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ABSTRACT

To protect from the external environment the solutions stored in the single use plastic bags used in the biopharmaceutical industry, perfect sealing of the bag is necessary to maintain confinement integrity. These single use plastic bags are manufactured from two different multilayer films, an EVA (ethyl vinyl acetate)/EVOH (ethyl vinyl alcohol)/EVA film and a PE (polyethylene)/EVOH/PE film. The EVA or PE contact layer provides chemical biocompatibility with the bag content (biological solution, food, etc.) in contact with the plastic while the EVOH layer provides oxygen barrier properties. Our first objective was to study the impact of the gamma irradiation dose (from 0 kGy to 270 kGy) on the mechanical tensile behavior of the seals. Our second objective was to evaluate the impact of the location of the seals on their tensile properties. The study showed that the seals are never impacted during tensile testing: this evaluation reveals that *in fine* cracking of the film occurs before any modification of the seal. Its function of closure and content protection from the external environment is fully achieved, whatever the gamma irradiation dose and the seal location. Only the multilayer film on both sides of the seal is altered after 100 % elongation strain. The EVA/EVOH/EVA and the PE/EVOH/PE multilayer films showed no degradation for a y-irradiation dose up to 115 kGy whereas they were altered at 270 kGy. The seals at different locations on the EVA bag showed different film mechanical behaviors, in correlation with the orientation of the polymer film extrusion process.

1. Introduction

Plastic bags used in the biopharmaceutical and food industries are designed for the preparation and storage of biopharmaceutical solutions and foods, among other things. To protect their content from the external environment, these bags must be hermetically closed, meaning they must not present any opening affording contact between the solution with gas or microorganisms and they must prevent any loss of the substance they contain (Brown et al., 2000; Hron & Macák, 2013). To satisfy these criteria, plastic bags are composed of appropriate multilayer polymer films such as polyethylene/ethyl vinyl alcohol/ polyethylene (PE/EVOH/PE) or ethyl vinyl acetate/ethyl vinyl alcohol /ethyl vinyl acetate (EVA/EVOH/EVA) providing sealing and gas barrier properties (Dorey et al., 2019; Dorey et al., 2020).

The technique used in the packaging industry to seal two plastic films is the direct bonding technique (Amanat et al., 2010). The main advantage of direct bonding is that no other material or adhesive is used to join the films. Direct bonding principle consists in, in a first step, heating the polymer (close to its melting temperature) at the interface, which provokes an inter-diffusion of the polymer chains and, in a second step, cooling the polymer to allow seal consolidation (Amanat et al., 2010).

Depending on the type of heat generation, the direct bonding techniques can be classified as: thermal bonding, friction bonding and electromagnetic bonding (Stokes, 1989). With the increase in new materials and components and in the aim of covering a large panel of applications, complementary techniques have been developed besides these three direct bonding techniques (Stokes, 1989). Indeed, the thermal bonding techniques are classified as hot gas sealing, extrusion sealing, hot-tool (hot-plate) sealing, and infrared heating. The friction sealing techniques are classified as spin sealing, angular vibration sealing, orbital sealing, vibration sealing, and ultrasonic sealing. Finally, the electromagnetic bonding techniques are subdivided as resistance sealing, induction sealing, high frequency sealing, and microwave heating (Stokes, 1989). In this study, to seal two multilayer films and form a single-use bag, two main techniques are used: the hot tool sealing and the high frequency sealing. The hot tool sealing technique makes it possible to melt the polymer between two plates previously subjected to Joule heating. The sealing is performed during the cooling under pressure. For the high frequency sealing, a high frequency generator causes a discharge between two cold electrodes holding the polymers to join. The fusion is produced by induction (REYNE, 2020).

In the biopharmaceutical industry, to ensure the function of closure and non-contamination from the external environment, the sealing must fulfill several parameters taken as guidelines from the standards (ASTM D882, 2012; ASTM F2097, 2008ASTM F2097, 2008; ISO 15747, 2018). The film/film seal must show no bubble, water ingress, channel, or fold, and its width must be constant. The bag must present the same parameters as the film/film seal, showing no leak or pressure decay (ISO 15747, 2018).

After their manufacturing, biopharmaceutical bags are sterilized by ionizing radiation (mainly by gamma rays) to reach the Sterility Assurance Level (S.A.L) target and prevent the presence of microorganisms inside the bags. It is well known that polymers can be modified under gamma irradiation. Irradiation causes the formation of radical species, leading, in the presence of other organic compounds to the formation of unsaturated compounds and carboxylic acids (Gaston et al., 2016a, 2016b). The pH of water stored in biopharmaceutical bags may decrease, this acidification being due to the formation of carboxylic acids, such as ethanoic acid (Dorey et al., 2018; Manso et al., 2015; Yoshida et al., 2014). Also, irradiation can cause polymers to change color (Gaston et al., 2018) – because of changes in the color of the antioxidants present in the polymer recipe. A number of studies have been published dealing with the seal mechanical properties in the aim to achieve the best possible optimization of the sealing process (Küçükrendeci, 2019; Mehrpouya et al., 2019). However, very few studies deal with the impact of gamma irradiation on plastic seals (Wang et al., 2018) and even fewer report on the mechanical behavior of gamma irradiated seals (B.G. Porto et al., 2018).

