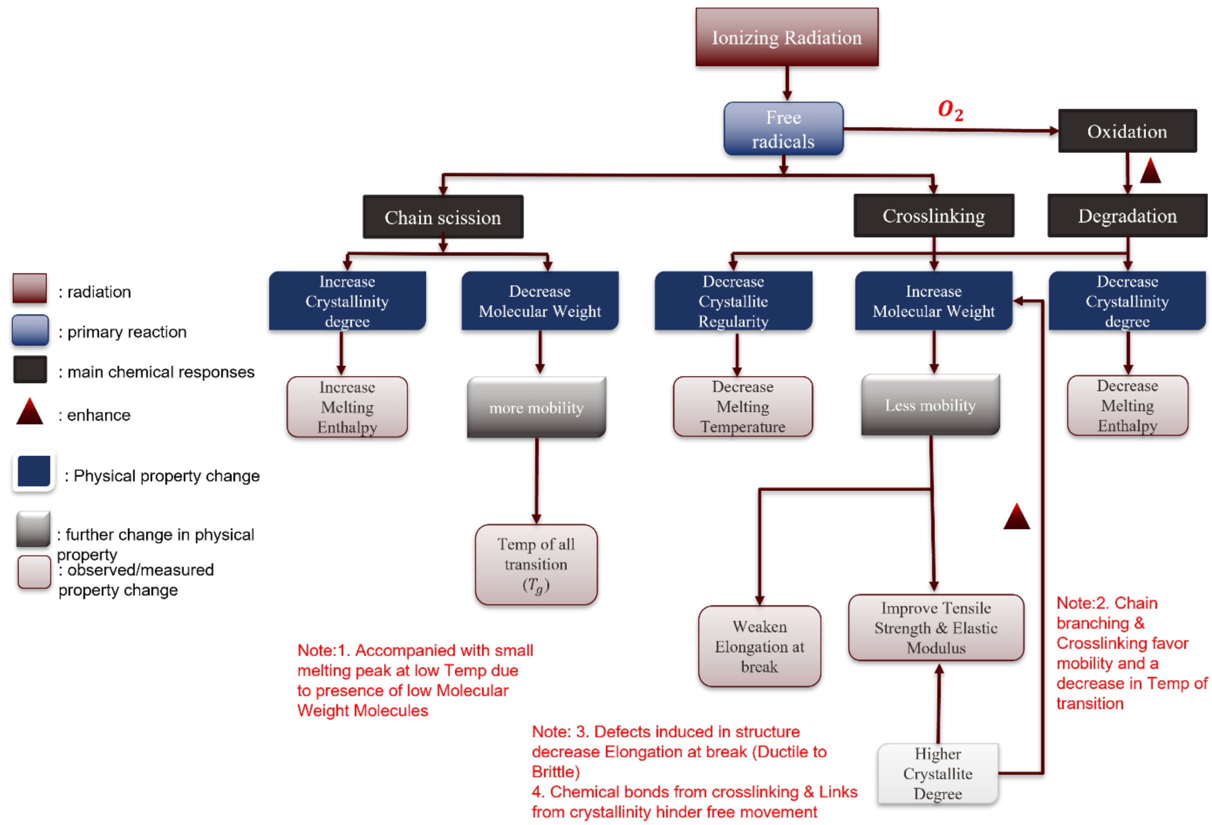

Figure 4. The relationship frame among molecular modification, irradiated-induced particles, and polymer properties (thermal behavior, mechanical properties, and electrical properties)

Discoloration

Discoloration of polymers made for medical device applications turns out to be a significant factor influencing its market due to the negative impression from doctors and patients, even though such degradation has not been proven to connect to changes in mechanical properties. The formation of annealable and permanent color centers has been given as two sources of discoloration. The annealable color centers appear to be primarily associated with free radicals trapped within rigid polymeric matrices, whereas permanent color centers must correspond to the formation of stable, conjugated chromophores within the polymer [11]. Given the formation of permanent color centers, J. Wallace put forward three potential sources: 1) stable radicals formed during the course of irradiation; 2) reaction products resulting from radical-radical coupling reactions during annealing; 3) oxidation products from O_2-annealing [12]. Most discoloration phenomena observed are attributed to the permanent color center. Depending on the nature of the polymer, the delivered dose, and radiation source, different polymers have different magnitudes and ratios of the generation of annealable and permanent color centers. Discoloration will be further influenced by impurities and additives of the materials.

