Healthcare Solutions

DuPont™ Liveo™ Pharma TPE Tubing for the biopharmaceutical processing industry

Stephane Cornelis

Abstract

For several years, the development of new therapeutic agents beyond traditional small molecules profitably has supported the biopharmaceutical industry, which has experienced steady and rapid growth. The growth of cell and gene therapies and cancer treatments, the continuing trend of increasing life expectancy, and the unexpected and unprecedented demand for vaccines to control the COVID-19 pandemic surpassed even the most optimistic growth forecasts. This unpredictable growth in demand has put notable challenges on the upstream supply chain, especially on single-use-system (SUS) supply. While the bioprocessing supply sector works to adapt to this rapid expansion, DuPont is accelerating investments in the healthcare industry's future by expanding its supply of silicone elastomers and tubing and enlarging its single-use pharma product lines. The latter materialized in 2021 with the commercialization of DuPont™ Liveo™ Pharma TPE Tubing, an alternative thermoweldable thermoplastic elastomer (TPE) tubing solution to efficiently respond to SUS supply pressures.

The launch of Liveo™ Pharma TPE Tubing marks a historic milestone for DuPont – adding a range of extruded pharma tubing based on TPE technology, made from a Liveo™ styrenic-based copolymer and dedicated to fluid transport and single-use bioprocessing applications. These new TPE products are made under similar high-quality and high-performance principles as Liveo™ Pharma Silicone Tubing and Liveo™ Pharma Overmolded Assembly (OMA) products and provide an effective complement to these established Liveo™ product lines.

Liveo™ Pharma TPE Tubing is targeted for use in biopharmaceutical processes to enable aseptic connection and disconnection of tubing without connectors (e.g., for sample collection) and can be used in peristaltic pump applications. Strong from its heritage built on purity, quality and performance, the new ISO Class 7-manufactured TPE tubing offers an outstanding purity profile and low extractables. This new generation of high-clarity pharma TPE tubing meets the most stringent requirements to be the complementary offering to silicone tubing.

Introduction

Thermoplastic elastomer (TPE) material increasingly has been adopted in single-use tubing for bioprocessing applications thanks to its thermoweldability. In the current context of accelerated demand for single-use tubing in the biopharmaceutical industry and stress on supply chains due to the COVID-19 pandemic, Liveo™ Pharma TPE Tubing represents an additional competitive offering with the quality and performance the industry is accustomed to receiving.

A complete benchmark analysis was carried out to highlight the improvement of the most stringent technical requirements enabled by this new TPE tubing. A brief overview of performance will be covered through review of the following aspects of Liveo™ Pharma TPE Tubing performance:

- Weldability and co-weldability performance
- Spallation following use of peristaltic pump
- Chemical resistance
- Extractables overview
- Health data (bacterial endotoxins, bioburden, and subvisible particulate matter)
- Sterilization (steam, gamma and X-ray irradiation)

An extended version of this white paper is available. Please contact your DuPont representative for details.

Results

A. Overview of weldability performance

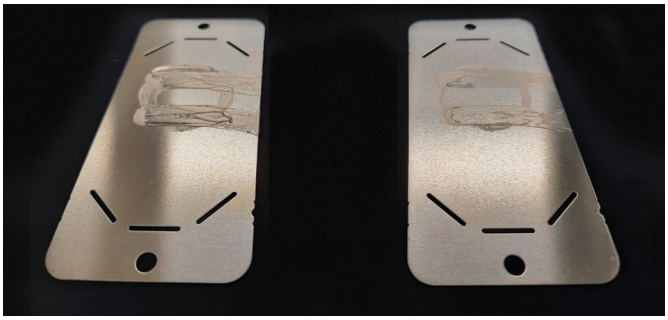
To maintain aseptic conditions, thermal welding enabled by TPE tubing technology can be used to prevent exposing the stream of biopharmaceutical products to the production environment. This reduces the risk of external contamination thanks to connection and disconnection that can be executed rapidly using welding and sealing machines. There is a need to ensure robust welding of single-use TPE tubing – not only to avoid any risk of leakage, but also to resist the pressure generated during the biopharmaceutical manufacturing process. Compatibility between different TPE tubing is another critical attribute in providing the flexibility needed when designing single-use systems (e.g., combining in the same line tubing material specifically designed to be used in peristaltic pump applications with generic fluid transfer type of tubing).

Extensive studies were carried out to evaluate the thermoweldability of DuPont™ Liveo™ Pharma TPE Tubing, employing conditions as close as possible to actual biopharmaceutical processing conditions by using welding machines readily available on the market, such as the Biowelder® TC and Cytiva™ Sterile Tube Fuser-Dry. The first phase of the study used the Biowelder® TC that came with predefined settings specific to TPE tubing currently available on the market. The welding performances was assessed using different methods natively available within the welding machine, which mainly differ by the welding temperature being between 185°C and 270°C and the welding and cooling duration steps.

Following the welding process, a visual inspection of the outer and inner weld was carried out to detect particles that could have been generated due to incompatible process conditions, such as too low/too high of welding temperature or too short of welding time. Moreover, a determination of mechanical and functional properties was performed through the evaluation of tensile strength of the weld with a strain-stress device and the determination of burst pressure resistance.