The aim of our study was to investigate the seal resistance during handling by studying the seal mechanical tensile behavior after sterilization by gamma irradiation. The seals were qualified with optimized parameter settings prior to irradiation. To do so, tensile tests were performed on the seals of two lots of PE/EVOH/PE bags and EVA/EVOH/EVA bags, for different gamma irradiation doses (0, 30, 50, 115 and 270 kGy) and for different seal locations in the EVA and the PE bags. Seal mechanical resistance results were analyzed and discussed using the chemometric technique of Principal Component Analysis (PCA), and the benchmark method for data analysis (Esbensen et al., 2006; Kumar et al., 2014; Martens & Naes, 1989).

2. Material & methods

2.1. Samples

The two types of single-use plastic bags investigated were made of two different multilayer films (Fig. 1): an EVA film, composed of one layer of ethylene vinyl alcohol (EVOH) sandwiched between two layers of ethylene vinyl acetate (EVA) (total thickness ~360 μm) and a PE film, composed of one layer of ethylene vinyl alcohol (EVOH) sandwiched between two layers of polyethylene (PE) (total thickness ~400 μm). To evaluate any lot effect, two different lots were studied. For the multilayer film extrusion process, two directions were taken into account as per ISO527 (ISO 527-1, 2019): machine direction (MD), along the direction of the polymers chains during the extrusion process, and transversal direction (TD), perpendicular to MD.

2.2. Gamma irradiation

EVA bags and PE bags were wrapped in PE-packaging and irradiated at room temperature by a ^{60}Co gamma source. This ^{60}Co gamma source provides a dose rate of 10 ± 3 kGy/h - as given by Synergy Health Marseille (France) - affording doses of 30 (± 1), 50 (± 1), 115 (± 2) and 270 (± 5) kGy. The targeted dose was obtained after several cycles of 25 kGy.

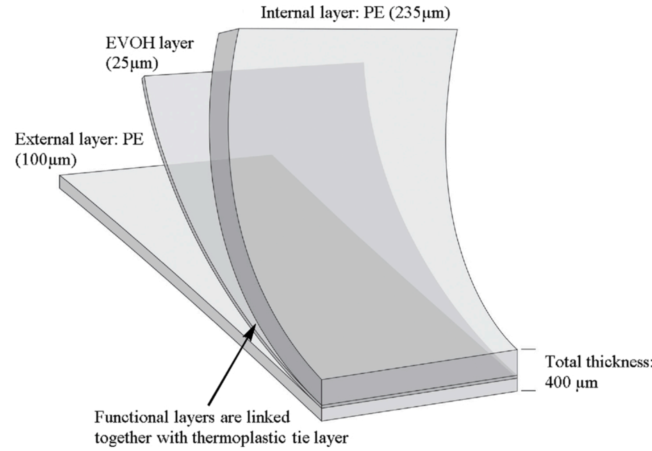


Fig. 1. Example of PE bag.

2.3. Sealing

2.3.1. EVA bag manufacturing

The EVA bag (Fig. 2a) were manufactured using the high frequency sealing technique (electromagnetic bonding). Two lots (corresponding to two different sizes of bag, 4 L and 50 L) as well as three bags from each lot, irradiated at five different gamma doses (0, 30, 50, 115 and 270 kGy), were investigated. Five different seal locations were selected, locations 3 and 4 being selected to study sealing at the corners.

2.3.2. PE bags manufacturing

The PE pre-made bags (Fig. 2b) were manufactured using the hot-tool (hot-plate) sealing technique (thermal bonding). Two lots, corresponding to different sizes of bag, 200 L and 100 L) as well as two bags from each lot, irradiated at five different gamma doses (0, 30, 50, 115 and 270 kGy), were investigated. Sixteen different seal locations were selected. Only the longitudinal seals were studied here (orange lines).

2.4. Tensile tests

The mechanical properties of irradiated and non-irradiated seals were measured using a universal testing machine, Zwick Z005. The specimens were cut according to ASTM F88/F88 M (ASTM F0088, 2015) (150 mm length, 15 mm width). More details are provided in a previous article (Dorey et al., 2019). Seal strength is expressed in N per a 15 mm width specimen (N/15 mm).

The different sample locations were selected in order to study the mechanical resistance of the seal all over the bag. For the EVA bags, five samples were cut corresponding to five different seal locations, as shown in Fig. 2a. As for the PE bags, 16 samples were cut corresponding to 16 different seal locations, as shown in Fig. 2b.

2.5. Principal component analysis and software

PCA is a multivariable technique used to reduce a larger set of variables to a smaller set of variables called “principal components” (Martens & Naes, 1989). The principal components represent the highest variances in the original variable matrix. All computations were performed using the Unscrambler x 10.5 software.

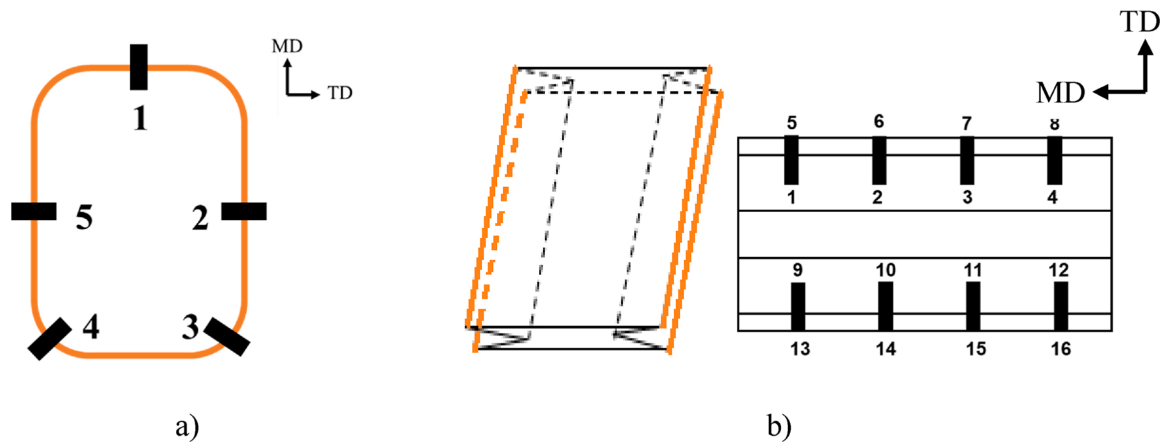


Fig. 2. Five seal locations on EVA bags (a) and 16 seal locations on PE bags (b). Black dashes correspond to seal samples (1-5 for (a) and 1-16 for (b)). Orange lines show where sealing is performed.

