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Review Article

Using X-ray Technology to Sterilize Medical Devices

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Abstract

Half of single-use medical devices are sterilized using irradiation. Probably more than 80% of the industrial irradiation capacity is dedicated to sterilization of disposable or single-use medical devices. There are three main industrial irradiation technologies: gamma (based on ^{60}Cobalt radioactive sources) which counts for about 80% of radiation capacity installed worldwide; electron beam which counts for about 20% of the total radiation capacity installed; and X-ray which has started to gain a foothold in the irradiation market. The adoption of alternative technologies is of highest importance to many medical device manufacturers due to the fact that the ^{60}Cobalt sources in the world are ending and thus the price for the gamma sterilization services is increasing. Alternate sterilization method is X-Ray which is comparable to gamma. High-energy X-rays are similar to gamma rays. Radiation sterilization by X-rays is another option for sterilization of medical devices and other products.

Key words: X-ray; Gamma; Sterilization; Polymers; Ionizing radiation; Medical devices

Abbreviations: AAMI: Association for the Advancement of Medical Instrumentation; ABS: Acrylonitrile-Butadiene-Styrene copolymer; CIIR: Rubber; DUR: Dose Uniformity Ratio; ETO: Ethylene Oxide; EVA: Ethylene-Vinyl Acetate; EVOH: Ethylene Vinyl Alcohol; HIPS: High Impact Polystyrene; IAEA: International Atomic Energy Agency; LDPE: Low Density Polyethylene; LLET: Low Linear Energy Transfer; NNSA/ORS: United States National Nuclear Security Administration (NNSA) Office of Radiological Security (ORS); PE: Polyethylene; PET: Polyethylene Terephthalate; PBT: Polybutylene Terephthalate; POE: Polyolefin Elastomer; PNNL: Pacific Northwest National Laboratory; PP: Polypropylene; PPE: Personal Protective Equipment; PPH: Polypropylene Homopolymer; PVC: Plasticized Polyvinylchloride; PS: Polystyrene; PVC: Polyvinyl Chloride.

Introduction

Historical background and development of irradiation over the years

Ionizing radiation used in medical device irradiation includes gamma (γ)-rays, X-rays, and electron beams (e-beams). X-rays and γ-rays were discovered in the 1890s and research showed that these kinds of irradiation can kill bacteria. Not until the 1940s, where electron beam accelerators were created and ionizing radiation was able to be produced at a much lower cost. However, the efficiency of X-ray machines prohibited them from being used in the industry. Until the 1940s, accelerators were developed for electron beam and ionizing radiation was produced at a substantially less expense. Commercial irradiators that use X-rays are relatively new. The X-ray technology has been available for several years, but the first commercial facility designed and dedicated to sterilization of medical devices was opened in 2010. Nowadays, more and more X-ray irradiators are being installed for the sterilization of healthcare products [1,2].

Overview of the X-ray technology

Sterilization is a key process in medical device manufacturing and the pharmaceutical industry. In developed countries, approximately 40 to 50% of disposable medical products manufactured are sterilized using ionizing radiation, which includes gamma, X-ray and e-beam [3]. X-ray sterilization combines the best characteristics of e-beam and gamma techniques, offering

speedy turnaround times, good processing flexibility, pallet setup processing, and relatively low dose ratios.

Products sterilization by irradiation is an internationally recognized and widely used technology for the processing of medical devices, pharmaceuticals, tissues, and biological substances as well as disposable laboratory equipment. Radiation sterilization, a product sterilization method known since the 1950s, is still gaining significant market share due to processing speed, parametric release, and cost competitiveness. These two sterilization techniques, gamma radiation, and electron beam, used by medical device manufacturers are now widely accepted by regulatory agencies around the world [4-6].

While the two sterilization methods mentioned above are widely used in the medical device industry, X-ray sterilization is not that well known. However, despite not being widely used, it combines the best of both, combining short electronic beam lead times and processing flexibility with gamma palette configuration processing and relatively low dose rates.

