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Comprehensive investigation on physical and chemical properties of γ -irradiated multilayer PE/EVOH/PE film: A multiscale approach

Fanny Gaston¹ | Nathalie Dupuy² | Nina Girard-Perier¹ | Sylvain R. A. Marque³ | Samuel Dorey¹

¹Sartorius Stedim FMT S.A.S, Aubagne, Cedex, France

²CNRS, IRD, IcheMBE, Aix-Marseille University, Avignon Université, Marseille, France

³CNRS, ICR, Aix Marseille University, Marseille, France

Correspondence

Fanny Gaston and Samuel Dorey, Sartorius Stedim FMT S.A.S, Z.I. Les Paluds, Ave de Jouques CS91051, 13781 Aubagne Cedex, France,
Email: fanny.gaston@sartorius.com and samuel.dorey@sartorius.com

Abstract

The study evaluates findings on the impact of γ -irradiation on the single-use, multilayer plastic film that is manufactured for the biotechnological and biopharmaceutical environments. It is comprised of a multilayer film that offers durability and gas (O_2 , CO_2 and H_2O) shielding properties. Polyethylene (PE) and ethylene vinyl alcohol (EVOH) are the parts within this film, which as a whole, is PE/EVOH/PE. The impact of γ -irradiation on the nonirradiated and γ -irradiated (from 30 kGy up to 270 kGy) PE multilayer film is investigated by colorimetry measurement, Fourier transform infrared and Raman spectroscopies, pH measurement, ion chromatography and conductivity measurement, tensile tests, X-ray photoelectron spectroscopy, differential scanning, and oxygen and water vapor transmission rate. AComDim and Principal Components Analysis are two chemometric tools that are utilized to understand both physical and chemical changes, along with the main factors contributing to polymer degradation in the PE multilayer film while under γ -irradiation.

KEYWORDS

γ -irradiation impact, ethylene vinyl alcohol, holistic testing approach, multilayer film, pharmaceutical and biotechnological single-use system, polyethylene

INTRODUCTION

The single-use device is commonly used in the biotechnological and biopharmaceutical fields today [1]. Selected for their properties of barrier protection and flexibility [2], these polymers are constructed of multilayer films including ethylene vinyl alcohol (EVOH) and polyethylene (PE). The multilayer film is assembled into bioprocessing bags made for transportation, storage and preparation of intermediates, biopharmaceutical preparations and solutions, and final bulk products. This single-use device avoids the need for cleaning and the risk of

cross-contamination that come with traditionally used stainless steel, rigid plastic, and glass options. EVOH forms a barrier against CO_2 and O_2 molecules, while PE repels water with its barrier.

The outlook for single-use plastic bags in biopharmaceutical and biotechnological environments will still require sterilization, and the most popular radiation treatment in the biopharmaceutical industry is γ -irradiation, while other radiation treatments such as X-rays are implemented step by step and will be discussed in upcoming publications. Per regulations, the industry uses and requires a dose >25 kGy [3]. It is able to penetrate at a high level and penetrates the

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entire single-use plastic bag [4, 5]. γ -sterilization and its effects on individual EVOH and PE polymers have been extensively studied [6-16]. Findings have indicated that single-use plastic containers undergo changes at chemical, optical, and physical levels when exposed to γ -rays. Factors such as the radiation dose, additives within the plastic's composition and atmospheric properties of irradiation determine changes.

The primary result of γ -rays interacting with polymers is the creation of free radicals, which then evolve further, causing a range of effects. They include degradation of polymer additives, release of gases, scission, and/or cross-linking events, and changes in both mechanical and gas permeability properties [17-22]. Very few findings [23] of γ -irradiation being exposed to the PE/EVOH/PE multilayer film involving a multitechnique approach have been studied. This experiment is one of very few that uses a holistic approach [24]. This study will report the effects of γ -irradiation doses on the PE multilayer film.

MATERIALS

Film samples

The structure of the multilayer, plastic single-use PE film analyzed in this study was PE/EVOH/PE. Figure 1 presents the anatomy of the film and its polymers. Its thickness measured 400 μm .

Different layers of the PE film possessed additives that stabilized its quality during both manufacturing and shelf life. Additives usually found in polyolefin manufacturing are in the antioxidant (AO) family and include phenols (primary AOs) and phosphites (secondary AOs) [25-27]. For some tests, like permeability and mechanical tests, several lots of PE film are analyzed. Lots correspond to the manufacturing order of the PE films, the composition, and nature of AOs are the same whatever the lot.

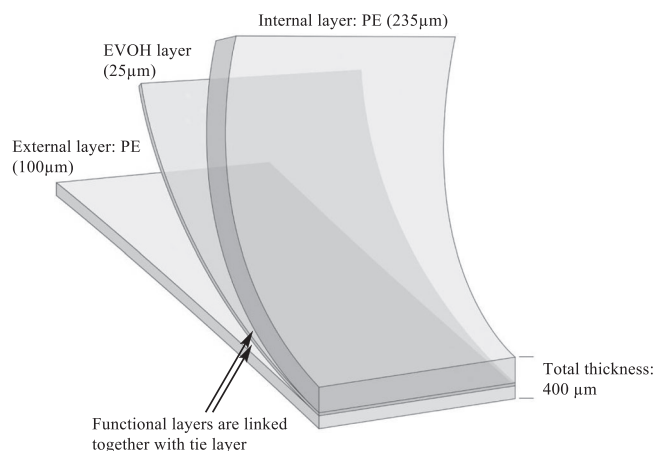


FIGURE 1 Structure of PE-film. EVOH, ethylene vinyl alcohol; PE, polyethylene.

Highlights

- γ -irradiation's effects on multilayer films used by biotechnological industries
- Define and explain the changes activated by γ -irradiation on the studied polymers
- Ethylene vinyl alcohol polymers create radical's species
- Polyethylene modifications evolve linearly for up to 6 months' time

γ -irradiation

The PE film samples were specifically packaged in PE and irradiated in a ^{60}Co γ -source at room temperature. Temperature increased by nearly 5°C during the time of irradiation. According to (Synergy Health), a dose rate of 8-13 kGy/h is provided by this source. It afforded doses of 30 (± 1), 50 (± 1), 115 (± 2), and 270 (± 5) kGy. Since a sterilization cycle corresponds to roughly 25 kGy, multiple sterilization cycles would be required to reach the targeted dosage. In a noncontrolled storage atmosphere, the wait time between two sterilization cycles was noncontrolled for this experiment. Ten days after γ -irradiation concluded, analysis began on the samples. Results between irradiated and nonirradiated samples were compared to evaluate the effect had by γ -irradiation. To amplify modifications stimulated by this irradiation, doses of γ -irradiation are researched up to the level of 270 kGy. It is hypothesized that modifications recorded at high γ -doses also occur with lower ones, but in lower amounts.