3. Results & discussion

Each tensile curve was decomposed into 6 characteristic values which were evaluated with PCA: Ultimate Tensile Strength at Break (UTS), Ultimate Elongation or Elongation at Break, 1st Yield-Strength (Y1 Strength), 1st Yield-Strain (Y1 Strain), 2nd Yield-Strength (Y2 Strength), 2nd Yield-Strain (Y2 Strain). Ultimate tensile strength at break and ultimate elongation are defined as the maximum strength and maximum elongation which the material can withstand (ISO 527-1, 2019). Yield strength (or strain) is the strength (or strain) level at which plastic deformation initiates. Importantly, in this section, regarding the EVA and PE bags, the seal part is never damaged during

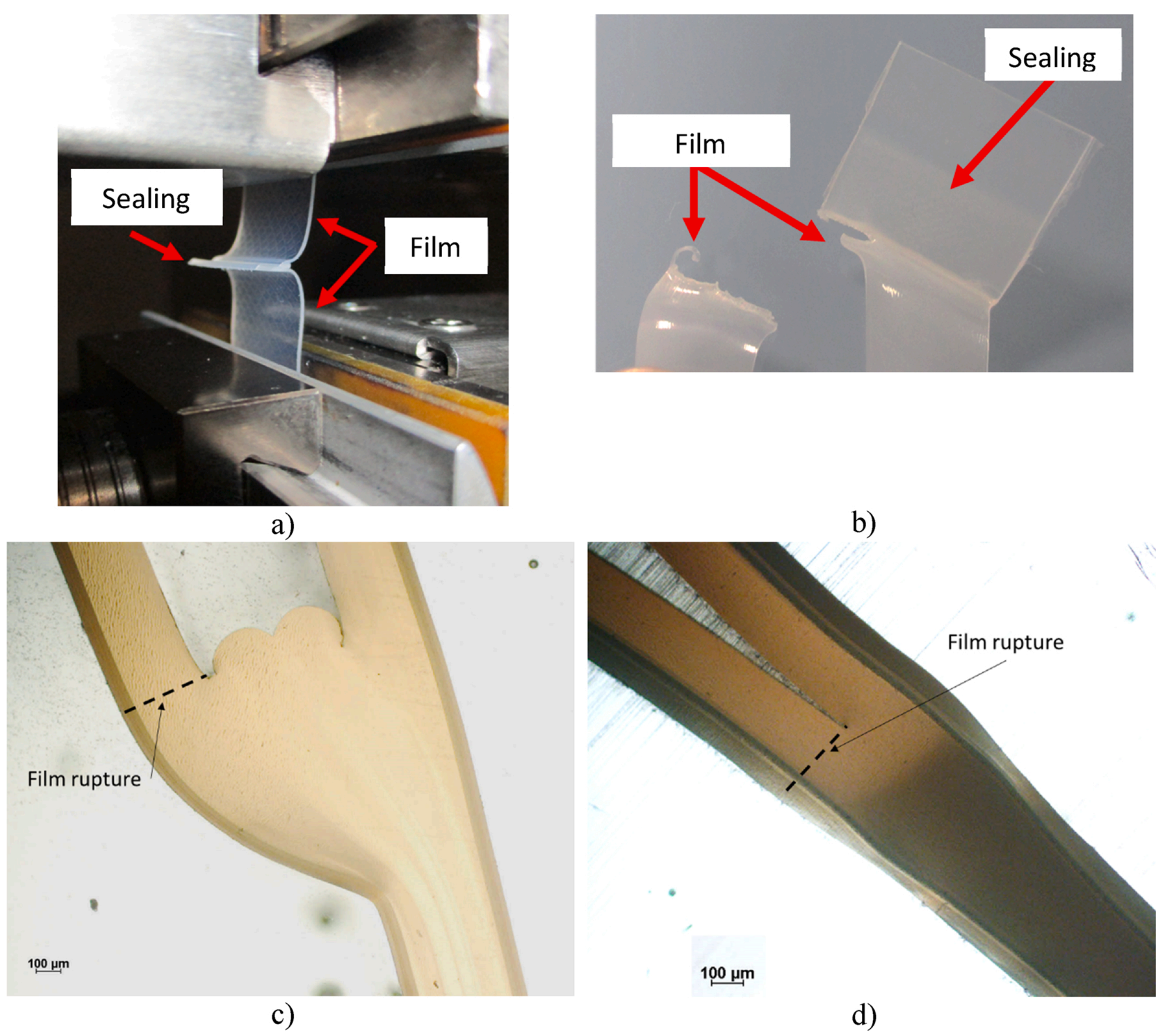


Fig. 3. Example of one of EVA seals before the beginning of the tensile test (a) seal after the end of the tensile test. The seal was not impacted by the test (no opening, no break), only the film was broken (b). Optical microscope pictures of the EVA bag seal (c) and PE bag seal (d).

the mechanical test. This means that only the film part is broken by the strain applied (Fig. 3). As observed in Fig. 3b-d, the seal shows no opening or tear and no delamination takes place. Once the interpenetration of the polymer chains has occurred, the seal then keeps its function of sealing, whatever the gamma irradiation dose and the seal location. The film/film sealing was performed with optimized parameter settings prior to irradiation and no defects, such as bubbles, infiltrations, channels, or folds, were visually observed after gamma irradiation and before tensile testing. The seal width remained constant after the gamma irradiation treatment.