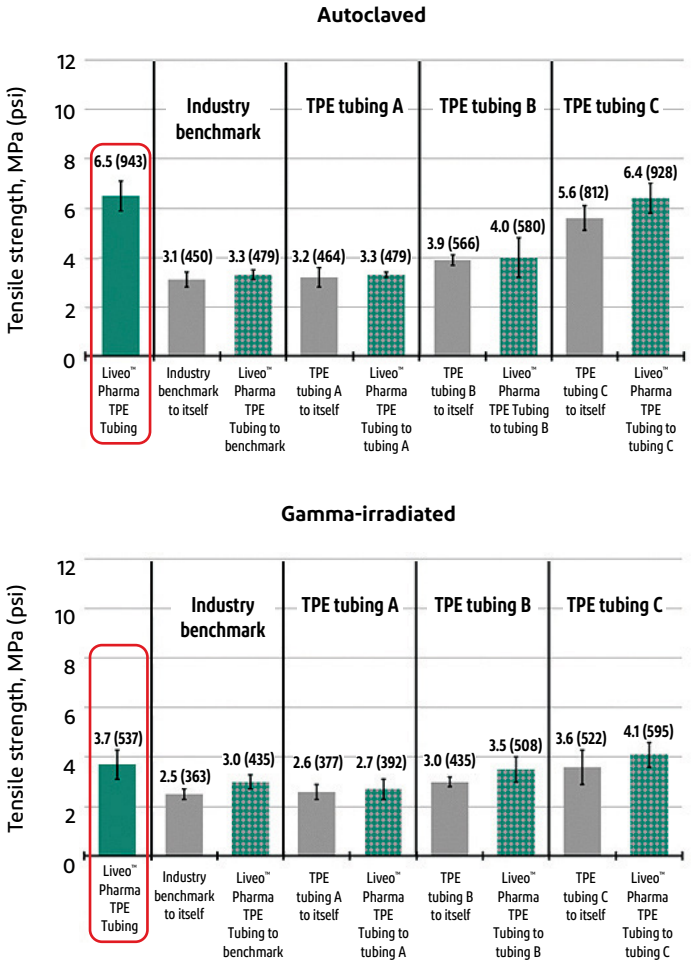
The working principle of the welder was based on the use of a disposable stainless-steel cutting blade heated to high temperature, allowing its depyrogenation (around 400°C) prior to being cooled down to the welding temperature. The blade cut the tubing, and the holder rotated to establish a connection of the new TPE tubing material. Residue left on the welding blade is an indication of the likeliness of a TPE tubing to generate particles at the inner surface of the weld, which ultimately could contaminate the media during biopharmaceutical processing. As shown in Figure 1, Liveo™ Pharma TPE Tubing was welded with minimal material residue left on the blade.

Figure 1. Difference in residue on the front of the blade after a single welding cycle; industry benchmark TPE tubing is on the left, and Liveo™ Pharma TPE Tubing is on the right.



Prior to the welding step, Liveo™ Pharma TPE Tubing was sterilized with the most frequently used methods: 1) moist heat sterilization via autoclave set at 121°C for 30 minutes; and 2) gamma irradiation with a dose of 50 kGy. Regardless of the tubing dimensions, sterilized Liveo™ Pharma TPE Tubing exhibited superior tensile strength (assessed with ASTM D412 Die C methodology) when welded to itself compared to other TPE tubing brands. Not only was Liveo™ Pharma TPE Tubing compatible with other TPE tubing brands, but it also improved the weld strength versus other kinds of TPE tubing welded to themselves, as shown in Figure 2.

Figure 2. Tensile strength of sterilized I.D. 3/8" x O.D. 5/8" TPE tubing material after (co-)welding.



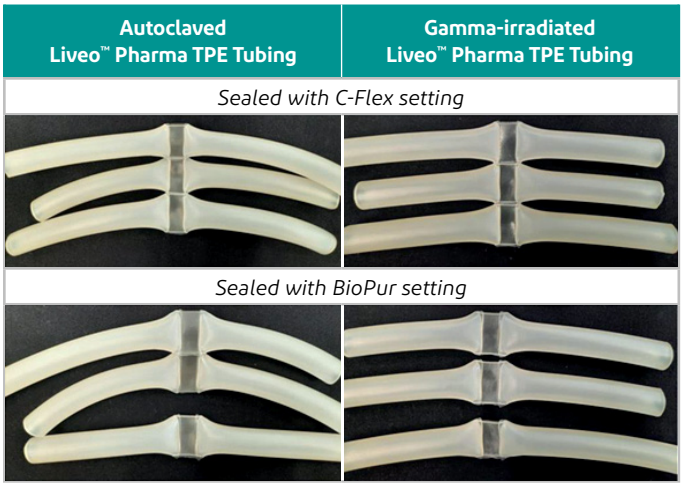
The use of the Cytiva™ Sterile Tube Fuser-Dry welding machine confirmed that Liveo™ Pharma TPE Tubing could be welded successfully with the default settings. The TPE tubing material was tested and considered successfully welded when the weld was continuous and the material remained intact after it was pulled, twisted and pulled again by hand to assess the robustness of the weld.

An independent laboratory with recognized expertise in the biopharmaceutical processing industry conducted a complementary evaluation of the sealing performance of Liveo™ Pharma TPE Tubing in a biopharmaceutical context using the Cytiva™ Hot Lips Tube Sealer™, which is a readily available sealing machine on the market.