TECHNIQUES AND METHODS

Research on the PE multilayer film was performed with multiple physical, chemical, and physicochemical methods: colorimetry measurement [28], Fourier transform infrared (FTIR) [29] and Raman spectroscopies [30], total organic carbon (TOC) measurement and ion chromatography (IC), pH measurement, conductivity measurement [31], X-ray photoelectron spectroscopy (XPS) measurements [32], and electron spin resonance (ESR) [33]. Next, oxygen transmission rate (OTR), differential scanning calorimetry (DSC), tensile tests, and water vapor transmission rate (WVTR) were implemented [34]. Many chemometric methods were applied, including analysis of variance common dimensions (ACoMDim, Analysis of Variance in Common Dimensions) [35] and principal component analysis (PCA).

RESULTS AND DISCUSSION

Once γ -irradiated for biopharmaceutical and pharmaceutical applications, shades of yellow discoloration appear on PE multilayers films. A specific odor is also present [28].

Macrophysical properties macroscopic and chemical properties

The experiments show that γ -irradiation creates chromophore compounds, which are produced via by-products of the additive package, and include phenol and phosphite, and/or the polymer matrix.

Film yellowness

There is a direct correlation between the change of color and absorbed γ -doses [28]. They (γ -doses) induce a modification of color for the four AOs studied (Figure 2). Yellow discoloration forms as the result of free radicals produced by the interaction of γ -rays and polymers.

It has been shown in another study that the presence of phenolic AOs in polymer contributes to the yellowness in comparison with

polymer containing no stabilizer [36, 37]. Authors have listed the ultraviolet (UV) and visible absorption characteristics of by-products of phenolic AOs. Previous study has shown that the phenolic AO undergoes a cascade of reaction through radical degradation pathway [38]. The yellow discoloration could provide a method to monitor evolution of AOs and their by-products. It would reveal that reactive species of radicals and peroxides are present.

Permeability

Water permeability characteristics are tracked by the WVTR. PE has notable water barrier properties (Figure 3), as it is not altered at any irradiation dose. This quality is attributed to its hydrophobicity. Any changes present in PE layers are not substantial enough to change their barrier property. This result agrees with the absence of

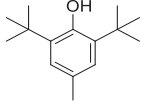
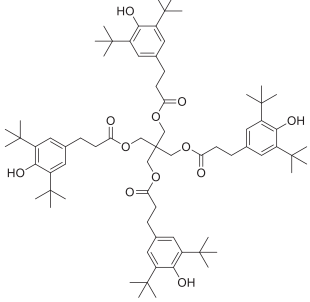
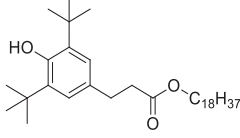
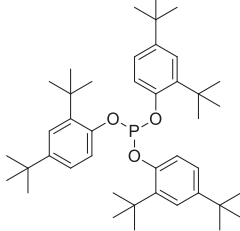
Additive	Structure
AO-1: BHT (2,6-Di-tert-butyl-p-cresol) CAS 128-37-0	
AO-2: Pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate) CAS 6683-19-8	
AO-3: Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate CAS 2082-79-3	
AO-4: Tris (2,4-di-tert-butylphenyl) phosphite CAS 31570-04	

FIGURE 2 Structure of primary and secondary AOs: AO-1: 2,6-di-tert-butyl-p-cresol, AO-2: pentaerythritol tetrakis (3-(3,5-di-tert-butyl-4-hydroxyphenyl)- propionate), AO-3: octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate, AO-4: tris (2,4-di-tert-butylphenyl)phosphite.

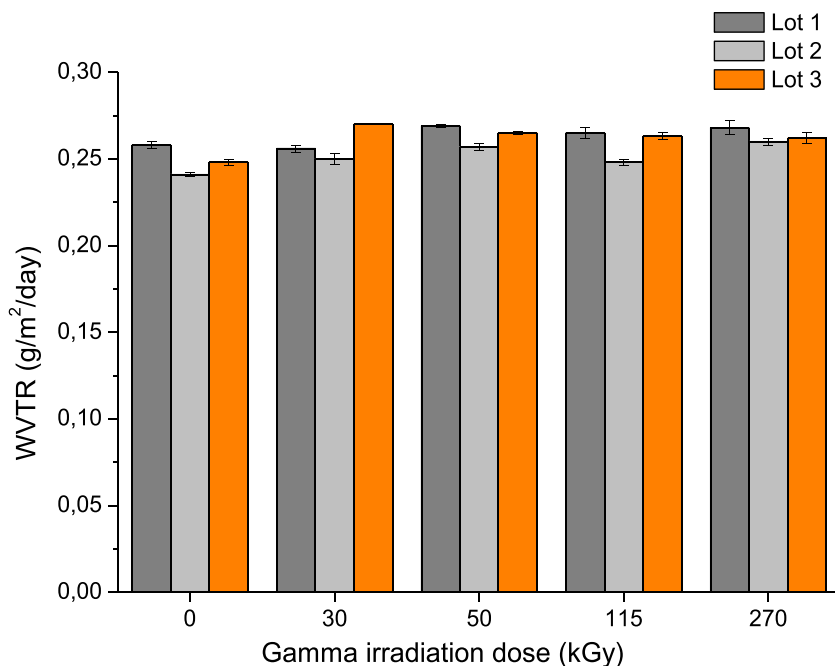


FIGURE 3 WVTR of PE/EVOH/PE multilayer film according to the γ -irradiation dose. EVOH, ethylene vinyl alcohol; PE, polyethylene; WVTR, water vapor transmission rate.

