Cambridge Polymer Group

Packaging for Medical Devices & Pharma

By Jaimee Robertson, Director of Consulting

Summary

Packaging design for medical devices and pharmaceuticals extends far beyond appearance. As materials science experts with extensive product development experience, Cambridge Polymer Group (CPG) understands the importance of careful material selection and thorough characterization/testing of medical device and pharmaceutical packaging. Upfront consideration of the barrier properties, sterilization modality, biocompatibility, user interface, and shelf stability requirements is necessary to avoid costly packaging design changes downstream in the product development process.

Materials

Packaging material selection requires consideration of the desired performance properties as well as packaging compatibility with the product and processing methods. For medical devices and pharmaceuticals, performance requirements typically include barrier properties (e.g. oxygen, moisture, light, biologics), sterilization compatibility, and biocompatibility.

Barrier properties

Barrier properties are evaluated by standardized/instrumented test methods such as those listed in the table below. Different materials range in their ability to protect against the influx of potential contaminants. Ethylene vinyl alcohol (EVOH), for example, is a superior oxygen/gas barrier and is often used in packaging for products susceptible to oxidative degradation, such as polyethylene orthopedic implants. EVOH's complex crystal structure creates a tortuous pathway for molecular diffusion, thereby slowing the rate of gas transport across the film. However, due to its hygroscopic nature, EVOH is not a functional moisture barrier. Water absorbed by EVOH plasticizes the polymer, causing a loss of oxygen barrier properties. For this reason, EVOH is often used in multilayer packaging, in which an outer layer serves as a moisture barrier to both protect the product and preserve EVOH's performance.

Barrier to:	Test Method/Instrument:	Common Packaging Materials:
Oxygen	- Headspace gas analyzer	Ethylene vinyl alcohol (EVOH) Nylon
Moisture	- ASTM D6701 *Standard Test Method for Determining Water Vapor Transmission Rates Through Nonwoven and Plastic Barriers* - ASTM E96 *Standard Test Method for Water Vapor Transmission of Materials* - ASTM F1249 *Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor*	Polyethylene Polypropylene
Light	- USP <671> *Containers – Performance Testing*	Aluminum
Biologics	- ISO 11737 *Sterilization of Health Care Products – Microbiological Methods*	Polymer films* Tyvek®

*Solid polymer films comprised of common packaging materials suitable as barriers for other environmental contaminants (e.g. oxygen, moisture, light), multilayered films, or films with a foil lamination are generally suitable for use in packaging to protect against biological contamination.

Multi-layer or multi-level (e.g. primary, secondary) packaging is often required to achieve the necessary performance. CPG analyzes layered packaging materials to characterize properties or identify constituents in the case of an unknown system. Analysis methods include microscopy, spectroscopy, and thermal analysis. As shown in Figure 1 (left), optical microscopy and scanning electron microscopy (SEM) can be used to determine the number and thickness of layers present in a packaging material. When SEM is combined with energy dispersive spectroscopy (EDS), elemental information can be used to aid in identification. For example, in the multilayer packaging material shown in Figure 1 (left), there was an aluminum lining contained within two different polymeric layers. The EDS map identified the aluminum lining and indicated a thicker carbon-based lining on one side and a carbon- and oxygen-based lining on the other side, but identification of the polymers required Fourier transform infrared spectroscopy (FTIR) analysis.

Multi-layered polymer systems can be challenging to identify due to lack of visual or elemental contrast. However, careful sample preparation may allow for visualization of the interface between layers or separation of layers for subsequent analysis. When layers cannot be separated, spectroscopic techniques, such as FTIR or Raman spectroscopy can be employed. FTIR can be used to scan the exposed surfaces using attenuated total reflectance (ATR), and if the film is sufficiently thin (< ~250 µm) and transparent, scanning in transmission can indicate whether one or more intermediate layers is present. Raman spectroscopy can scan through the depth of the film to not only identify the polymer constituents in each layer but also provide a layer thickness measurement. Differential scanning calorimetry (DSC) can also be used to identify polymers by detection of characteristic glass or melt transition temperatures (Figure 1 (right)).