The purpose of the sealing tests was to demonstrate that Liveo™ Pharma TPE Tubing could be sealed using the Cytiva™ Hot Lips Tube Sealer™ and the settings commonly used for other commercial TPE tubing. Two different settings were used: C-Flex and BioPur default methods.

Visual inspection and qualitative evaluation of the seal were carried out. Liveo™ Pharma TPE Tubing could be manually pulled, twisted and pulled again without breaking. Liveo™ Pharma TPE Tubing did not exhibit any change of color at the seal. No air bubbles, defects or cracks at the seal were observed, either, as shown in Figure 3.

Figure 3. Actual sealed, sterilized DuPont™ Liveo™ Pharma TPE Tubing material using the C-Flex and BioPur default settings of the Cytiva™ Hot Lips Tube Sealer™.



B. Spallation evaluation following pumping

Multiple steps are required during biopharmaceutical processes:

- The upstream process consists mainly of growing cells that will be used to produce the drug substance (e.g., protein).
- In the harvesting step, the goal is to separate the cells and cellular debris from the drug substance production.
- The downstream process mainly deals with protein purification.
- The final filling allows for adjusting the drug substance concentration and ensuring its stability via addition of excipients and stabilizers.

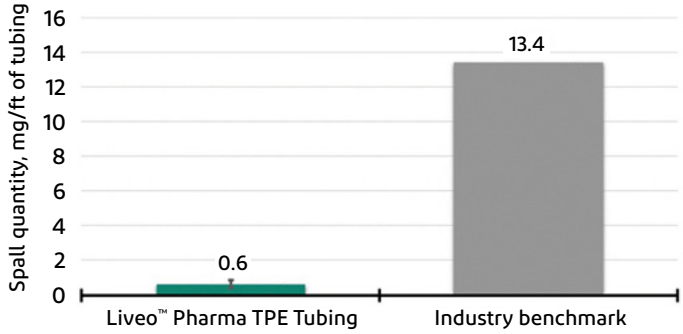
Throughout the biopharmaceutical process, the fluid is transferred with the help of peristaltic pumps, which allow the media to be pumped without being in contact with moving parts to ensure the highest aseptic conditions. The major drawback of using a peristaltic pump is the inevitable abrasion of the inner surface of the tubing material due to mechanical stresses of the pump head, ultimately leading to the generation of particles (referred to as "spall").

A typical example of an application in which the particulates generated during pumping must be minimal is in cell therapies that require the use of automated wash-and-concentration devices that rely on centrifugation process or filtration. The latter operation, which is more cost-effective, would be highly impacted by the presence of particles that may block the membrane-based filter.

Normal-flow filtration (known as NFF) is a widely used filtration method because of its cost-effectiveness and rapidity. This filtration method is efficient, provided that the amount of solid content is low. Hence, low spallation (i.e., likeliness to generate spall particles during pumping operations), is critical to avoid clogging membrane-based filters that may significantly extend the duration of this step and eventually would annihilate the benefit of faster-process filtration over centrifugation-based technology. Other types of filtration less sensitive to particles, such as tangential-flow filtration, could be employed, but this technique could generate damaging shear forces and thus impact the viability of the cells in the filtrate – a critical attribute for an effective biopharmaceutical manufacturing process.

Autoclaved Liveo™ Pharma TPE Tubing was tested to evaluate spallation by employing a Cole-Parmer® Masterflex® I/P® peristaltic pump set at 650 RPM, continuously operated for 24 hours at room temperature, and fed with purified water circulating through a thoroughly clean vessel. The spall residues were removed by physically scraping the adhered spall particles from within the tubing and by filtering the content of the vessel through 10 µm filter paper. The filter paper and scraped particles were dried and weighed. The difference of weight before (filter paper only) and after (filter paper and dried particles) was the amount of spallation, expressed as mg of spall per foot of tubing.

Figure 4. Spall particles collected after 24 hours of continuous pumping using autoclaved TPE tubing.



Autoclaved Liveo™ Pharma TPE Tubing exhibited significantly lower spall particles than the autoclaved industry benchmark TPE tubing (Figure 4) after 24 hours of continuous pumping.

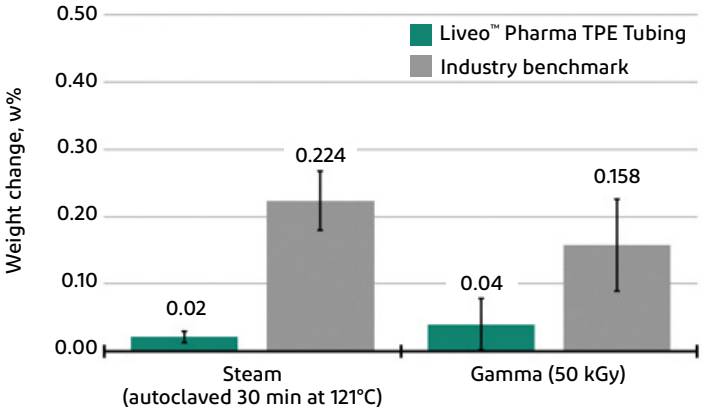
C. Comparison of chemical resistance of Liveo™ Pharma TPE Tubing vs. industry benchmark TPE tubing

Single-use tubing materials are likely to be in contact with various solvents during manufacturing, storage and transportation of bioprocessing substances. The solvent choice not only accounts for growth of the cells while preserving their viability, but it also influences the conservation of the properties of the drug substance of interest (e.g., conformation of proteins). For example, sodium hydroxide commonly is used for pH adjustment of process streams, and dimethyl sulfoxide (DMSO) often is employed to preserve cells when stored and transported in low-temperature conditions.