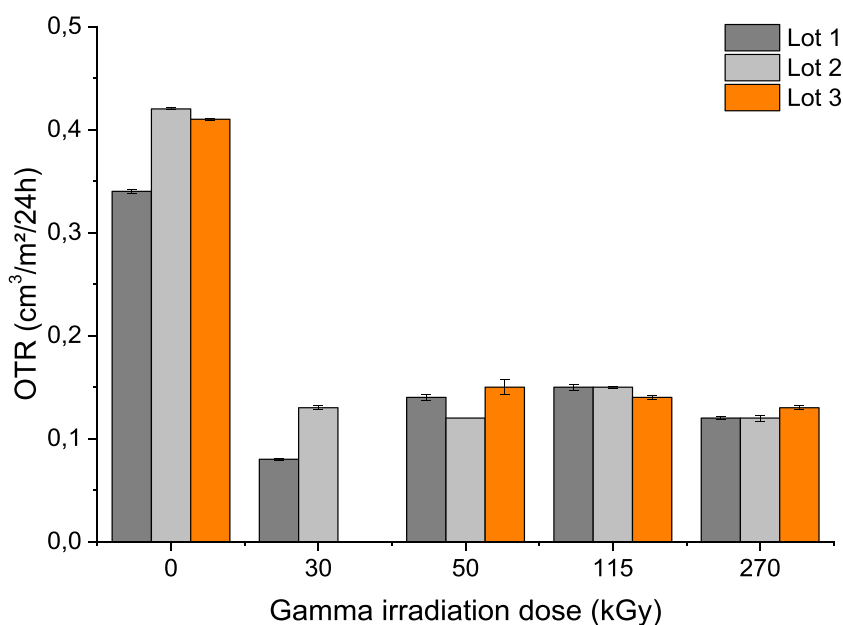


FIGURE 4 OTR of the EVA/EVOH/EVA multilayer film according to the γ -irradiation dose. EVOH, ethylene vinyl alcohol; OTR, oxygen transmission rate.

substantial changes noted in mechanical properties. The irradiated film sample shows a 300% increase in O₂ barrier regardless of γ -irradiation dose (Figure 4), assigned to the EVOH layer, which is strikingly different from the lack of effect seen on both the H₂O barrier and mechanical properties.

Mechanical test

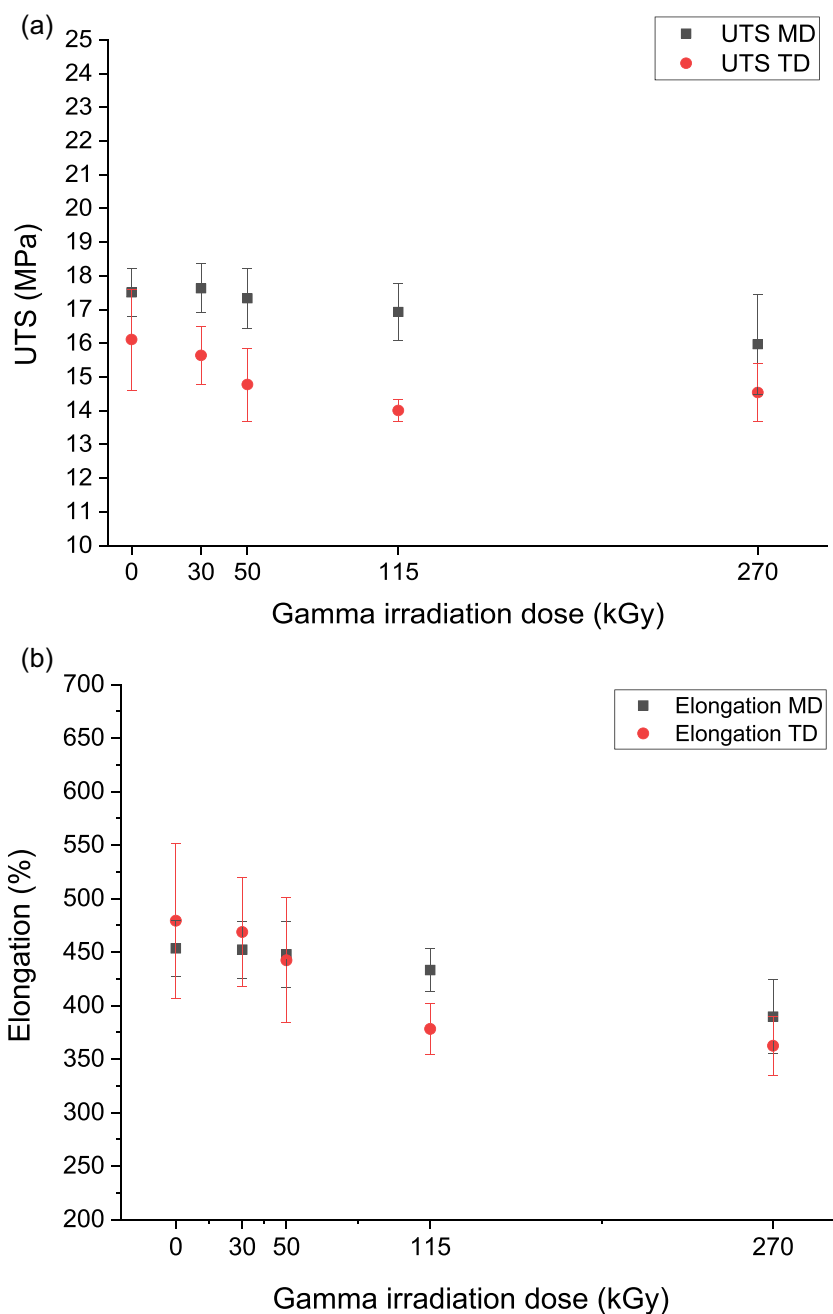
Ultimate tensile strength (UTS), yields, toughness (resistance to fracture of a material when stressed), and elongation were measured on the PE multilayer film (Figure 5). Tensile tests were executed on

the films in both machine direction (MD) (the direction in which the film is extruded/direction of polymer chains) and transverse direction (TD), which is perpendicular to MD [34].

UTS-MD and elongation increase slightly after irradiation up to 50 kGy [34]. A drop in UTS-MD is recorded for doses between 115 and 270 kGy (Figure 5). When measuring UTS and elongation in TD mode, a slight decrease in UTS is recorded for a dose between 30 and 50 kGy [34].

Orientation of chains is activated during tensile testing. If a temperature exceeds the glass transition temperature, the PE and EVOH layers react differently. PE unfolds as strain is received and shows an increase in flexibility. EVOH, however, has a higher UTS in

FIGURE 5 (a) UTS for TD and MD and (b) elongation for TD and MD as a function of the γ -irradiation dose. Each point corresponds to the average of four lots. MD, machine direction; TD, transverse direction; UTS, ultimate tensile strength.