Advantages of X-ray sterilization

The use of X-rays in sterilization has many advantages [4-6]:

a. Excellent penetration and improved Dose Uniformity Ratio (DUR). X-ray sterilization provides better penetration characteristics than either γ-rays or e-beam techniques. While the e-beam can be used for sterilizing low-density, and evenly packaged products that don't have challenging geometries, it has a limiting capacity in sterilizing metals, liquids, and high-density or multipart products. And while γ- sterilization is slightly better at penetrating dense products, it may not always achieve the required DUR. X-ray sterilization, on the other hand, is well suited for processing products on pallets rather than in totes. In addition, it can also sterilize products with individual box configurations and those requiring narrower dose ranges, even in carriers or pallets.

b. Enhanced polymer modifications. Due to the very short exposure times of X-ray sterilization, its radiation effect on materials—especially polymers—is often measurably smaller than those caused by γ-rays processing. In fact, the effects of X-ray processing are comparable to those connected to e-beam sterilization. The combination of shorter exposure times and improved DUR enables customers to apply X-ray sterilization technology to medical devices that are currently treated with processes such as ethylene oxide (EtO).

c. Fast and efficient processing and flexibility. The shorter processing times associated with X-ray sterilization provide advantages over conventional EtO and γ-ray cycles, reducing supply chain turnaround times by several days. In addition, x-ray technology can process multiple products with different dose requirements within the same irradiation cycle, offering shorter turnaround times than both γ-ray and e-beam methods.

d. Environmental safety. While both gamma and EtO sterilization are recognized and accepted by regulatory authorities throughout the world as providing safe and sterile medical devices, these technologies have some detrimental environmental implications. While sterilization service providers strive to ensure the safety of their processing technologies and workers, stricter regulation can result in increased production costs and marketed device costs. In contrast, since X-ray technology relies on the use of electricity as the sterilant rather than ^{60}Co or EtO gas, it provides a much cleaner and more sustainable solution.

e. Regulatory Approvals and Validations. The layout and workings of an X-ray facility are designed to meet international standards, including ISO 13485 (quality management system standards for medical devices) and ISO 11137 series (Sterilization of Healthcare Products—Radiation), GMP, and FDA guidelines. In ISO 11137, X-ray technology is accepted as an alternative to γ-ray and e-beam methods. Furthermore, research has shown that the microbicidal effectiveness is not significantly different when treated by either gamma rays or X-rays conditions.

Applications of X-rays

Due to the penetrating properties of ionizing radiation and their ability to inactivate microorganisms, ionizing radiation is used for many different purposes [7,8] including, virus inactivation for research laboratories, as well as to sterilize or reduce the microbial bioburden of many different types of products such as medical devices, packaging, cosmetics, foods, and agricultural products. It is also used to alter the properties of a wide variety of polymers through numerous chemical reactions.

Ionizing radiation such as X-rays and gamma rays can easily penetrate most tissues, and kill bacteria by causing irreparable DNA damage. Many Gram negative bacteria such as E. coli, Salmonella, and P. aeruginosa can be effectively killed by X-rays [9,10]. Results also showed that X-rays of lower energies were effective in inactivating bacterial spores [11].

Food irradiation has found successful applications in increasing the microbiological safety of foods and shelf-life extension, hence, reducing food losses by using X-ray technology [12]. Directly over 50 nations have affirmed applications to irradiation over 60 distinctive foods [13]. More than half a million tons of food is irradiated around the globe annually.

Irradiation is also a common sterilization method of connective tissue allografts, such as skin, cartilage, bone, tendons, heart valves and corneas [14]. A key concern for tissue allografts is the risk of

disease transmission to the recipient. Hazardous microorganisms may be of donor origin or may have been transferred during tissue procurement, processing, storage and handling of the tissue. To reduce the possibility of transmission of bacterial, fungal or viral diseases, tissue samples must be sterilized before introduction into the potential transplant recipient. Different processes and procedure are available to deactivate viruses or bacteria in donor bone. The X-ray and gamma sterilization performed on the donor bone graft are the most efficient procedures widely used to prevent toxicity or migration of virus/bacterial infections from donors to receiver [15].

For many years, low linear energy transfer (LLET) ionizing radiation, such as γ-rays, X-rays, and e-beams, has been the main tool to produce many products through polymerization reactions [16]. On the other hand, the impact of X-rays on the polymeric structure of materials used in biomedical applications has been raised.

Pathogens on the surface or within a medical device can cause severe infections and can even lead to an explantation surgery. Hence implant devices intended for human use require sterilization in order to fulfill regulatory issues. Recently, the impact of commonly used irradiation sterilization methods (e -beam, gamma and X-ray irradiation) on biodegradable polymers such as polycaprolactone fiber mats were investigated by de Cassan et al. [17].