To study the chemical compatibility of Liveo™ Pharma TPE Tubing, chemical resistance tests were carried out on sterilized material, consisting of exposing TPE tubing specimens to solvents commonly used in biopharmaceutical processes. Hemostatic clamps were secured at both ends of the TPE tubing, which was exposed to the chemical for 24 hours without agitation (with a surface-area-to-volume ratio of 4:1). After one day, the clamps were removed, and the tubing specimens were thoroughly rinsed with highly purified water, fully dried and weighed. The weight loss, expressed as a relative percentage, was obtained by gravimetry (weighing the tubing specimens before and after chemical exposure).

Weight loss tests were performed on DuPont™ Liveo™ Pharma TPE Tubing and industry benchmark TPE tubing sterilized by autoclave and gamma irradiation. Pure DMSO solution was diluted with water at 20% (v/v) for the test. (As previously mentioned, DMSO is a solvent commonly used during storage and transportation of drug substances at low temperature in biopharmaceutical processes.)

Figure 5. Summed weight loss measured on autoclaved and gamma-irradiated TPE tubing after 24 hours of 20 v% DMSO exposure.



Sterilized (i.e., autoclaved or gamma-irradiated) Liveo™ Pharma TPE Tubing exhibited a significant improvement when exposed to DMSO, with almost no weight loss observed – unlike the industry benchmark TPE tubing, which showed 0.16% to 0.22% weight loss, depending on the sterilization method (Figure 5).

D. Overview of purity through extractables test as per the USP <665> protocol

Establishing the extractables (release of chemical species during forced extraction under laboratory conditions) and leachables (release of chemical species under conditions of normal use) profile of single-use systems (SUS) is critical to achieve a high-quality drug substance production that ultimately will be beneficial to the patient. The goal of the extraction study is to identify and quantify material chemical constituents likely to be extracted from the tubing material in the conditions specified in the USP <665> protocol, which represent worst-case conditions.

A recognized independent laboratory conducted an extractables study on autoclaved and gamma-irradiated Liveo™ Pharma TPE Tubing. The study was based on the protocol described in the enforceable USP <665> "Polymeric Components and Systems Used in the Manufacturing of Drug Products," which defines the use of three different extraction solvents: phosphate-buffered saline (PBS) adjusted to pH 3.0 with ortho phosphoric acid, PBS adjusted to pH 10.0 with sodium hydroxide and 50% aqueous ethanol, with the surface-area-to-volume ratio being at a minimum of 6:1. After 21 days, solvent extracts were collected from the tubing (single data point collection) and analyzed by appropriate analytical methods. The detection of species such as nonvolatile, semi-volatile, volatile organic compounds, low to high polarity substances, aromatic hydrocarbons, aldehyde, and polymer residues were achieved by the use of gas chromatography (GC) and high-performance liquid chromatography (HPLC) techniques. Elemental impurities were detected by inductively coupled plasma equipped with a mass spectrometer (ICP-MS) and eventually a measure of nonvolatile residues (NVR) completed the collection of extractables data.

Upstream processing is concerned with growing the cells that produce the therapeutic protein. The more cells, the higher the amount of drug substance produced. Similarly, healthier cells lead to a better-quality product. The presence of contaminants within the culture media affects both the quality and the number of cells available to produce the protein. It is essential to preserve the structural integrity of the protein, which also could be affected by the presence of undesirable leachables, and Liveo™ Pharma TPE Tubing is well-differentiated in that regard versus TPE tubing from other brands.

Antioxidants are inevitable additives present within TPE tubing and thermoplastics in general. Tris(2,4-di-tert-butylphenyl) phosphite – usually known as Irgafos® 168, its commercial name – is a common antioxidant found in TPE tubing material. It often is added to prevent severe molecular changes of the polymer during processing and sterilization. During these latter steps, Irgafos® 168 is likely to be oxidated into bis(2,4-di-tert-butylphenyl)phosphate (bDtBPP).

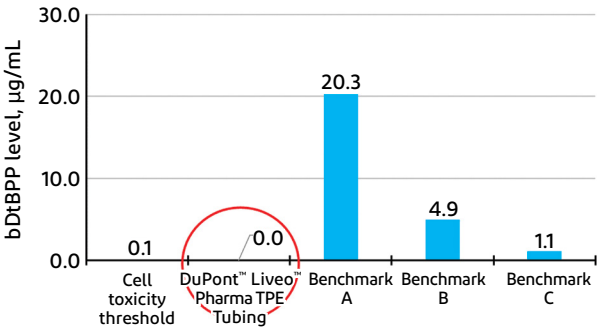
The presence of bDtBPP in SUS – and especially in tubing – can inhibit growth of cells such as Chinese Hamster Ovary (HMO) cells that are used widely during biopharmaceutical cell culture upstream processes. Several articles from the literature, including Paul S Kelly et al.[3] and Hammond et al.[4] papers, mention a cell toxicity threshold in the range of 0.10 µg/mL to 0.73 µg/mL.