MD tied to the frictions that occur between chains during the applied strain. PE being unchanged in thermal properties (Figure 6) demonstrates the lack of significant alteration in structure of molecular size and cross-linking that coexist with mechanical properties.

When compared to nonirradiated specimens, the PE/EVOH/PE multilayer film does not experience structural modification of significance when investigated for tensile properties during γ -irradiation doses up to ~ 100 kGy (i.e., less than 25% of elongation loss) [39]. It would be unlikely for cross-linking, chain breaking, or chain-ending events to take place at a great extent at these dose levels. When a dose greater than 50 kGy is applied, a 10°C drop of melting temperature (T_m) for EVOH is recorded (Figure 6) and correlates with chain breaking or destruction within

the H-bonding network. These changes do alter the EVOH layer's mechanical properties at a notable level.

Equivalence tests were performed thanks to Minitab[®] 19.1.1 software with 35% of variation for UTS data and 25% of variation for elongation data [39]. γ -dose of 50 kGy can be considered as the reference, as a γ -dose used to qualify multilayer films. The results will be considered as equivalent if the ratio between the averages of UTS results at 30 kGy and UTS results at 50 kGy is in the equivalence interval of (0.65; 1.35). It is the same with UTS results at 50 kGy and UTS results at 115 kGy. Regarding the elongation, the results will be considered as equivalent if the ratio between the averages of elongation results at 30 kGy and elongation results at 50 kGy is in the equivalence interval of (0.75; 1.25). It is the same with elongation

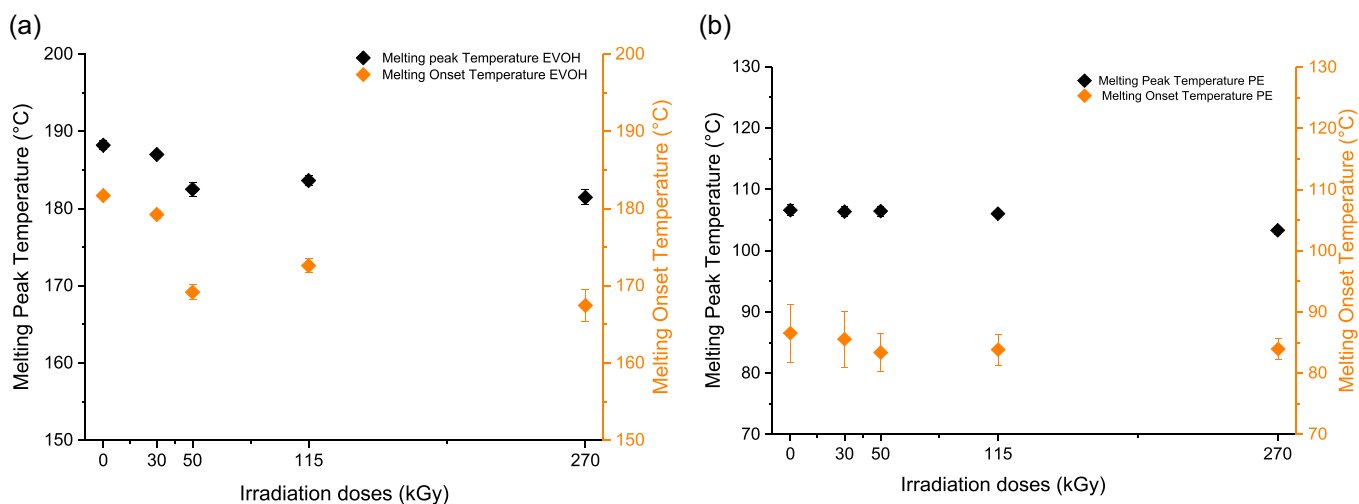
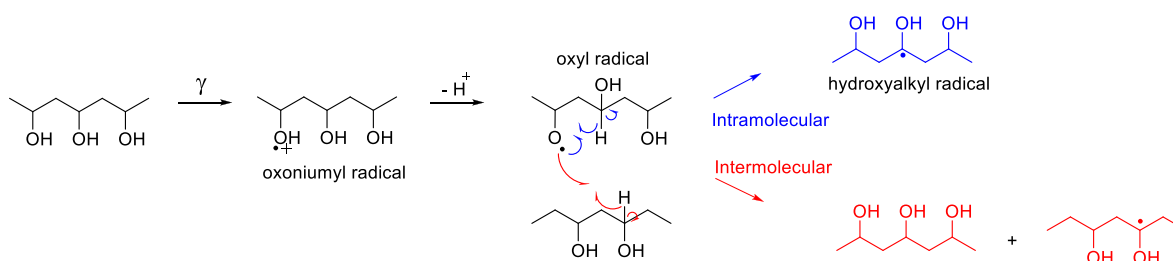


FIGURE 6 Melting points and melting onset points for the EVOH layer (a) and the PE layer (b) used in the PE/EVOH/PE multilayer film according to the γ -irradiation dose [34]. EVOH, ethylene vinyl alcohol; PE, polyethylene.



SCHEME 1 Different radical pathways to generate hydroxyalkyl radical-type

results at 50 kGy and elongation results at 115 kGy. Mechanical behavior of multilayer films irradiated at 30 kGy can be considered as equivalent to multilayer films irradiated at 50 kGy, and multilayer films irradiated at 50 kGy can be considered as equivalent to multilayer films irradiated at 115 kGy. p Values are contained between 0.000 and 0.015

Microphysical properties microscopic and chemical properties

Presence of radicals

ESR is used to research the effect of γ -irradiation doses of 30, 50, 115, and 270 kGy on AOs and the PE/EVOH/PE multilayer film; particularly, in regard to radical species that form with the duration of time. For this study, the following films and resins were investigated: monolayer PE film, monolayer EVOH film (plus resins with different grades of EVOH) and PE/EVOH/PE multilayer film.

For all γ -irradiation doses under air and vacuum, no ESR signals were present in the PE film. Generated radicals indicate their instability in room temperature air and degassed conditions [33].