3.1. EVA bags

The strength-strain curves for the sealing performed on the EVA bags are displayed in Fig. 4. There are two different groups of curves, depending on the seal location. The curves at the top of the figure represent seals 1,3 and 4, while the curves at the bottom of the figure represent seals 2 and 5. For a thorough study, PCA was performed on the six characteristic points of all EVA strain strength curves (Fig. 5a and b). This PCA analysis provides a quantitative discussion about the variability of each factor and highlights any inter-dependence between parameters (i.e., Ultimate Tensile Strength (UTS), Y1 Strength, Y1 Strain, Y2 Strength, Y2 Strain).

Fig. 5a shows the correlation between the six characteristic points of the tensile curve. On the one hand, Y1 Strength, Y2 Strength and Ultimate Elongation are correlated. UTS, Y1 Strain and Y2 strain are correlated. On the other hand, Y1 Strength, Y2 Strength and Ultimate Elongation are anti-correlated with UTS, Y1 Strain and Y2 strain. Indeed, these two groups are both in the same hemisphere but in different quadrants. The start of the plastic deformation (Y1) is linked to the break. In Fig. 5b, the first and second components account for 78 % of the variance. The first component, which represents 54 % of the total variance, is linked to the seal location. Seals 1,3 and 4, in blue, green and grey, respectively, are separated from seals 2 and 5, in red and dark red (Fig. 5b). This observation indicates that seals 1,3 and 4 have a different mechanical behavior from seals 2 and 5, as shown in Fig. 4. Seals 1,3 and 4 display an earlier rupture, a higher UTS and a lower ultimate elongation value. The Y1 Strength and Strain and Y2 Strain values are the same for both groups whereas the Y2 Strength is higher for seals 1,3 and 4 than for seals 2 and 5.

The separation of these two groups is accounted for by the direction of the film extrusion. Seals 1,3 and 4 exhibit the same mechanical behavior as the EVA/EVOH/EVA multilayer film, when they are analyzed in Machine Direction (MD) mode (the direction of the polymers chains) and seals 2 and 5 exhibit the same the same mechanical behavior as the multilayer film when analyzed in Transversal Direction (TD) mode (perpendicular to the polymers chains) (Dorey et al., 2020).

The EVA bag seals thus have the same mechanical behavior as the EVA/EVOH/EVA multilayer film, depending on the direction in which the seals are analyzed. However, tensile results for the EVA/EVOH/EVA multilayer film along the machine direction reveal a lower ultimate tensile strength at break. This observation confirms once again that the seal part is not damaged during the tensile test.

PCA is performed on seals 1,3 and 4 (Fig. 6a and Fig. 6b) and on seals 2 and 5 (Fig. 6c and Fig. 6d), as Fig. 4 shows different UTS and ultimate elongations according to the gamma dose within these two groups.

As for seals 1, 3 and 4 (Fig. 6a), the UTS, Ultimate Elongation, Y2 Strength, Y2 Strain are correlated and observed along PC1. Y1 Strength and Y1 Strain are correlated between them (and not correlated with the others) and observed along PC2. The influence of gamma irradiation is represented along PC1 (Fig. 6b). Gamma irradiation is correlated with UTS. The 270 kGy samples (green points) are away from the 115 kGy, 50 kGy, 30 kGy and 0 kGy samples (red, brown, grey and blue points, respectively.) For the bags irradiated at doses higher than 115 kGy, the seals break earlier (low UTS and Ultimate Elongation) than with lower irradiation doses.

For seals 2 and 5, PCA is performed, showed in Fig. 6c and Fig. 6d. The correlations between parameters are different in this case from those obtained for seals 1,3 and 4. These differences observed with the correlation loadings of both groups of seal locations (Fig. 6a and c) confirm once more the different seal mechanical behaviors according to the seal location and according to the polymer chain orientation. In this case, UTS, Ultimate Elongation, Y2 Strength and Y1 Strength are observed along PC1. UTS and ultimate elongation on the one hand and Y2 Strength and Y1 Strength on the other hand are anticorrelated. Y1 Strain and Y2 Strain are non-correlated and observed along PC2. The influence of gamma irradiation is represented along PC1 (Fig. 6d).

The same observations are obtained for seals 1,3 and 4 vs 2 and 5; for bags irradiated at doses higher than 115 kGy, the seals break earlier (low UTS and Ultimate Elongation) than with lower doses. Moreover, Y2 strength and Y1 strength increase with the gamma dose.

Fig. 7a represents UTS as a function of the gamma dose. As observed before in Fig. 4, the UTS values for seals 1, 3 and 4 are higher than those for seals 2 and 5. For non-sterile, 30 kGy, 50 kGy and 115 kGy irradiated bags, seals 1, 3 and 4 have a UTS ~ 40 % higher than seals 2 and 5. This value is lower for the 270 kGy dose with a difference of ~25 %.