The extractables data indicated detection of <0.05 µg/mL bDtBPP in autoclaved Liveo™ Pharma TPE Tubing, and no bDtBPP was found in the gamma-irradiated Liveo™ Pharma TPE Tubing using 50% aqueous ethanol as extraction solvent. Using PBS pH 3.0 and pH 10.0 as extraction solvents, bDtBPP was not found in *any* of the autoclaved or gamma-irradiated Liveo™ Pharma TPE Tubing samples.

The presence of bDtBPP previously was studied in existing TPE tubing readily available for the biopharmaceutical industry. The values collected from the literature[5] are assumed to be measured from gamma-irradiated TPE tubing material using 50% aqueous ethanol, the extraction solvent that is most likely to extract the most bDtBPP by-product.

Figure 6 summarizes the bDtBPP levels found in three different TPE tubing brands, as well as the cell toxicity threshold, in comparison with DuPont™ Liveo™ Pharma TPE Tubing.

Figure 6. Quantified bDtBPP concentration on different gamma-irradiated TPE tubing (50 kGy dose).



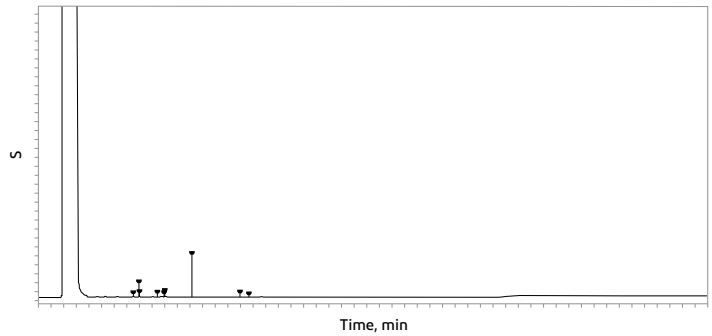
Liveo™ Pharma TPE Tubing can be combined with appropriate materials (e.g., reactor bag) to limit the presence of bDtBPP during the manufacturing process – especially the cell culture step – to improve productivity and the quality of the cells and, ultimately, the drug substance.

D1. Example of extractable profile obtained by GC-FID/MS

The chromatogram presented in the Figure 7 was obtained by gas chromatography coupled to a flame ionization and mass spectrometry detection (GC-FID/MS) after using 50% aqueous ethanol extraction solvent with gamma-irradiated Liveo™ Pharma TPE Tubing. The combination of the high extraction power from 50% aqueous ethanol solvent and gamma irradiation sterilization treatment was the condition that showed the highest number of peaks (extracted material chemical constituents). Given the very low concentration of the extracted species, it was necessary to concentrate the solvent extracts with a concentration factor of 10 to allow for an easier identification and quantification of those chemical constituents.

Figure 7 shows the GC-FID/MS chromatogram obtained with the original concentration of 50% aqueous ethanol extract collected from the gamma-irradiated Liveo™ Pharma TPE Tubing. Despite its strong extraction power, the chromatogram obtained from the 50% aqueous ethanol extract remained particularly clear, highlighting the purity of Liveo™ Pharma TPE Tubing.

Figure 7. GC-FID chromatogram of gamma-irradiated Liveo™ Pharma TPE Tubing, extract 50 % EtOH, original concentration.



D2. Brief overview of purity data through bioburden, endotoxins and subvisible particulate matter tests

Among all the health certification testing carried out on Liveo™ Pharma TPE Tubing by accredited independent laboratories, ISO 11737-1 (Sterilization of health care products – Microbiological methods – Part 1: Determination of a population of microorganisms on products), known as bioburden, describes the population of viable microorganisms present on or in a product and/or a sterile barrier system. For the bioburden counts, the result was well below (by a factor 10) the acceptable limit of ≤0.1 CFU/mL (CFU = colony-forming unit) for sterile biological drug products.

The USP <788> Particulate Matter in Injections test was used to quantify the count and size of subvisible particles in parenteral drug containers. The test requires using a light obscuration particle counter (Method 1) or counting particles on a filter by microscopy (Method 2). Method 2 for counting subvisible particulates was selected as being more appropriate for enumerating solid particulates. This was justified from previous particulate testing investigations of tubing material. The data showed that the material passed the criteria for solid particulate count with values well below the threshold as set by USP <788> (Method 2) being:

- ≤3,000 for ≥10 µm particulates size
- ≤300 for ≥25 µm particulates size

The particulate counts were, respectively, ~0.1 and ~0.01.

The Bacterial Endotoxins Test (BET) is a test to detect or quantify endotoxins from Gram-negative bacteria using amoebocyte lysate extracted from the horseshoe crab (Limulus polyphemus).

Endotoxins are a component of the lipid polysaccharide layer of Gram-negative bacterial cell walls. The semi-quantitative gel clot method of detection of USP <85> was used by the quality control laboratory at the DuPont Healthcare Industries Materials Site (HIMS) in Hemlock, Michigan, USA.

Under specific conditions, the extract of lysed amebocytes from the horseshoe crab reacted with bacterial endotoxin to polymerize and form a clot. DuPont has deep experience with this gel clot test, which historically has been used to test Liveo™ Pharma Tubing and Liveo™ Medical Rx Tubing.