EVOH film and resins under air or vacuum with γ -irradiation doses show a 1:4:1 triplet. Under air or vacuum conditions, EVOH• produced by 50 kGy of γ -irradiation are stable for 3+ months [33]. Under air, γ -irradiation of EVOH did not produce radical species with significant stability that could be detected by ESR. The exception was the EVOH• species [33]. EVOH•, being a radical that is C centered, had stability that remained identical under air and vacuum. EVOH's O_2 barrier properties are displayed by these results [33]. The PE/EVOH/PE multilayer film was sterilized in two separate campaigns: 30, 50, 115, and 270 kGy and 50 kGy. Under vacuum, the ESR signal for irradiated PE/EVOH/PE multilayer films present a sharp difference from EVOH resin and film results. Under air, irradiated PE/EVOH/PE multilayer films show ESR signals of 1:4:1 that mirror finding for EVOH resins and film. The signal for irradiated PE/EVOH/PE multilayer films remained stable for 13 weeks.

A definitive conclusion can be drawn that γ -irradiation causes hydroxyalkyl radicals in EVOH regardless of dose and experimental factor. They are likely to be three generations from the oxoniumyl radical, which spontaneously emits a proton to create an oxyl (Scheme 1). From there, a hydroxyalkyl radical is generated via H-abstraction in one of two ways: another chain or an intramolecular process (1, 4-H-transfer).

Observation of unsaturated compounds and carboxylic acids

Irradiation leads to radical production [33], which can change the structure and surface of the polymer. It is established knowledge that oxygen mixed with free radicals comes before the generation of highly reactive peroxide species, also known as reactive oxygen species (ROS).

γ -irradiations create changes in polymer films. PCA arranges surface modifications into an order based on absorbed doses and natural aging. A variation in unsaturated compounds and rising of the acid band are discovered [29].

ATR-FTIR results display the effect of absorbed dose from 0 (the unsterilized material) to 270 kGy. Observed changes in signal (Figure 7) are found in the carboxylic acid zone (about 1714 cm^{-1}) and trans alkene zone/unsaturated groups ($880\text{--}980\text{ cm}^{-1}$) [29].

These changes can be observed as we used exacerbated conditions at 270 kGy. Growth within the zones display variations that are correlated with absorbed dose. Effects of absorbed dose on film are not homogeneous. Overlap is present with 30 and 50 kGy irradiated groups and the nonirradiated group (Figure 8). Above 115 kGy, irradiation impact is notable. As absorbed γ -dose increases, so does intensity of peak at 1714 cm^{-1} as the fingerprint for C=O within acid. Amounts of aldehyde, ester, or ketone should not be excluded since there is a nonsymmetrical peak and shoulder tracked at 1714 cm^{-1} . Variation does not occur over time, which characterizes by-products as having no migration from the core layer. In addition, carboxylic acid is generated during γ -irradiation, then stays consistent [29].

XPS was utilized to find surface compositions of polymers and highlight chemical moieties created during γ -irradiation. Carboxyl groups appear on PE surfaces following bond scission from irradiation

FIGURE 7 Overlay of spectra for not sterilized and γ -irradiated PE. Inset: enlargement of carbonyl zone (left) and of trans alkene zone (right). PE, polyethylene.

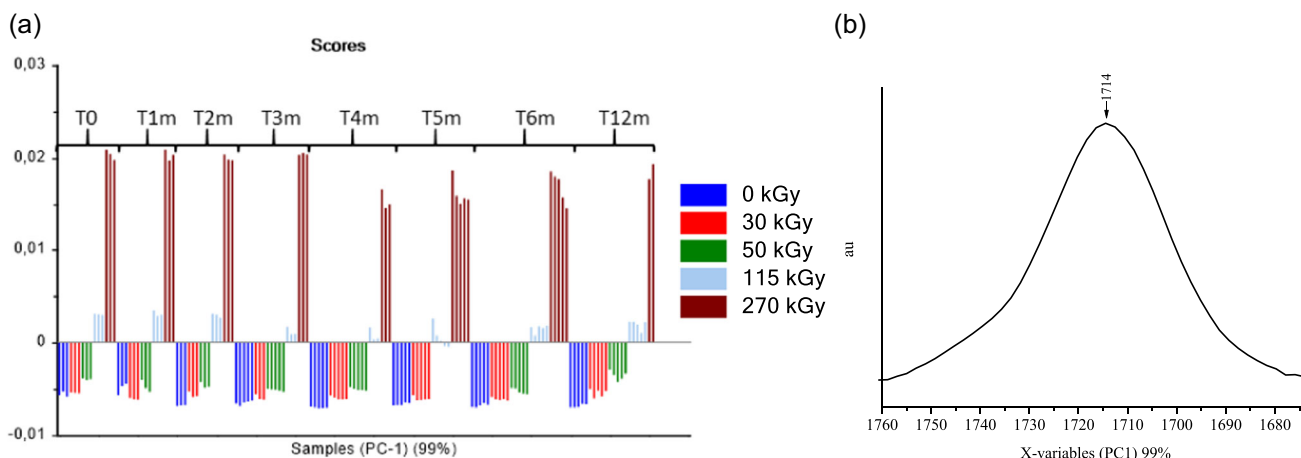
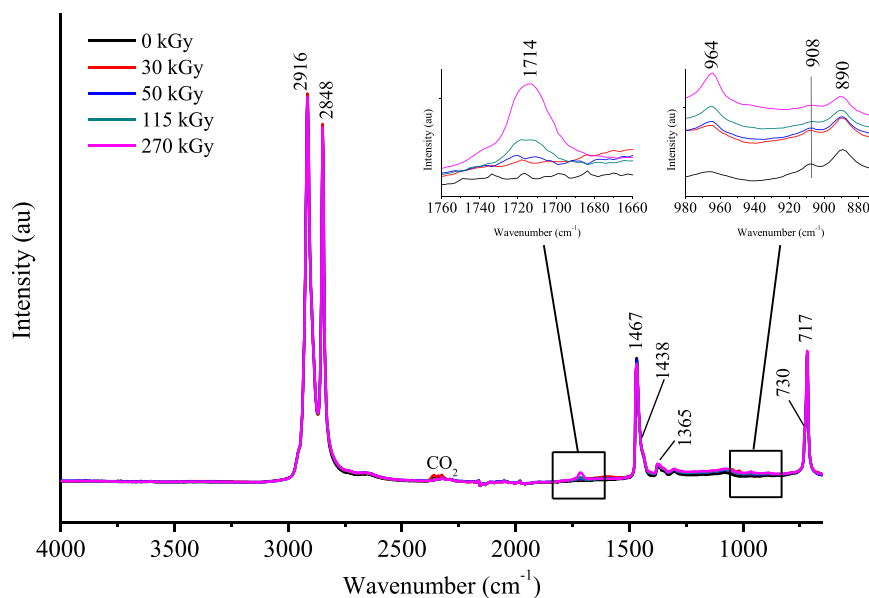


FIGURE 8 PCA of PE spectra at all γ -irradiation doses ($1760\text{--}1670\text{ cm}^{-1}$). Spectra are adjusted with baseline correction and smoothing Savitzky Golay algorithm. (a) Scores plot of PCA; (b) loading plot of PC1. PCA, principal component analysis; PE, polyethylene.

of O₂ monomer ions. Increased dosage of γ -irradiation leads to more production of oxygenated compounds. Distinguishing between aldehydes, ketones, and acids will not fit on a curve due to weak peak values. Results indicate that oxidation occurs at a weak level on a PE film. In addition, no presence of hydrogen peroxide has been detected.