Till now, only a few papers compare the effects of exposing different types of plastics that are commonly used in medical devices to gamma or to 5MeV X-rays. In one study the results of irradiating polymer test samples under commercial processing conditions at existing 5MeV X-ray and ^{60}Co gamma irradiators were presented [18]. The irradiation parameters of both facilities were set to deliver a dose of about 7.5 kGy per hour. The polymers selected for testing were polyethylene (PE), polypropylene (PP), polystyrene (PS), plasticized polyvinylchloride (pPVC) and an acrylonitrile-butadiene-styrene copolymer (ABS). Replicate samples of each type of polymer were exposed to nominal doses of 30, 60 and 120 kGy using X-rays for a first set and gamma photons for a second set. Each sample series was accompanied by control samples. A separate group of controls was retained at the polymer manufacturer.

After irradiation half of the exposed samples as well as half of the accompanying controls were kept at room temperature during 8 weeks, whereas the other test pieces were stored at 50°C for 7.5 weeks in order to simulate a 52 weeks aging period at room temperature. Following storage all samples were tested at an accredited laboratory for colour change and for mechanical properties.

For all polymer types investigated and for both storage conditions applied, measurements of the tensile yield strength showed comparable results between samples exposed to 5MeV X-rays and those irradiated with ^{60}Co. Irradiation affected a polymer's colour. An increase in the yellow colour component upon irradiation was observed for all polymer types used in this study. None of the polymers submitted to the accelerated aging programme had returned to their original colour. No practically relevant colour differences were obtained between the samples irradiated by gamma photons and the ones exposed to 5MeV X-rays. The difference in the photon energy spectrum of both technologies was found not to generate any differences that were of practical interest in the investigated material properties. This suggests that industrial sterilization using X-rays would have similar effects on medical polymers as compared with sterilization using gamma photons.

The influence of high energy radiation on polypropylene were studied by Portnoy et al. [19] using three different sources of ionizing radiation: γ-rays, e-beam, high current X-radiation. Each portion of tested material was irradiated with either γ-rays, e-beam or X-ray at doses of 25, 50, 75, and 100 kGy. After the irradiation, specimens were subjected to accelerated ageing, for 21 days at 60°C and tested for mechanical and color properties according to ASTM specifications. The study showed that radiation sources, such as e-beam and X-ray, can be used for the sterilization of a wide variety of PP formulations without causing the polymer to become brittle or discolored to what is commonly experienced with γ radiation. Taken together, both of the alternative methods appeared to cause less oxidative degradation of PPs than do γ-rays. Therefore, the authors concluded that it should be possible with either e-beam or X-radiation to use higher doses of radiation and/or extend the shelf life of a sterilized medical device than when using a γ-ray source.

Structural studies on polymer materials used in medicine have developed rapidly in recent years, e.g., for the production of contact lenses. In another study Filipecka et al. [20], of was to examine changes in the polymer structure of Narafilcon A soft silicone-hydrogel contact lenses (a very popular type of contact lens) due to exposure to X-ray irradiation. The finding showed that X-ray radiation did not affect or damage polymer bonds and can in the future contribute to the use of X-ray and γ- radiation to sterilize contact lenses.

Due to the outbreak of the novel coronavirus disease, COVID-19 there is an increased demand in medical and personal protective equipment (PPE). Since the supplies may take a long time to meet the global demand, reusing PPEs will help health care workers in their response to the COVID-19 pandemic. To ensure the safety and well-being of the medical first responders, PPE needs to be sterilized before reuse. The recent study, examined various sterilization techniques, including X-rays/ γ-rays, that can be used to sterilize

PPEs and point out its limitations. The authors concluded that under certain licensed operating conditions, the X-rays produced by electron linear accelerator can deliver dose rates sufficient for PPE sterilization in minutes to hours. The findings from this review can provide hospitals with a technique that could be used to sterilize PPEs [21].

Finally, the induced radioactivity in medical devices when sterilized with 7.5MeV X-rays has been investigated. The experimental setup has been chosen to simulate closely the situation in a commercial irradiation facility. The study compared activation of medical devices with regulatory limits and evaluated corresponding dose exposure of persons in contact with those devices. The paper concludes that provided some precautions were considered, sterilization with X-rays from 7.5MeV electrons can be regarded safe from the standpoint of public health and personal safety [22].