For seals located at positions 2 and 5 (black square), the UTS increases slightly from 0 kGy to 30 kGy (~10 %), seems to reach a plateau from 50 kGy to 115 kGy (~45 N), and decreases from 115 kGy to 270 kGy (~20 %) to reach 38 N. As for seals 1,3 and 4 (red spheres), the UTS shows the same increase from 0 kGy to 30 kGy and reaches the same plateau for 30, 50 and 115 kGy, whereas the decrease is more significant from 115 kGy to 270 kGy (~37 %). In conclusion, the UTS, and therefore the mechanical behavior, is significantly affected for seals irradiated at doses higher than 115 kGy. This represents the film behavior after ionizing radiation. This is explained by the fact that with gamma irradiation the chains are less flexible and they will then start to break, because of a lower tensile strength (Dorey et al., 2019; Dorey et al., 2020).

Fig. 7b shows the ultimate elongation (or elongation at break). The same tendency is observed for the two seal types (2 and 5 vs 1, 3 and 4): the ultimate elongation would be maximal at 30 kGy and remain constant in the range 50-115 kGy.

The resistance strength of the film in contact with the seal is lowered by 35 % for the TD mode (corresponding to seals 2 and 5) and 58 % for the MD mode (seals 1, 3 and 4). For Ultimate Elongation, the film in contact with the seal shows values ~35 % lower (for both types of seal, i.e., 2,5 and 1,3,4.) (Dorey et al., 2020).

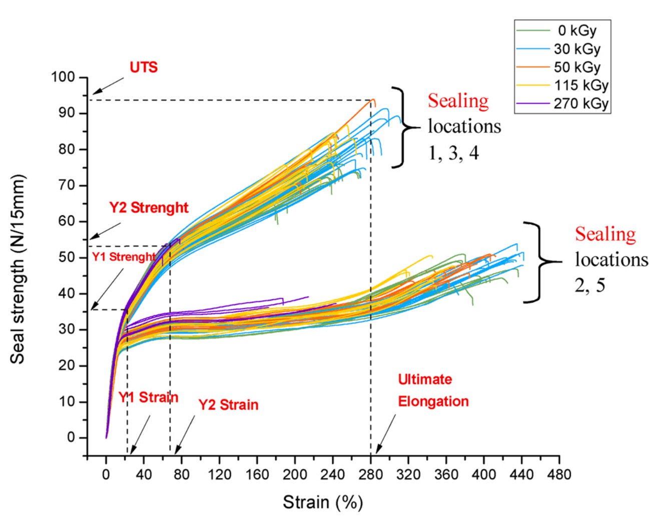


Fig. 4. Strength-strain curves for each seal location (1-5) and each gamma dose (0-270 kGy) for the EVA bags. Colors according to gamma doses.

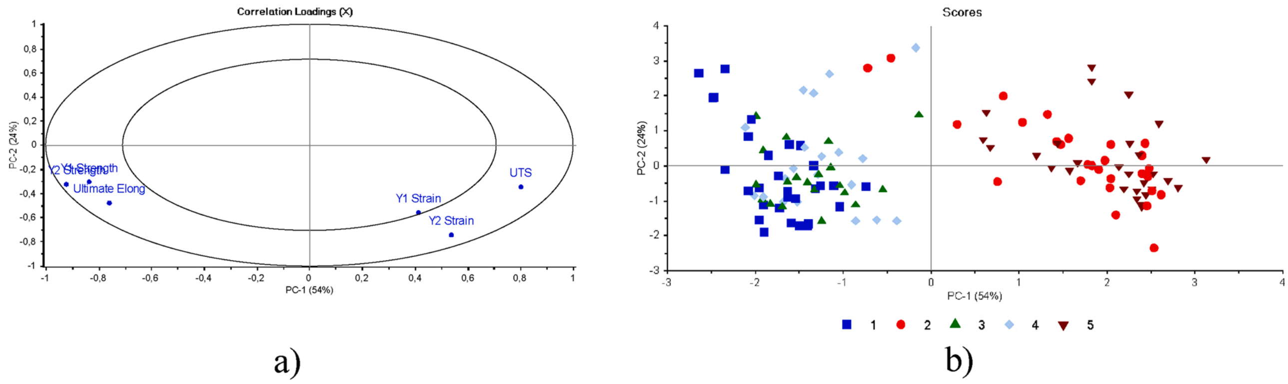


Fig. 5. PCA performed on the six characteristic points of each tensile curve for the EVA bags obtained for the 2 lots and all the gamma doses. a) Score plots with seal locations. b) Correlation loading (ellipses represent, from outside to inside, 75 % and 100 % of the correlation).