When irradiating samples of the PE film, XPS analysis does not conclude that high oxygen content is present [32]. Clear identification of the chemical groups produced was not possible on PE films, and asymmetric shapes of C1s and O1s display weak intensity when it comes to forming a peak on chart. XPS did not allow for detection of hydrogen peroxides (which must exist to induce oxidation of polyolefin chains that lead to generation of oxygenated species) created during γ -irradiation [32].

Several modifications are noted in the PE chain: a peak at 908 cm⁻¹ (-R-CH = CH₂, vinyl end groups), which decreases as the absorbed dose increases, and a peak at 964 cm⁻¹ (-R₁-CH = CH-R₂, trans vinylene groups), which increases with an absorbed dose increase. Trans vinylene groups are generated by the irradiation. Vinyl end groups are degraded by irradiation. Irradiation does not change vinylidene groups. Vinylidene groups (890 cm⁻¹) undergo modifications which decrease over time. The following groups are not affected by natural aging: trans vinylene (964 cm⁻¹) and vinyl end groups (908 cm⁻¹). When nonirradiated samples are investigated for aging, no significant changes in spectra are found [29].

This study investigates two processes of aging. One shows that γ -irradiation produces polymer modifications more aggressively when oxygen is present. The other shows a minimal impact of natural aging in the vinylidene group [29].

Tracking PE and EVOH layers modification via Raman spectroscopy and SIMPLISMA treatment

Information on the fundamental vibrations of molecules can be provided by Raman spectroscopy. This process analyzes cross-sections of films before and after sterilizations of differing doses. The PE film is characterized by it with the following properties: four peaks in the EVOH layer spectrum at 3051, 1597, 1028, and 995 cm⁻¹. They should also correspond to additive compounds [30].

SIMPLE-to-use Interactive Self Modeling Analysis (SIMPLISMA) is an interactive method used to self-model mixture analysis via resolving mixture data into pure component spectra and concentration profiles without assistance from past data of the mixture. Plastics comprise a mix of additives and polymer. It will measure the purity of either a mixture or mono-material that will evolve identically during irradiation.

For the purpose of assessing variability in polymer fingerprints that are given a dose of γ -irradiation, three reconstructed spectra that underwent SIMPLISMA were obtained for the PE layer (one), the EVOH layer (one), and the additive compounds contained in the EVOH layer (one). Both PE and EVOH underwent no observed change after various γ -irradiation doses were applied [30]. Through

SIMPLISMA, we obtain the spectra of the EVOH layer's main additive compounds [30]. The fingerprints observed under Raman spectroscopy for PE and EVOH are unmodified.

The EVOH layer's concentration profile shows that additive compounds have an evolution present for an irradiation dose of 0–270 kGy. It is attributed to a decrease in intensity of the fingerprint peaks in the additive compounds (3051, 1597, 1028, 995 cm⁻¹).

γ -irradiation creates a modification that demonstrates a contribution from fluorescence. It can be seen through a drift in the baseline, which means that species with high ϵ (molar extinction coefficient) are generated. Fluorescence is caused by many minor and unidentified compounds which exhibit it. They are not strong enough to have bands detected by Raman spectroscopy. Profiles of constant concentration for PE and EVOH layers conclude that they are not impacted by γ -irradiation, but variations of these profiles for the EVOH layer's additive compounds display the impact of it. The γ -irradiation dose has no correlation with changing the Raman PE and EVOH fingerprints. For example, any modification of the PE or EVOH polymers is not detectable, and integrity of the polymer is preserved. γ -irradiation does impact additive compounds found within the EVOH layer, as they degrade into byproducts on purpose.

The PE film's entire structure is not ruined during γ -irradiation during modifications at the additive package level; in other words, functional attributes are not lost.

Tracking PE layer evolution over time via FTIR spectroscopy and AComDim treatment

To highlight the contributing factors leading to modification of the PE multilayer film during γ -irradiation and time periods, the AComDim method was applied on FTIR spectra. The factors that contributed to the greatest changes were the γ -dose, the γ -dose, and its combination with aging and natural aging recorded up to the 6-month mark. Over time, the PE film produces a linear variation (the EVA film layer does not) upon being combined with γ -irradiation, and it is suggested that cross-linking and scission events occur [35]. Both the irradiated and nonirradiated PE samples present changes in signal at the carboxylic acid zone (near 1714 cm⁻¹) and trans alkene zone (880–980 cm⁻¹). When the γ -dose increases, the peak is measured at 1714 cm⁻¹, and corresponds to carboxylic acid. Therefore, γ -irradiation may contribute to polymer oxidation. For the trans vinylene group (-R₁-CH = CH-R₂), a peak of 964 cm⁻¹ is identified. It increases when the γ -dose is raised. Natural aging does not appear to have an effect on carboxylic acid. The modifications induced in PE film evolve linearly over time (Figure 9).

Content/containing interaction

Acidity indirectly weighs the present amount of carboxylic acid, and oxidized methionine measures peroxide moieties indirectly. Both factors were studied. The peroxide moieties are present after γ -irradiation but cannot be directly detected.