This is a pass/fail test, with endotoxin extraction from the inner lumen of the tubing with pyrogen-free water. The tubing extract was exposed to a reagent with a sensitivity of ≥0.125 EU/mL (EU = endotoxin units), which defined DuPont's acceptance criteria. The test is considered as "pass" if no gel formation is detected due to the reagent not reacting (clotting) with the extract that had <0.125 EU/mL, while the test is considered as "fail" if gel formation is visible due to the reagent that reacted (clotted) with extract that had ≥0.125 EU/mL.

This criterion is more stringent than the USP <85> Water For Injection (WFI) criteria of 0.25 EU/mL. WFI is the highest grade of pharmaceutical water and is used in drug formulations directly injected into the patient.

All Liveo™ Pharma TPE Tubing passed the test based on DuPont's stringent acceptance criteria of <0.125 EU/mL.

E. DuPont™ Liveo™ Pharma TPE Tubing performance after sterilization

In the biopharmaceutical industry, the supply relationship is complex. Before being used by biomanufacturers, SUS require the intervention of several players –the component manufacturers, the integrators and eventually the sterilization experts. Indeed, SUS need to be sterilized before utilization. Among the most common sterilization methods being used – such as steam and, more rarely, ethylene oxide – gamma irradiation is the preferred method, and X-ray irradiation is getting increasing consideration from the industry.

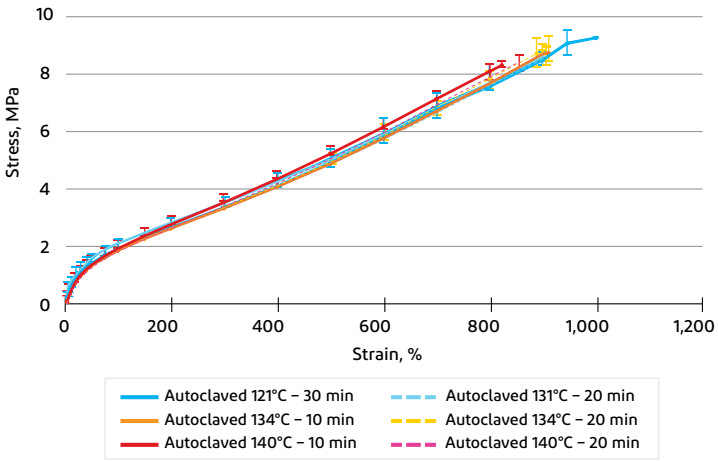
E1. Steam sterilization using high-temperature autoclave conditions

Moist heat sterilization is used widely in the biopharmaceutical processing industry. However, unlike silicone-based tubing, thermoplastic elastomer material is sensitive to high temperature due to its molecular structure and phase transition.

DuPont conducted evaluation of Liveo™ Pharma TPE Tubing to ensure the tubing remained stable when exposed to a wide range of temperatures that potentially could be applied during an autoclave cycle. Standard conditions for sterilization of TPE tubing material with steam are a 30-minute autoclave cycle at 121°C. Liveo™ Pharma TPE Tubing not only exhibited stable mechanical and functional properties in these standard conditions, but also after increasing the temperature up to 140°C for 20 minutes.

Liveo™ Pharma TPE Tubing was tested in different conditions by autoclaving the tubing specimens at 131°C for 20 minutes, 134°C for 10 minutes and 20 minutes, and 140°C for 10 minutes and 20 minutes. Figure 8 shows the results of the TPE tubing specimens being tested in a tensile machine to evaluate the impact on the stress-strain curve versus the standard conditions of 121°C for 30 minutes.

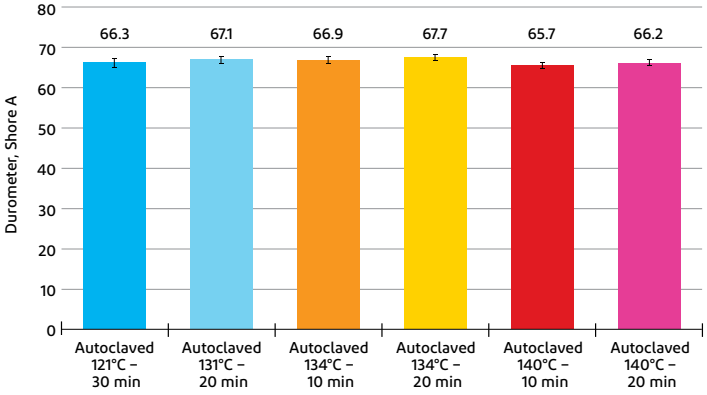
Figure 8. Stress-strain of autoclaved Liveo™ Pharma TPE Tubing (I.D. 3/8" x O.D. 5/8").



Liveo™ Pharma TPE Tubing exhibited no significant change of stress-strain behavior, regardless of the temperature/duration combination used during the autoclave cycle. However, a slight decrease in maximum elongation was observed. The decrease in maximum elongation could be the consequence of phase organization with an increase of the rigid phase content that potentially could be seen by differential scanning calorimetry (DSC).

Complementary to the stress-strain data provided in Figure 8, a comparison of durometer is provided in Figure 9, confirming the stability of the material hardness after being autoclaved at temperatures ranging from 121°C to 140°C.

Figure 9. Shore A durometer of Liveo™ Pharma TPE Tubing (I.D. 3/8" x O.D. 5/8") after various autoclave cycle conditions.