Knowledge Gap

Increasing regulatory demands governing ^{60}Co use, supply chain costs, the time needed for γ-rays sterilization, and the inability to use γ-rays for sterilization during product manufacturing, are key aspects triggering the switch to e-beam or X-ray radiation alternatives for some medical devices. However, there are obstacles that make it difficult for manufacturers of medical devices to navigate this transition. One of these hurdles was highlighted in the Fermilab report in 2017, which concludes that: "…there is a knowledge gap in how the different radiation sources (^{60}Co, e-beam and X-ray irradiation) affect common medical device materials. Because of this, irradiation effects on materials for all three modalities need to be documented in peer-reviewed references and made publicly available to encourage use of different irradiation modalities" [23,24].

To address these issues, Pacific Northwest National Laboratory (PNNL), one of the United States Department of Energy national laboratories leads a project in developing testing standards and obtaining reliable data to transition medical products from traditional γ-based irradiation to irradiation alternatives such as e-beam and/or X-ray [23].

This issue was also highlighted in a recent IAEA Consultancy Meeting Report entitled "Radiation effects on polymer materials", which concluded: "…there are two main areas that can be improved in the radiation processing community – scientific knowledge and improved accessibility of information on accelerator-based sterilization processes. Due to gaps in data, processes and know-how, adoption of e-beam and X-ray sterilization has suffered despite their acceptability in the pertinent regulations and standards. Improvement in these areas is important because it directly involves the health and safety of hospital patients and consumers of health care products and can affect the future availability of alternative sterilization technologies that can solve potential capacity issues with ^{60}Co and EtO" [23,25].

In order to fill these missing data and close education gaps, and to assess whether polymers sterilization with e-beam or X-ray radiation can be as effective as γ-rays methodology, Pacific Northwest National Laboratory was requested by United States National Nuclear Security Administration (NNSA) Office of Radiological Security (ORS) NNSA/ORS, to build a team with industry partners. As a result, a team consisting of nine member was formed (including leading medical devices manufacturers, sterilization facilities, and polymer testing laboratories. The main goals for the resulting "Team Nablo" were to [26]:

1. Identify specific polymers/elastomers used in medical products that present the greatest data gaps for radiation effects and would be of greatest industry impact if transitioned to e-beam or X-ray.

2. Measure any physical effects that these materials exhibit when they are given sterilization-level radiation doses from e-beam or X-ray.

3. Determine whether these effects would preclude the use of e-beam or X-ray for associated medical products.

4. Execute an industry and public outreach component that will identify and fill knowledge and education gaps that impede the transition to e-beam and X-ray sterilization.

5. Encourage increased use of e-beam and X-ray for sterilization of single-use medical products.

Team Nablo performed product functionality, coloration, and hardness testing on Becton Dickinson (BD) medical products used abundantly in healthcare settings. These tests were performed on products after being irradiated to γ-rays, e-beam and X-ray at dose levels ranging from 10-80 kGy and simulated the physical forces and movements that these products undergo when used by the end-users (healthcare professionals and patients). The product functionality results provided evidence that there was no statistical decrease between γ-rays irradiation, e-beam and X-ray for the products tested.

Small statistical differences were found for certain polymers and irradiation sources, for the coloration tests, most at doses above 50 kGy. However, even if these discoloration defects (browning or yellowing) did not impact the function or safety of the polymeric products, they are unacceptable in terms of aesthetics and consistency, and can be important for marketing and end-user perception of quality. Additionally, six polymers (LDPE, CIIR, PPH, POE, PET and PVC) were subjected to various mechanical tests including, tensile modulus, tensile strength, strain at break, and hardness. The results showed that it was minimal or no statistical

difference between γ-irradiation, e-beam and X-ray for the four polymers tested. These data support the expectation that e-beam and X-ray methods are viable alternatives to γ-rays sterilization [27].

Furthermore, the testing was extended to additional products (ABS, HIPS, butyrate, PBT, PVC, silicon, and Buta-N) from new team members, Stryker Corporation (lower-body joint replacement products) and a manufacturer of polymer bio-reactor bags used in pharmaceutical production. Additionally, the team started testing of products of S71 films, consisting of layers of EVA/EVOH/EVA, from new team members, Sartorius Corporation a manufacturer of buffer and drug substance storage bags used in pharmaceutical production [28].

Conclusions

Due to its advantages in efficiency, flexibility, and technological advancement, X-ray processing will become the preferred sterilization method for many medical device products. And as the inherent strengths of this technology are better understood, it will expand and attract global interest.

Conflict of Interest

The author is employee of HTL-Strefa S.A.

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