2. Materials and Methods

2.1 Materials

Polymer test samples that we used were the raw materials implemented in actual medical devices and were generously provided by BD. They were provided as ASTM D638 Type 1 injection-molded tensile specimens of 165 mm overall length, 50 mm gauge length, 13 mm gauge section width, and 3.2 mm thickness. The LDPE is Purell PE 1840H (LyondellBasell), the PPH is product 3620WZ (Total Polymers), and the POE is ENGAGE™ 8440G Polyolefin Elastomer, an ethylene-octene copolymer (The DOW Chemical Company).

2.2 Radiation processing

To directly compare the effects of sterilization dose from the three modalities on these three polymers, batches of polymers were processed to common target doses ranging in 0-100kGy under gamma-ray, e-beam, and X-rays. The targeted and delivered doses are listed in **Table 2**, and processing details of the three irradiation modalities are listed below:

1) Gamma processing was performed in the research loop of a nominal 3.5 megacurie cobalt-60 BD irradiation cell in Broken Bow, Nebraska.

2) Electron beam (E-beam) processing was performed using a 10 MeV, 15 kW s-band Varian linear accelerator at the National Center for Electron Beam Research at Texas A&M University in College Station, Texas. The associated beam current/scan settings were 1.6mA/61 cm. The dose rate was previously empirically calculated as approximately 3000 Gy/second (10.8 MGy/hr). The conveyor speed was adjusted as needed to achieve the desired minimum target dose.

3) X-ray processing was performed using a 7.5MeV, 30 kW X-ray machine at Steri-Tek in Fremont, California. The associated beam scan settings were 30.5 cm from the target and the conveyor speed was 0.025 meters per minute. At this conveyor speed, 11 kGy was applied per pass. The speed was increased to deliver the final doses to the devices to achieve desired total doses.

Table 2. Target sample doses and average measured doses (in kGy) for each modality.

Modality	**10 kGy**	**35 kGy**	**50 kGy**	**80 kGy**
Gamma	10.1	36.2	51.3	85.2
Electron-beam	12.4	40.8	51.4	86.2
X-ray	11.0	36.0	51.5	83.5

2.3 Mechanical testing and yellowness index testing

All mechanical tests and yellowness index tests were implemented at Texas A&M University. Yellowness Index (YI) (ASTM E313, 2015) [13] was measured in the three polymers, and the detailed methods can be found in our previous published papers [14]–[16]. Tensile testing and hardness testing were chosen for mechanical properties characterization, and associated details can also be found in the same published papers.

3. Results

3.1 Yellowness Index (YI) and tensile testing

Both yellowness index and tensile testing results (hardness, tensile strength, elongation at break) were published, and all results support e-beam and X-rays as being two viable alternatives to gamma-ray for sterilization of tested polymers [16]. The discrepancy between gamma-ray and the other two can only be observed in the value of YI, but it is worth noting that the analytically detectable differences between modalities were not identifiable by the unaided eye.

3.2 Comparison between NABLO and literature

In this section, detailed analysis, and comparison of three polymers (LDPE, POE, and PP) will be discussed. Due to limited consistent work, only 3 polymers (LDPE, POE, and PP) and two mechanical tests (tensile strength and elongation at break) are available to be used for comparison with our NABLO's results. **Figure 5** (a-b) shows the elongation at break trend along with changing dose for LDPE and POE. **Figure 6** (a-c) shows the tensile strength trend along with changing doses for LDPE, POE, and PP. There is an obvious difference existing between NABLO's results and literature. Elongation at break of LDPE and POE from NABLO's results, as shown in **Figure 5** (a-b), appears to be around 75% and 67% smaller than literature results, respectively. Elongation at break decreases with increasing dose in literature, while NABLO has slightly increased with increasing dose. It is also noticeable that the tensile strength for the three polymers does not match the values reported in the literature, as shown in **Figure 6** (a-c). Unlike elongation at break, the changing behavior of tensile strength has no strong discrepancy between literature and NABLO. Except for the e-beam irradiated LDPE (50kGy/pass), gamma treated POE (0.003kGy/s) and e-beam treated POE (20kGy/pass) having over 14% increase with increasing dose in literature, the other irradiated polymers have nearly constant (less than 8% variation) tensile strength with varying dose. To investigate the potential explanation for the discrepancy, the summary of irradiation and material properties were extracted from literature, listed in **Table 3** (a-c). The difference in density of POE used in each reference and NABLO may be a partial explanation for the discrepancy of the pre-treatment tensile strength. It is worth noting that POE behavior in reference [17] is consistent with NABLO's results with the same density of POE. Nevertheless, the incomplete data of irradiation process, specimen preparation, tensile testing standards, and specimen geometry makes the comparison less systematical and hard in explanation of the discrepancy. Overall, comparing individual studies from literature is problematic. This issue highlights the need (as taken up by the NABLO team) to perform systematic studies that compare differences among modalities for samples treated and tested under identical conditions (polymer formulation, irradiation dose, pre-treatment conditions, geometry, mechanical test conditions, etc.).