E2. Considerations of X-ray irradiation in lieu of gamma

Gamma technique using Cobalt-60 (60Co) has been used for decades to sterilize biopharmaceutical equipment by irradiation; however, due to supply chain constraints on 60Co, alternative irradiation techniques have been considered, especially X-ray sterilization. X-ray irradiation presents the same efficiency thanks to its higher penetration and better dose uniformity than gamma. For X-ray, the source of photons – unlike gamma irradiation, which relies on the use of Cobalt-60 isotope – comes from a tantalum or tungsten material (Bremsstrahlung effect)[1].

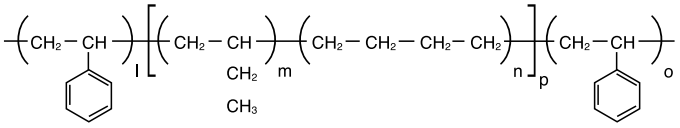
The irradiation treatment could make the material radioactive by neutron activation. For this purpose, the sterilization laboratory conducted activation testing using 7 MeV (60 kGy to 70 kGy), representing the very maximum sterilization dose. No activation was detected on Liveo™ Pharma TPE Tubing under these X-ray irradiation conditions using tantalum target. The resistance of Liveo™ Pharma TPE Tubing to X-ray sterilization was evaluated, confirming the stability of the material properties and performance after gamma and X-ray sterilization treatments. For this purpose, 50-foot coils of Liveo™ Pharma TPE Tubing were submitted for gamma and X-ray sterilization, both at 50 kGy dose (considered as the worst case), and the performance of each was tested before and after treatment, comparing the stress-strain relationship; any deviation, especially in the low-moduli region, could indicate some changes of the functional properties.

E3. Irradiation's effect on TPE tubing material

Irradiation often induces reactions in polymers, especially dehydrogenation leading to the formation of unsaturation in the polymer backbone and resulting in further crosslinking or degradation through chain scission.

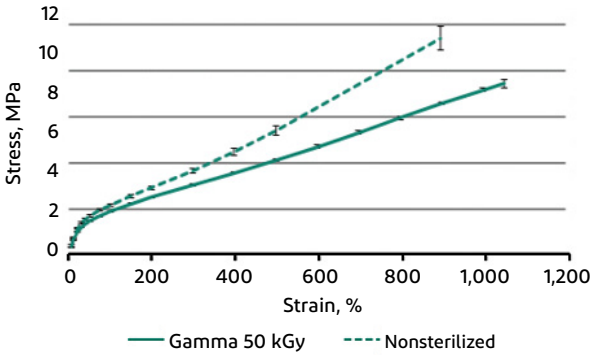
Crosslinking increases the strength of the material but decreases the elongation, whereas chain scission is responsible for loss of strength and higher elongation. The oxidation process is influenced by the presence of styrene-ethylene-butylene-styrene (SEBS) thermoplastic elastomer material, which is more resistant to ionizing radiation due to mechanisms directing the dissipation of energy straightforward into heat[2]: "In the SEBS copolymer the central chain is composed of ethylene and butylene monomers (poly[ethylene-co-butylene]) that influences the rate at which oxygen diffuses through the matrix and hence the formation of peroxide radicals."[2]

Figure 10. SEBS thermoplastic elastomer.



To illustrate the molecular change following irradiation, Figure 11 shows the impact on the stress-strain relationship of gamma irradiation compared to unsterilized TPE tubing material: Nonsterilized DuPont™ Liveo™ Pharma TPE Tubing had a lower maximum elongation but a higher tensile strength, whereas the gamma-treated TPE tubing showed a higher maximum elongation but a lower maximum tensile strength. Consequently, it is expected that following gamma irradiation, the TPE material has undergone more degradation through chain scission than crosslinking, as previously explained.

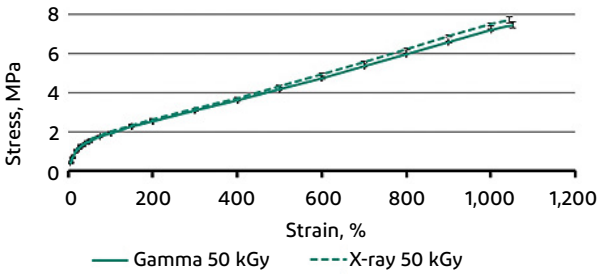
Figure 11. Stress-strain of gamma-irradiated vs. unsterilized Liveo™ Pharma TPE Tubing (I.D. 3/8" x O.D. 5/8").



E4. Comparison of the impact on TPE tubing of gamma vs. X-ray irradiation

The stress-strain of Liveo™ Pharma TPE Tubing demonstrated a slight statistical impact for strain above 600%. A maximum of 3% difference of stress was observed at 1,000% elongation (7.45 MPa after gamma versus 7.70 MPa after X-ray), as reported in Figure 12.

Figure 12. Stress-strain of gamma-irradiated vs. X-ray-irradiated Liveo™ Pharma TPE Tubing (I.D. 3/8" x O.D. 5/8").



Conclusions

Material component selection to design SUS is a critical step that requires multiple criteria to be considered, such as material availability – which, in the case of single-use TPE tubing, is a significant challenge amplified by the COVID-19 pandemic's disruption of the supply of thermoplastic elastomeric material.