Acidity

Conductivity and pH variations are direct consequences of the presence of carboxylic acids extracted and generated according to the γ -irradiation dose. In a sample with storage time greater than 7 days, dispersion is present within each series of data correlating to the γ -irradiation dose. Carboxylic acids in solution and contact with the PE film accumulate due to migration from the material core to the solution, not because of direct solvation of acids

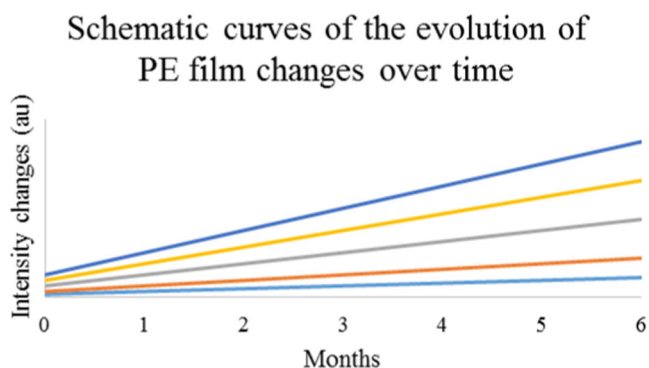
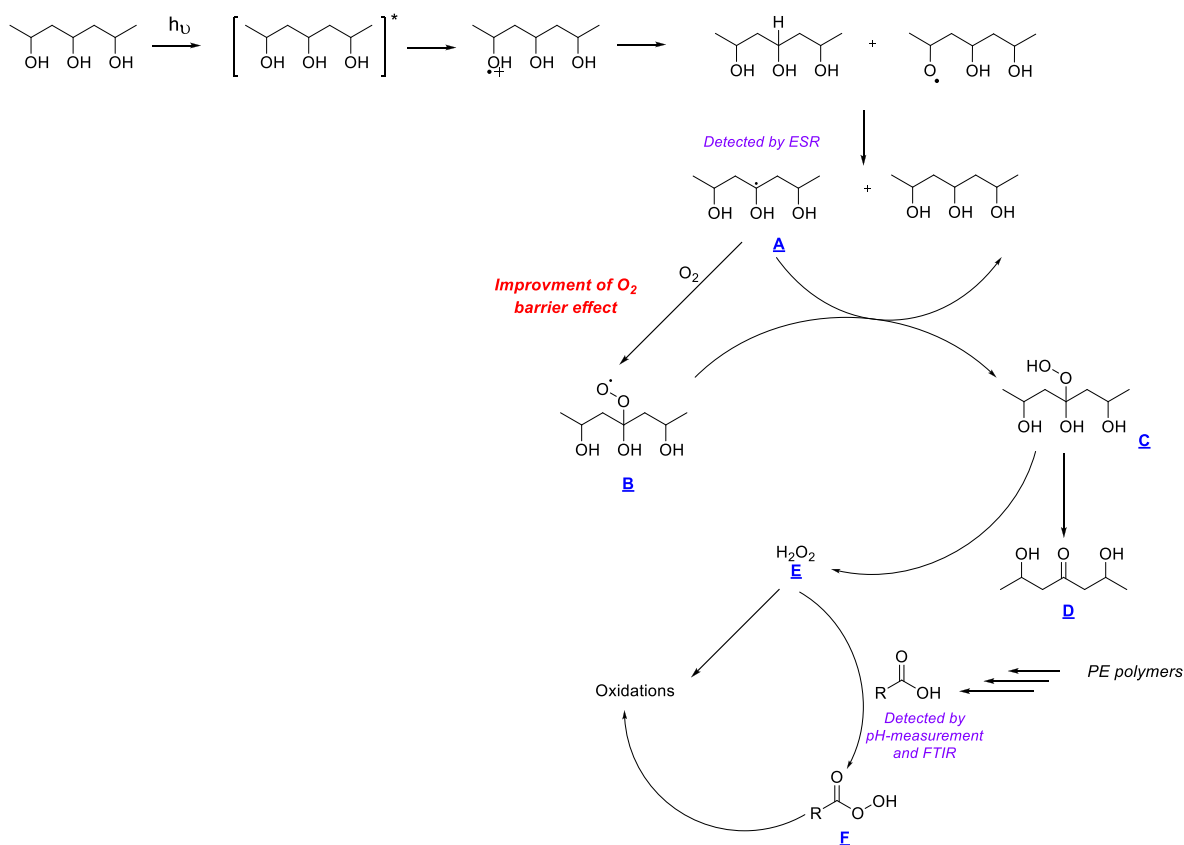


FIGURE 9 Schematic representation of the changes over time for the materials. 0 kGy corresponds to the lowest curve and 270 kGy to the highest curve. PE, polyethylene.

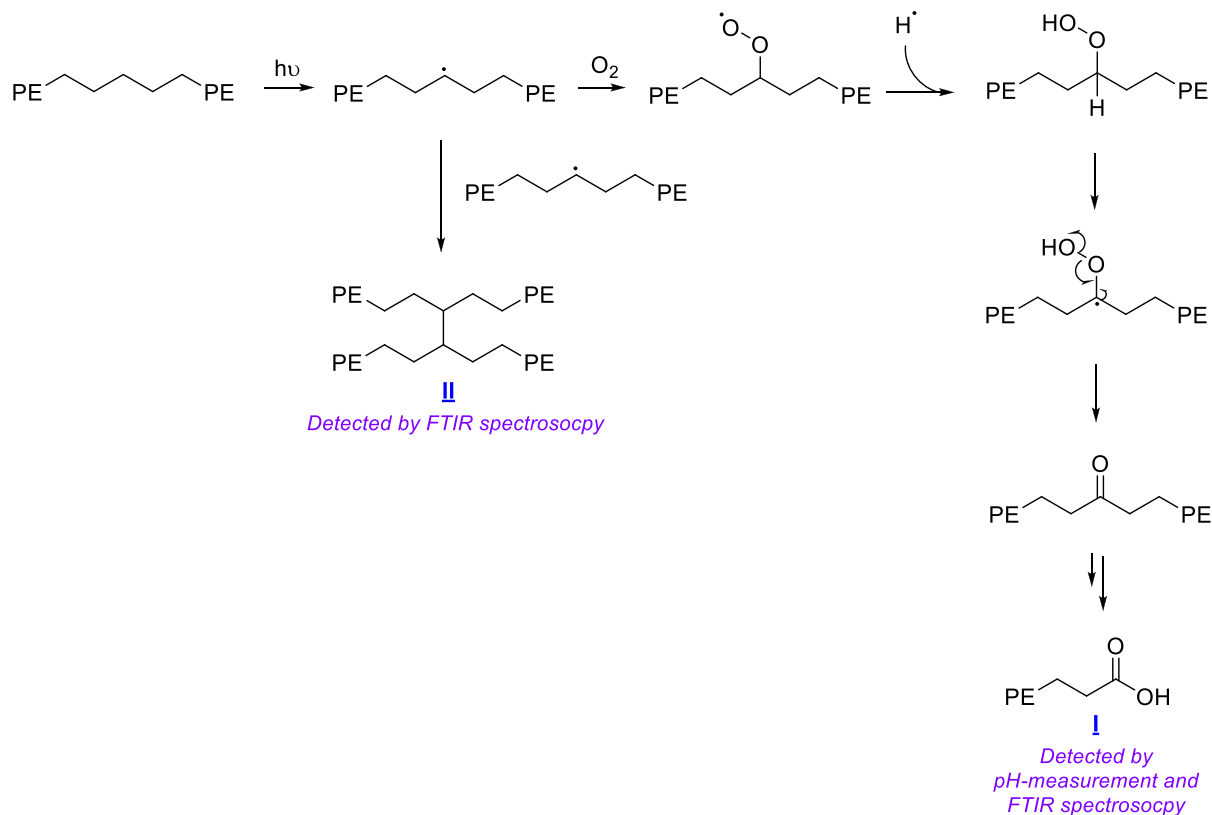
detected on the film's surface after γ -irradiation [20]. To calculate pH and conductivity from IC, the PE film is placed in contact with aqueous solution.