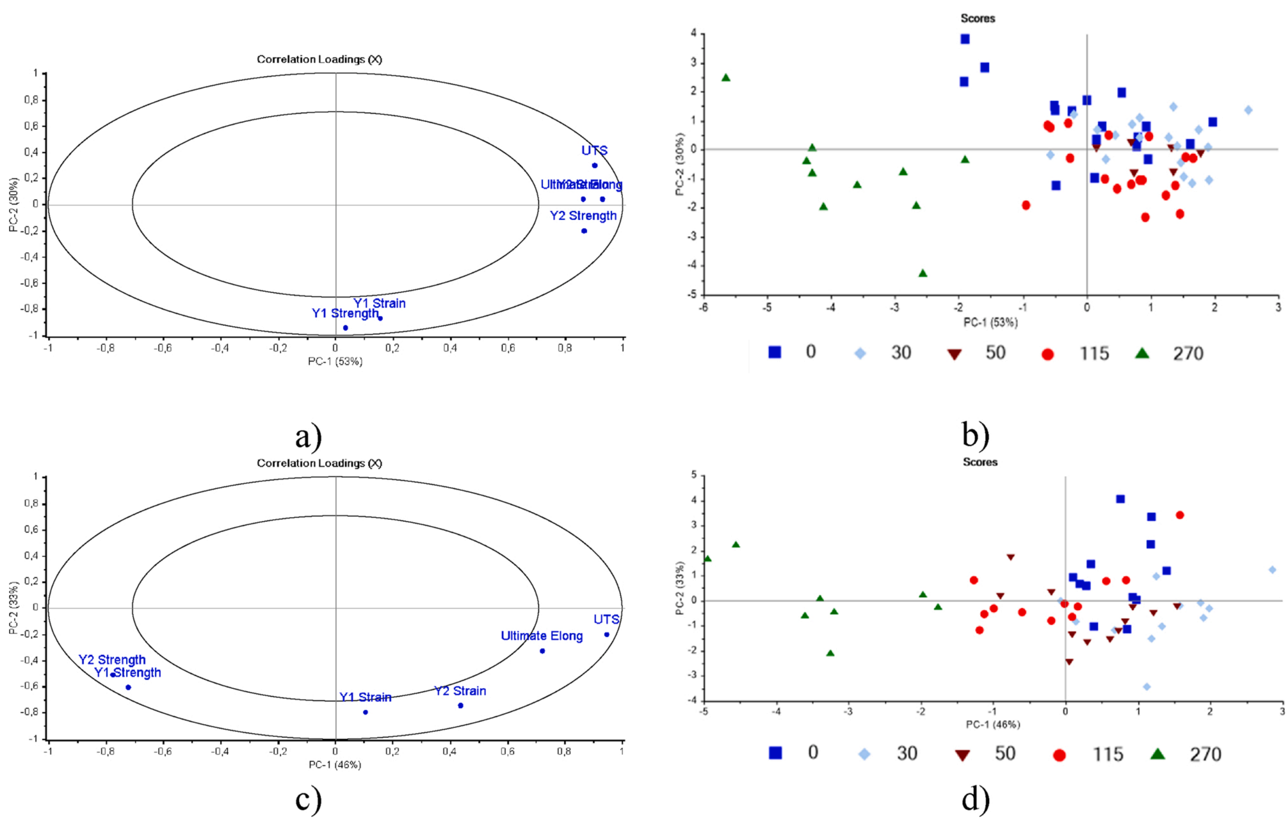


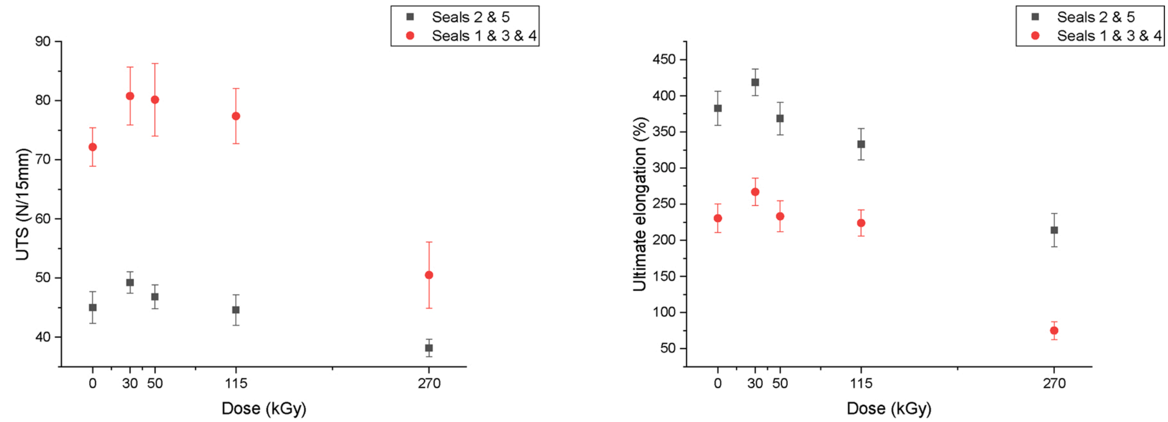
Fig. 6. PCA performed on the six characteristic points of each tensile curve for the EVA bags obtained for 2 lots, all gamma doses. a) Correlation loadings for seals 1,3 and 4. b)) Score plots with gamma doses for seals 1, 3 and 4. c) Correlation loadings for seals 2 and 5. b) Score plots with gamma doses for seals 2 and 5.

3.2. PE bags

The PE bag seals are all oriented in the same direction, as strain-strength curves constitute one single group (Fig. 8). Similarly to what happens for EVA seals, the strain applied to PE seals impacts only the PE film and not the seal itself (Fig. 3).

In Fig. 9, PCA is performed on the six characteristic mechanical values (described in Fig. 8) of the PE seal tensile curve. Fig. 9c shows that UTS and ultimate elongation are correlated and UTS is observed along PC2. Importantly, the ultimate elongation in this case is not so significant, as it is placed close to the center in the model (Fig. 9c); the farther the position in the model, the higher the significance. UTS and ultimate elongation are non-correlated with Y1 and Y2 strain. Moreover, there is a minor anti-correlation percentage between UTS/ultimate elongation and Y1/Y2 strength. Y1 and Y2 strength are observed along PC1.