From the perspective of tensile testing, the strength increases with increasing the strain rate at a fixed thickness, while the strength decreases with increasing specimen thickness at a constant test rate [18]. Thickness, as an obvious variation, generally is related to the elongation at break, but detailed research indicates the correlation between thickness and elongation should be carefully analyzed under considering various factors, including nucleation, growth, and coalescence behavior of voids caused by the stress triaxiality in local deformation region [19]. Additives and impurities of polymer and specimen preparation are additional factors that affect mechanical properties. No detailed information about the polymer's physical properties in literature, on the other hand, highlights the significance of comparable, systematical, and detailed released work performed in the NABLO project.

Only small differences in tensile strength and elongation at break was observed from the NABLO's three irradiation sources results, as shown in **Figure 5-6**. Consistent specimen geometry, specimen preparation, and testing standards solidify the conclusion made in NABLO's work. Furthermore, mechanical testing for the dog-bone polymer of CIIR and yellowness index testing for LDPE, POE, PPH, and CIIR was also studied. The Yellowness Index of CIIR and LDPE appears to have the same insignificant discrepancy between irradiation sources, while POE and PP do show variation among sources. More detailed comparison information can be found in our previously published papers [14]–[16].

Table 3 (a). Irradiation and material properties comparison of LDPE

LDPE	Dose Rate	Density (g/cm^3)	Thickness	Ambient	Standard
Gamma [20]	0.0014kGy/s	0.92		vacuum	ASTM D-1822 TYPE-L 200mm/min
Ebeam [21]	50kGy/pass	0.921	2	Air	ASTM D-1928 50mm/min
Gamma [22]	0.0014kGy/s	0.92		Air	ASTM D 638 100mm/min
Gamma [23]	0.002kGy/s			Air	BS EN ISO 178
X-ray [23]	0.002kGy/s			Air	
NABLO-Ebeam [16]	3kGy/s	<1	3.2	Air	ASTM D 638 Type 1 500mm/min
NABLO-Xray [16]	0.03kGy/s	<1	3.2		
NABLO-Gamma [16]	0.003kGy/s	<1	3.2		

Table 3 (b). Irradiation and material properties comparison of POE

POE	Dose Rate	Density (g/cm^3)	Melt index (g/10 mi)	Thickness (mm)	Ambient gas during irradiation	Type and Company	Standard Followed (Test Rate)
Gamma [24]	0.003kGy/s	0.902	3		N_2	Engage 8450 (Dow)	GB/T1040-92
Ebeam [17]	unknown	0.87	5	0.6	Air	Engage 8200 (Dow)	500mm/min
Ebeam [25]	20kGy/pass	0.885	1			Engage 8003	ASTM D412 500mm/min
NABLO-Ebeam	3kGy/s	0.870	1.6	3.2	Air	ENGAGE 8440 (Dow)	ASTM D 638 Type 1 500mm/min
NABLO-Xray	0.03kGy/s	0.870	1.6	3.2			
NABLO-Gamma	0.003kGy/s	0.870	1.6	3.2			

Table 3 (c). Irradiation and material properties comparison of PP

PP	Dose Rate	MFI (g/min)	Thickness	Ambient	Standard
Gamma [23]	0.002kGy/s			Air	BS EN ISO 178
Xray [23]	0.002kGy/s			Air	
NABLO-Ebeam	3kGy/s	12	3.2	Air	ASTM D 638 Type 1 (50mm/min)
NABLO-Xray	0.03kGy/s	12	3.2		
NABLO-Gamma	0.003kGy/s	12	3.2		