IC has been used to study the impact that γ -rays and aging may have on ionic species that might be created. PE film in contact with aqueous solution results in acid concentration between 10^{-5} and 10^{-8} M [31]. Ethanoic acid is the most concentrated of the acids. In the same order of concentration (10^{-6} M) are hexanoic, pentanoic, butanoic, propanoic and methanoic acids [31]. They contribute equally to pH shift. Other detectable acids (lactic, acrylic, maleic...) are present in trivial amounts (10^{-7} – 10^{-8} M) [31]. Their contribution to pH shift is ignored. In aqueous solution, ethanoic acid is 10 times lower in concentration from the PE film ($\sim 3.10^{-5}$ M) than it is on EVA [31]. Theoretical pH is calculated when carboxylic acid's amount is measured by IC. When aqueous solutions are in contact with PE-film, differences of 0.1–0.2 a.u. differentiate measured pH values from calculated ones [31].

The amount of carboxylic acids produced is contingent on film material and subsequent increase in γ -dose levels. PE film had limited changes indicated when PCA analyzed the link between TOC and carboxylic acids. Low tendencies are due to small amounts of extractables present [31]. The PE film has 10 times less acid released than the EVA film. This result correlates with a prior XPS measurement finding [32], which showed weak oxidation present on the PE film.



SCHEME 2 EVOH reactivity after γ -irradiation. EVOH, ethylene vinyl alcohol.



SCHEME 3 PE reactivity following γ -irradiation. PE, polyethylene.

The chemistry behind the effects of γ -irradiation

The paragraph about permeability concluded that the PE/EVOH/PE multilayer film, once γ -irradiated, was more impermeable to oxygen. Scheme 2 shows a recap of EVOH reactivity following irradiation.

After EVOH undergoes γ -irradiation, it produces hydroxyalkyl radicals **A** that react with O_2 present in the environment. In situ peroxy radicals **B** then form, tearing away the hydrogen atoms in α position, and creating a new alkyl radical able to react with oxygen that is present. A barrier effect follows. An H atom can be added by peroxy radicals **B**, which can also give a hydroperoxide **C**. The molecule can now release H_2O_2 **E**. After acid and H_2O_2 interact, peracetic acid **F** is released following the reaction. Both carboxylic and acetic acids have previously been discovered in prior studies **F**. As a result, it is known that H_2O_2 can oxidate solution when it comes in contact with and has exposure to the PE/EVOH/PE multilayer film.

The Scheme 3 demonstrates the creation of carboxylic acid **I** that was noted by previous studies. Following γ -irradiation, PE appeared to generate more specimens of crosslinking than samples that did not undergo irradiation. This discovery was captured by FTIR spectroscopy and drawn by molecule **II**. All phenomena that had a reaction and are present on the PE film are capable of decreasing PE's crystallinity following γ -irradiation.

CONCLUSION

Results demonstrate how γ -irradiation affects the PE/EVOH/PE multilayer film. When applying the standard pharmaceutical doses of 25–45 kGy, and from a worldwide viewpoint, the observed findings are weakened, while the high doses of irradiation (greater than 50 kGy) are not. At doses of 115 kGy, no shattering impact is found. Via byproducts found in the additive package, γ -irradiation does produce chromophore compounds, including phosphite, phenol and the polymer matrix.

Techniques utilized for this study included colorimetry measurements, tensile tests, FITR spectroscopy, TOC measurement and IC, pH measurement, XPS, conductivity measurement, and various mechanical property measurements. Also utilized were OTR, DSC, and WVTR. For chemometric testing, methods including AComDim and PCA were applied.

Results from techniques were noted at physical, chemical, and optical levels. The water barrier (especially the PE layer) remains unchanged during all doses of irradiation during bag handling. At doses up to 50 kGy, mechanical properties remain unaltered during γ -irradiation doses, and this is confirmed by equivalence tests performed between mechanical results obtained at 50 and 115 kGy.

When H-atoms are lost or radical cations on the hydroxyl or carbonyl functions are generated, radicals are produced by the EVOH

polymers. Optically, varying degrees of yellow discoloration do appear on the EVOH layer, but they are temporary. The smell of acetic acid is also produced.

In addition:

- XPS analysis does not find high oxygen content when γ -irradiating PE film samples.
- Upon using the SIMPLISMA method under Raman spectroscopy observation, concentration profiles remain constant for PE and EVOH layers. Raman's PE and EVOH fingerprints do not change at any γ -radiation dose, resulting in no detectable degradation of PE and EVOH polymers. Additives degrade into byproducts at the package level, but do not lose their functional attributes.
- Conductivity, pH and TOC measurements are applied to samples irradiated at varying γ -doses. The highest dose is 270 kGy and is contrasted with a nonirradiated sample. Findings show that the amount of carboxylic acids that are generated correlate with film material (either PE/EVOH/PE or EVA/EVOH/EVA) and increase with a higher γ -dose.

Globally, there is no impact of γ -irradiation on the multilayer film, and no permanent impact is recorded on manufactured single use systems for biopharmaceutical/biotechnological applications.

Other existing sterilization processes are not utilized in this study, including e-beam sterilization and X-ray sterilization. Their impacts in regard to the γ -irradiation impacts will be investigated in future studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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