Fig. 9a represents the score plots with seal locations and it shows no influence of the seal location on the seal mechanical behavior, as data points are not tightly close. Indeed, the seals in that pre-made bag configuration are along the machine direction, which corresponds presently to the multilayer film extrusion orientation and the seal samples are all cut out along the film transversal direction. This would also mean that performing film/film sealing on another film direction would lead to homogeneous behavior even though the tensile property values could be different to the ones observed in that study. Fig. 9b represents the score plots with gamma doses. For doses 0-30- 50-115 kGy, gamma irradiation is represented along PC2. Indeed, the 0 kGy points (in blue) are at the bottom of Fig. 9b, whereas the 115 kGy points (in red) are at the top. This observation is accounted for by the fact that the film in contact with the seal and irradiated at 115 kGy has a lower



a) b)

Fig. 7. Ultimate tensile strength (UTS) for seals 2 and 5 (black squares) and seals 1, 3 and 4 (red spheres) – left and Ultimate elongation for seals 2 and 5 (black squares) and seals 1, 3 and 4 (red spheres) – right. The average of all the bag lots is represented for each gamma irradiation dose.

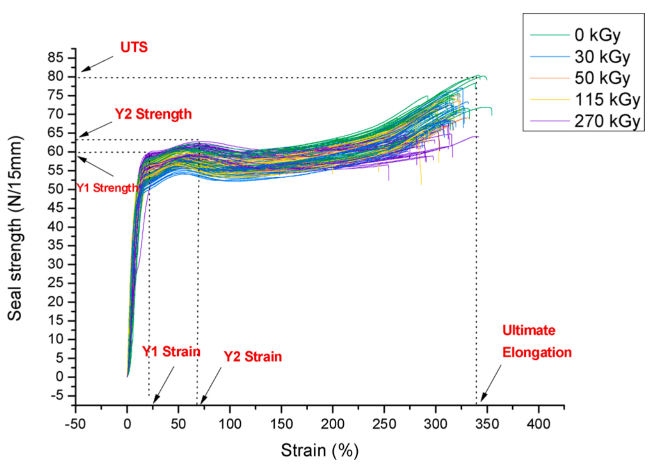


Fig. 8. Strength-strain curves for each seal location (1-16) and each gamma dose (0-270 kGy) for the PE bags. Colors according to gamma doses.

UTS (and therefore will break earlier) than the non-sterile film seal. Surprisingly, seals irradiated at 270 kGy are observed along PC1 (in green, on the right). Correlating that observation with Fig. 9c, the film in contact with the seal and irradiated at 270 kGy has a higher Y1 and Y2 strength than the 0-115 kGy film seal. Also, they have the same UTS value as the seal irradiated at 115 kGy. Fig. 10 confirms these first observations. Fig. 10a represents the UTS as a function of the gamma dose. The UTS decreases from 71 N (0 kGy) to 61 N (270 kGy), which represents a drop of 14 %. The decrease in UTS values with gamma irradiation was also observed by B.G. Porto et al. (B.G. Porto et al., 2018). Indeed, they noticed a 2–9 % decrease depending on the seal location, of the sealing resistance of the packaging (paper and plastic film) used for the sterilization of health products. The decrease in the mechanical resistance with the gamma dose has also been observed for the same multilayer film PE/EVOH/PE(Dorey et al., 2019). However, in that study, the UTS values for the film alone (i.e., not in contact with the seal) were ~30 % higher than for the film investigated in the current study. The ultimate elongation values for the film alone (not in contact with the seal) are between 20 and 40 % higher. This could be explained by the fact that the thickness of the film in contact with the seal is reduced compared with that of the film alone. Indeed, the pressure applied during sealing induces outflow, which reduces the film thickness.

Whatever the seal location and the irradiation dose, the mechanical tensile tests clearly show that there is no weakening of the seals and thus no loss of bag integrity is expected.

Fig. 10b shows the ultimate elongation as a function of the gamma dose. The tall error bars confirm that this parameter close to the model center in Fig. 9c does not significantly evolve with increasing gamma irradiation doses.

4. Conclusion

The tensile behavior of the seals of EVA or PE single use bags sterilized by gamma irradiation has been investigated. Different seal locations for EVA bags and for PE pre-made bags have been selected. This evaluation reveals that *in fine* the film shears before any modification of the seal. The mechanical behavior of the seals may depend on their location on the bags and is directly linked to the film extrusion direction. For the EVA bags, the rupture of the part of the film in contact with the seal is observed at lower strain and higher strength than those made perpendicular to the film extrusion direction. For the PE bags, the tested seal locations along one direction show no difference as for the seal tensile behavior.

The influence of the gamma irradiation has likewise been studied. Although at 270 kGy the tensile properties of the film are significantly altered, with a decrease in the film resistance, they remain unchanged at the doses required in the biopharmaceutical industry (ISO 11137-1, 2006) (i.e., ≥25- ~45 kGy). No bag features showed changes up to 115 kGy.

For both kinds of bags, the seals are never impacted during the tensile test, whatever the gamma irradiation dose and the seal location. At the end of the tensile test, the seals show no opening, no delamination and no tear. No bubble or channel is generated. The seal key features are entirely preserved, whatever the seal location and the gamma irradiation dose: the bag integrity is maintained, and the bag content is thus protected from the external environment. The work presented here demonstrates the seal resistance during the handling of the bag after sterilization by gamma irradiation.