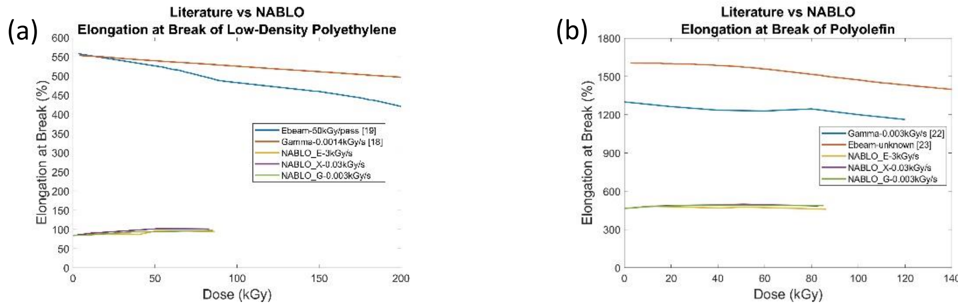

Figure 5. Elongation at break comparison between literature and NABLO project, (a). LDPE (b). POE

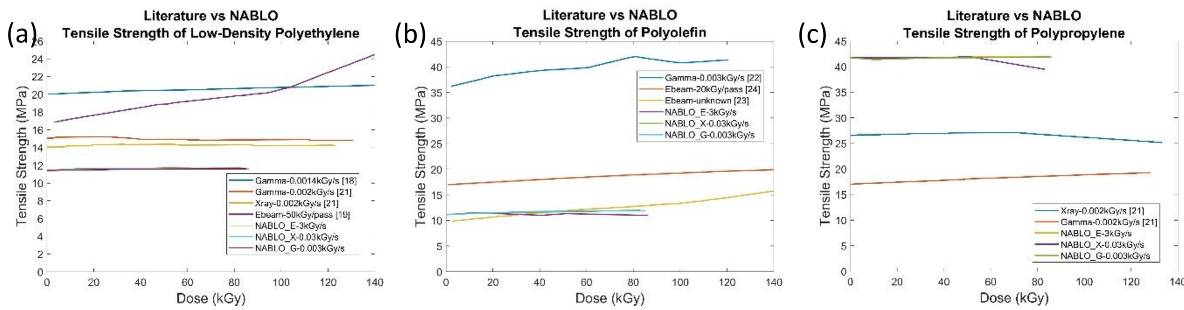

Figure 6. Tensile strength comparison between literature and NABLO project, (a). LDPE (b). POE (c). PP

4 Conclusions

Polymers are often exposed to intentional or unintentional irradiation, which gives rise to chemical reactions and results in changes in their physical properties. Primary reactions (excitation, ionization, generation of free radicals following chemical bond breakages, the formation of unsaturated bonds), secondary reactions (intermolecular crosslinking, chain scission, grafting, oxidation), and monomer polymerizations readily occur within the polymer. Thus far, over 17 polymers have been studied in the NABLO project for direct comparison of the effects of different irradiation modalities on the material properties of a polymer. Here we highlight three polymers (LDPE, POE, PP) in detail due to uncompleted literature information and the lack of testing of the same raw material as used in the real medical devices.

Based on our comparison between testing results and literature, the elongation at break for both LDPE and POE has a slightly increasing trend with dose, while it has a consistent decreasing trend in literature. Theoretically, a decrease of elongation at break is due to the dense crosslinking, which causes the chain less flexibility. However, the situation in our testing results is opposite from that in literature and may be attributed to the impurities and additives in the raw materials used for the medical devices themselves. The results from tensile strength from both literature and NABLO show a nearly constant or slight increase with an increasing dose. This trend can be explained by the increased crosslinking and less flexibility. With an increase in dose, the yellowness index of these three polymers has an obvious increase and is consistent with the qualitative description in the literature. Overall, these results underscore the need for systematic testing under identical fabrication and testing methods, as to appropriately compare the effects of irradiation modality on polymer properties.

Tensile testing, yellowness index testing, and functionality testing for 5 medical devices, supported by Becton, Dickinson and Company (BD), and Stryker Company, have been completed, along with 8 medical device parts and 4 dog-bone polymers. Direct comparison results for BD's devices have also been published in three journal papers, and show no significant differences among the three methods. As such, these studies suggest that X-ray and e-beam are two viable alternatives to gamma-ray. More comparison between literature and NABLO's dog-bone testing results should be performed to provide a systematic comparison.