With Liveo™ Pharma TPE Tubing, DuPont proposes an alternative solution to the existing TPE tubing for the biopharmaceutical processing industry. This TPE option from DuPont completes the Liveo™ Pharma product line based on silicone technology (Liveo™ Pharma Tubing, Liveo™ Pharma Overmolded Assemblies and Liveo™ Pharma Bottle Closures), which already is well-established in the bioprocessing market.

Apart from tubing material availability, tubing performance is the other criterion crucial to ensuring efficient and reliable bioprocesses.

Liveo™ Pharma TPE Tubing enables improvement of welding performance among all existing TPE tubing offerings. When welded to itself, the tensile strength of the weld section exhibits a high solidity to prevent any leakage during biopharmaceutical processing, and the high burst resistance – both before and after welding – allows for increased pressure of process streams for faster productivity if required.

The ability of Liveo™ Pharma TPE Tubing to co-weld onto other kinds of TPE tubing enables an unmet flexibility when it comes to material selection. When Liveo™ Pharma TPE Tubing is welded onto other TPE tubing brands, the tensile strength of the weld is improved in comparison to other TPE tubing materials when welded to themselves using default settings of welding and sealing machines readily available on the market.

Purity attributes inherited from the existing Liveo™ Pharma portfolio are confirmed through the low particulates generated during pumping, even following the low-storage-temperature conditions that are used with increasing frequency due to production of vaccines based on mRNA (messenger ribonucleic acid) technology.

With this latter technology, low storage temperature and cryopreservation usually require the use of dimethyl sulfoxide solvent (DMSO) to ensure viability of the cells – a solvent that Liveo™ Pharma TPE Tubing shows chemical resistance improvement against, especially versus industry benchmark TPE tubing. DMSO is not the only solvent well-compatible with this new TPE tubing material; other solvents typically employed by the biopharmaceutical processing industry, such as acid and alkaline aqueous solutions and alcohols, show similar compatibility with Liveo™ Pharma TPE Tubing.

The newly enforceable USP <665> protocol was utilized to establish the extractables profile of this Liveo™ Pharma TPE Tubing and showed cleanliness in the multiple chromatograms obtained thanks to the use of a wide array of analytical chromatography instruments employed to identify and quantify the chemical constituents that are likely to be extracted in the worst-case scenario.

A strong example of the superiority of Liveo™ Pharma TPE Tubing is demonstrated by the absence of by-products generated by the degradation of Irgafos® 168 antioxidant – by-products that would be detrimental to efficient cell growth, which not only would ultimately affect productivity, but also, more importantly, would affect the quality of the drug substance.

The sterilization of Liveo™ Pharma TPE Tubing can be realized with well-established treatments currently in use in the biopharmaceutical industry, such as steam (via autoclave), ethylene oxide and gamma irradiation – the latter of which soon may be replaced by X-ray irradiation due to limited availability of Cobalt-60.

DuPont demonstrates equivalency of gamma irradiation with X-ray irradiation through very similar viscoelastic, physical and functional properties of Liveo™ Pharma TPE Tubing.

And yet, despite the availability and relatively short lead time of Liveo™ Pharma TPE Tubing, the journey to quickly take advantage of this new offering presents some hurdles for the biopharmaceutical industry due to lengthy qualification times that often are required in the industry. These hurdles could be mitigated by Liveo™ Pharma TPE Tubing, which helps to circumvent the TPE tubing shortage through comprehensive guides. This includes required and expected USP and ISO tests, helping customers speed up the qualification process at their respective facilities.

For further details related to the performance of Liveo™ Pharma TPE Tubing, please contact your DuPont representative.

References

1. GIPA & IIA, "A Comparison of Gamma, E-beam, X-ray and Ethylene Oxide Technologies for the Industrial Sterilization of Medical Devices and Healthcare Products" | 2017.

2. Danuta Żuchowska, Zbigniew Paweł Zagórski, Grażyna Krystyna Przybytniak, Andrzej Rafalski, "Influence of Butadiene/Styrene Copolymers On The Stabilisation Of Polypropylene In Electron Beam Irradiation"; Pages 335-344 | Published online: 27 October 2010

3. Improvements in single-use bioreactor film material composition leads to robust and reliable Chinese hamster ovary cell performance, Paul S Kelly, Noemi Dorival-García, Samantha Paré, Sara Carillo, Christine Ta, Antonio Alarcon Miguez, Orla Coleman, Emma Harper, Maeve Shannon, Michael Henry, Lisa Connolly, Martin Clynes, Paula Meleady, Jonathan Bones, and Niall Barron, Research article – Biotechnology Progress

4. Hammond M, Marghitoiu L, Lee H, Perez L, Rogers G, Nashed-Samuel Y, Nunn H, Kline S. A cytotoxic leachable compound from single-use bioprocess equipment that causes poor cell growth performance. Biotechnol Prog. 2014;30(2):332-337. doi:10.1002/btpr.1869.

5. TuFlux TPE tubing for pharma processing, Pradnya Parulekar, Michael Drechsel, Single-use technologies III: Scientific and technological advancements, 2018

For further information about Liveo™ Pharma Tubing products

Please visit **liveo.dupont.com** or scan the QR code below.

DUPONT™

To learn more about DuPont™ Liveo™ Healthcare Solutions, visit **liveo.dupont.com**.

Smarter Healthcare.
Positive Patient Outcomes.

Form No. 05-1063-01-AGP0522 #16891