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CRediT authorship contribution statement

Nina Girard-Perier: Writing - original draft, Writing - review & editing. **Fanny Gaston:** Writing - original draft, Writing - review & editing. **Nathalie Dupuy:** Writing - original draft, Writing - review &

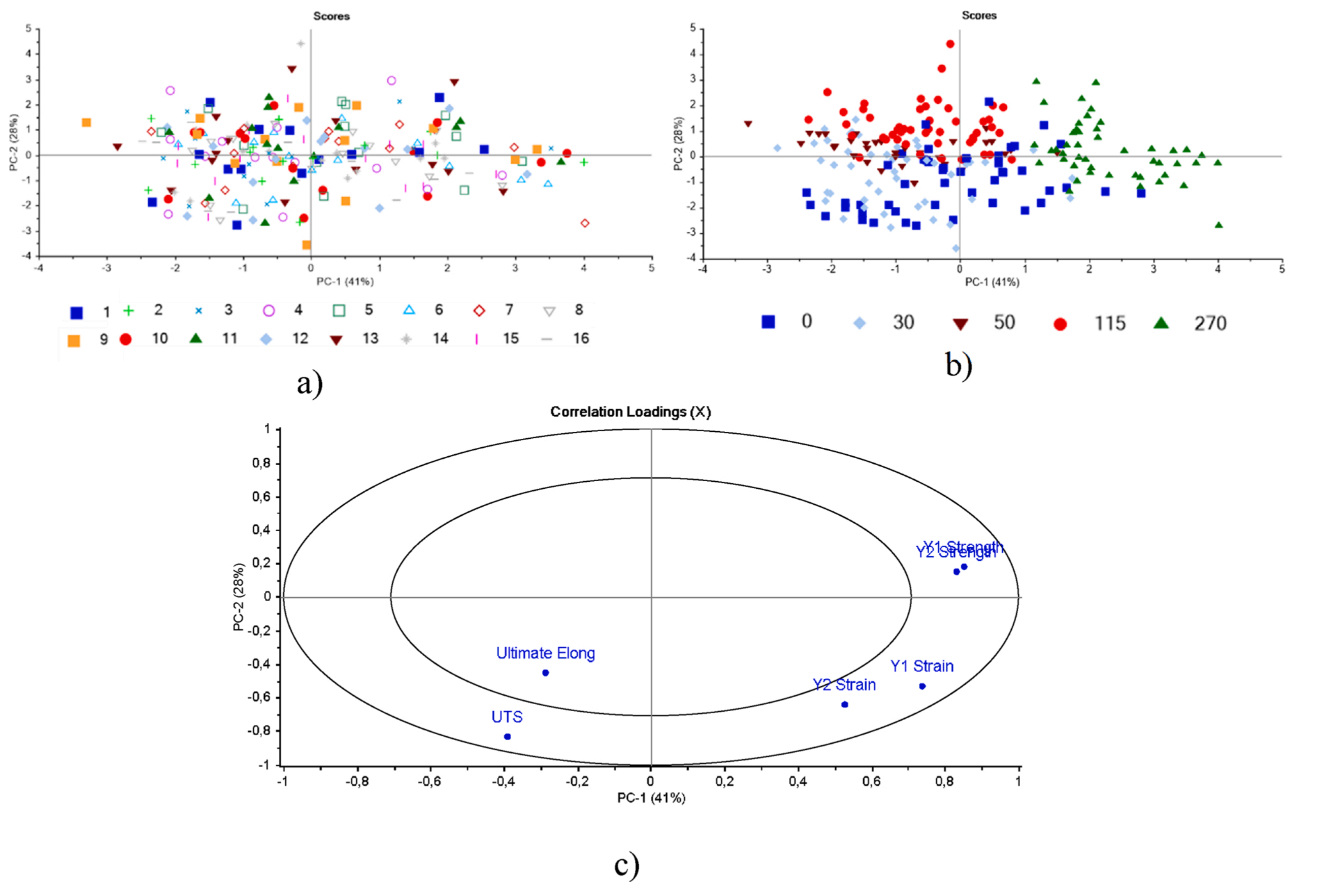

Fig. 9. PCA performed on the six characteristic points of each tensile curve for the PE bags obtained for 2 lots and all gamma doses. a) Score plots with seal locations. b) Score plots with gamma doses. c) Correlation loadings (ellipses represent 75 % and 100 % of the correlation).

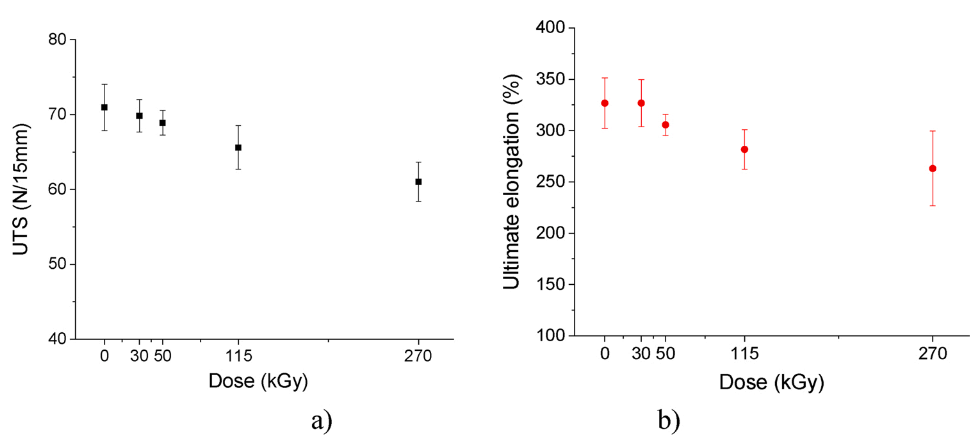

Fig. 10. Ultimate tensile strength (UTS)- a) and ultimate elongation – b). The average of all bag lots is represented for each gamma irradiation dose.

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