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ANNEX I

LIST OF PARTICIPANTS

Argentina	Ms Maria Nazarena Ciavaro Radiation Science and Applied Technology Management CAE, National Atomic Energy Commission (CNEA) Email: nciavaro@cnea.gob.ar
Brazil	Ms Aurea Beatriz Cerqueira Geraldo Nuclear and Energy Research Institute (IPEN) Email: ageraldo@ipen.br
Egypt	Mr Hassan Abd El-Rahim National Center for Radiation Research and Technology Egyptian Atomic Energy Agency (EAEA) Email: ha_rehim@hotmail.com
Egypt	Mr Ayman Massoud Nuclear Chemistry Department Egyptian Atomic Energy Authority (EAEA) Email: ayman_mass@yahoo.com
France	Mr Belkacem Otazaghine Equipe Polymères Composites & Hybrides Centre des Matériaux des Mines d'Alès (C2MA) IMT Mines Alès Email: belkacem.otazaghine@mines-ales.fr
France	Mr Nicolas Ludwig Aerial Email: n.ludwig@aerial-crt.com

India	Ms Hemlata Bagla Department of Nuclear & Radiochemistry Kishinchand Chellaram College Email: hemlata.bagla@kccollege.edu.in
Indonesia	Ms Farah Nurlidar National Nuclear Energy Agency of Indonesia (BATAN) Email: pair@batan.go.id
Philippines	Ms Bin Jeremiah Barba Philippine Nuclear Research Institute (PNRI) Email: bjdbarba@pnri.dost.gov.ph
Poland	Mr Slawomir Kadlubowski Institute of Applied Radiation Chemistry (IARC) Lodz University of Technology Email: slawomir.kadlubowski@p.lodz.pl
Portugal	Ms Maria Helena Casimiro Instituto Superior Técnico Email: casimiro@ctn.tecnico.ulisboa.pt
Russia	Ms Valentina Sharapova Ural Federal University Email: v.a.sharapova@urfu.ru
Serbia	Mr Edin Suljovrujic Vinca Institute of Nuclear Sciences Email: edin@vinca.rs
Tunisia	Mr Haikel Jelassi National Centre for Nuclear Sciences and Technologies (CNSTN) Email: haikel.jelassi@gmail.com

Turkey	Mr Tonguc Ozdemir Chemical Engineering Department Mersin University Email: tonguc.ozdemir@mersin.edu.tr
USA	Mr David Staack Department of Mechanical Engineering Texas A&M University Email: dstaack@tamu.edu
IAEA	Ms Valeriia Starovoitova Radiation Products and Radiation Technology Section Division of Physical and Chemical Sciences Department of Nuclear Sciences and Applications International Atomic Energy Agency Email: v.starovoitova@iaea.org
IAEA	Mr BumSoo Han Radiation Products and Radiation Technology Section Division of Physical and Chemical Sciences Department of Nuclear Sciences and Applications International Atomic Energy Agency Email: B.S.Han@iaea.org
IAEA	Ms Celina Horak Radiation Products and Radiation Technology Section Division of Physical and Chemical Sciences Department of Nuclear Sciences and Applications International Atomic Energy Agency Email: C.Horak@iaea.org

IAEA	Mr Wenbin Yang Radiation Products and Radiation Technology Section Division of Physical and Chemical Sciences Department of Nuclear Sciences and Applications International Atomic Energy Agency Email: W.Yang@iaea.org
IAEA	Ms Sarah Loftin Radiation Products and Radiation Technology Section Division of Physical and Chemical Sciences Department of Nuclear Sciences and Applications International Atomic Energy Agency Email: S.Loftin@iaea.org
IAEA	Mr Sang Hoon (James) Lim Radiation Products and Radiation Technology Section Division of Physical and Chemical Sciences Department of Nuclear Sciences and Applications International Atomic Energy Agency Email: S.H.Lim@iaea.org

ANNEX II

MEETING AGENDA

<u>Monday, 15 November 2021</u>

Session I:	**Introductory Session**
12:00 – 12:30	Opening of the meeting by: - Ms Melissa Denecke, Director NAPC (**IAEA**) - Ms Celina Horak, Section Head of RPRT (**IAEA**) - Ms Valeriia Starovoitova, Scientific Secretary, RPRT (**IAEA**) - Mr Bumsoo Han, RPRT (**IAEA**) - Mr Wenbin Yang, RPRT (**IAEA**) - Ms Sarah Loftin, RPRT (**IAEA**) - Mr Sang Hoon Lim, RPRT **(IAEA)** Scope and objectives of the meeting, adoption of the agenda, election of the chairperson of the meeting, introduction of the participants

Session II:	**Participants' Presentations**
12:30 – 13:00	Presentation from Mr Tonguc Ozdemir **(Turkey)** *"Effect of Radiation on Commonly Used Natural Rubber and Silicone Rubber in Medical Applications and Devices"*
13:00 – 13:30	Presentation from Mr Hassan Abd-El-Rehim **(Egypt)** *"Evaluation of some properties of gamma /electron beam irradiated polymeric devices"*
13:30 – 13:45	*Coffee Break*

14:15 – 14:30	Presentation from Ms Maria Helena Casimiro **(Portugal)** *“Radiation Effect on 3D Printed Medical Implants for Customized Tissue Repair”*
14:30 – 15:00	Presentation from Ms Aurea Geraldo **(Brazil)** *“Membranes and other polymeric and biopolymeric substrates modified by ionizing irradiation for medical materials”*

Tuesday, 16 November 2021

Session III:	**Participants’ Presentations**
12:00 – 12:30	Presentation from Ms Farah Nurlidar **(Indonesia)** *"The Influence of Gamma Irradiation on the Performance of Ultra High Molecular Weight Polyethylene/chitosan/hydroxyapatite Implant"*
12:30 – 13:00	Presentation from Ms Valentina Sharapova **(Russia)** *“The effects of sterilization irradiation on properties of commercially available polymeric materials used in the production of medical appliances”*
13:00 – 13:30	Presentation from Mr Edin Suljovrujic **(Serbia)** *“Comparative study of e-beam and gamma radiation effect in polyolefins commonly used in medical devices”*
13:30 – 13:45	*Coffee Break*
13:45 – 14:15	Presentation from Slawomir Kadlubowski (**Poland**) *“Influence of ionizing radiation on polymers and medical devices - a study on reaction mechanisms and changes in product functionality”*
14:15 – 14:45	Presentation from Mr Nicolas Ludwig **(France)** “*Irradiation modality and dose rate effects upon radiation sterilization of commercial polymers used in medical devices.”*
14:45 – 15:15	Presentation from Mr David Staack **(USA)** *“Direct Comparison of Gamma-ray, Electron Beam and X-rays Effect on Materials Property of Medical Device Polymers”*

Wednesday, 17 November 2021

Session IV:	**Participants' Presentations**
12:00 – 12:30	Presentation from Ms Bin Jeremiah Barba **(Philippines)** "*Direct Comparison of Gamma and Electron Beam Irradiation Effects on Raw Polymer Materials Used and Final Products of Single-Use Catheter Devices: Workplan and Related Studies*"
12:30 – 13:00	Presentation from Ms Hemlata Bagla **(India)** *"Gamma-radiation and e- beam induced degradation and probable subsequent growth of microbes in the polymeric structural materials used in the diagnostic catheters"*
13:00 – 13:30	Presentation from Mr Massoud Ayman **(Egypt)** *"Effect of Gamma Radiation and Electron Beam on Some Raw and Manufactured Polymeric Materials Commonly Used in Medical Devices and Tools"*
13:30 – 13:45	*Coffee Break*
13:45 – 14:15	Presentation from Mr Haikel Jelassi **(Tunisia)** *"Effect of E-Beam radiation on physicochemical, mechanical and biological properties of polymers with low density used in medical devices"*
14:15 – 14:45	Presentation from Mr Belkacem Otazaghine **(France)** *"Assessment of the impact of the irradiation process on the final properties of radio-resistant and customized polypropylene materials used for medical devices"*
14:45 – 15:15	Presentation from Ms Maria Nazarena Ciavaro **(Argentina)** *"Irradiation and its effects on polymers commonly use in medical devices"*

<u>Thursday, 18 November 2021</u>

Session V	**Discussion and Meeting Report Preparation** **(ALL PARTICIPANTS)**
12:00 – 13:20	Discussion on the CRP: Goals, Milestones, Issues, Recommendations
13:20 – 13:40	*Coffee Break*
13:40 – 15:00	Drafting of the Meeting Report

<u>Friday, 19 November 2021</u>

Session VI:	**Final Review and Acceptance of the Meeting Report** **(ALL PARTICIPANTS)**
12:00 – 13:20	Discussion on the CRP: Goals, Milestones, Issues, Recommendations
13:20 – 13:40	*Coffee Break*
13:40 – 14:50	Finalizing and Acceptance of the Meeting Report
14:50 – 15:00	Closing of the Meeting