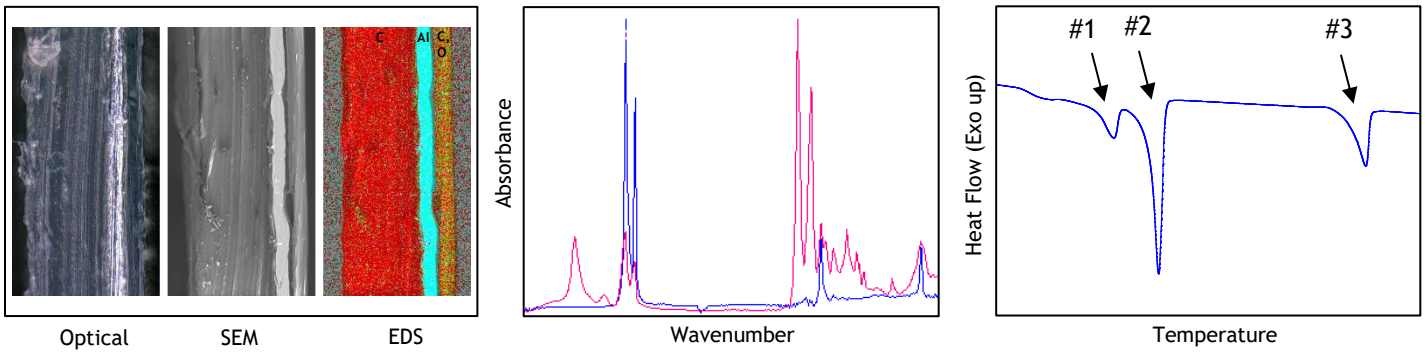

Figure 1: Left: Optical (left), SEM (middle), and EDS (right) micrographs showing the cross-section of a multi-layered packaging material with a polymeric outer layers and metallized lining; Center: FTIR spectral overlay showing spectra acquired from the two surfaces of a bi-layer packaging material comprised of polyethylene (blue) and nylon (pink); Right: DSC thermogram of a tri-layer packaging material, showing three distinct melt transitions consistent with the melting points of the polymers comprising the three layers.

Sterilization compatibility

When selecting packaging materials, considering compatibility with the intended sterilization modality is critical. For example, sterilization by ethylene oxide (EtO) requires packaging that is permeable by the EtO gas to allow exposure to and evacuation of the toxic gas. Because EtO requires humidity to catalyze the alkylation reaction that sterilizes the product, the packaging must also be compatible with moisture. Similarly, autoclaving requires packaging that is permeable to water vapor and, therefore, must be unaffected by moisture. The high temperatures used in autoclaving (typically 121 – 134 ºC) also require thermal resistance and dimensional stability when heated. While other packaging solutions are available for both EtO and autoclaving, a common solution is found in spunbond polyethylene fibers, often referred to by the tradename Tyvek®. The nonwoven construction offers a unique solution in that gas molecules can penetrate the porous barrier, but the randomly oriented fibers provide a sufficiently tortuous pathway to prevent penetration by microbes and other biological contaminants.

Gamma and electron-beam (e-beam) sterilization processes expose the product and packaging to ionizing radiation, so the packaging must be formulated to withstand potential degrading chemical reactions (e.g., through incorporation of antioxidants). Materials that are highly susceptible to degrading chemical reactions, such as conventionally stabilized polypropylene, are not suitable for gamma or e-beam sterilization. If a packaging material were to degrade during sterilization, the product shelf life or sterility may be compromised.

Biocompatibility

The complete material formulation as well as the contacting materials comprising the contained product must be considered when selecting a packaging material. Additives are often incorporated into materials to modify performance properties (e.g., to provide oxidative resistance), but the additives may not always be biocompatible. If the additives are biocompatible or can be demonstrated to remain contained within the packaging, the formulation may still be acceptable for use in medical or pharmaceutical packaging. The risk associated with transfer of packaging materials through contact, extraction (into a liquid product), or particulate generation, for example, must be evaluated through a chemical risk assessment. An extractables or leachables assessment per ISO 10993-18 *Biological evaluation of medical devices – Part 18: Chemical characterization of medical device materials within a risk management process* is necessary for the final product, though it may also be applied directly to packaging materials.

User interface

Beyond material selection considerations, packaging design must consider the end user interface. Packaging that cannot be opened or that opens prematurely is ineffective and can compromise the product shelf life. The forces required to peel apart or tear through a seal can be evaluated following standardized methods such as:

- **ASTM F88** *Standard Test Method for Seal Strength of Flexible Barrier Materials*
- **EN 868-5** *Packaging for Terminally Sterilized Medical Devices – Part 5: Sealable Pouches and Reels of Porous Materials and Plastic Film Construction – Requirements and Test Methods*
  - *Annex D Method for Determination of the Strength of the Seal for Pouches and Reel Material*
  - *Annex E Method for Determination of Peel Characteristics of Paper/Plastic Laminate Products*
- **ASTM D1938** *Standard Test Method for Tear-Propagation Resistance (Trouser Tear) of Plastic Film and Thin Sheeting by a Single-Tear Method*
- **ASTM D1876** *Standard Test Method for Peel Resistance of Adhesives (T-Peel Test)*
- **ASTM D6862** *Standard Test Method for 90 Degree Peel Resistance of Adhesives*
- **ASTM D903** *Standard Test Method for Peel or Stripping Strength of Adhesive Bonds*

These methods may be used to evaluate the effects of various manufacturing conditions, such as weld time/temperature/force, adhesive selection, etc. on seal performance. CPG has applied peel testing within a design of experiment (DOE) to optimize manufacturing conditions (Figure 2).

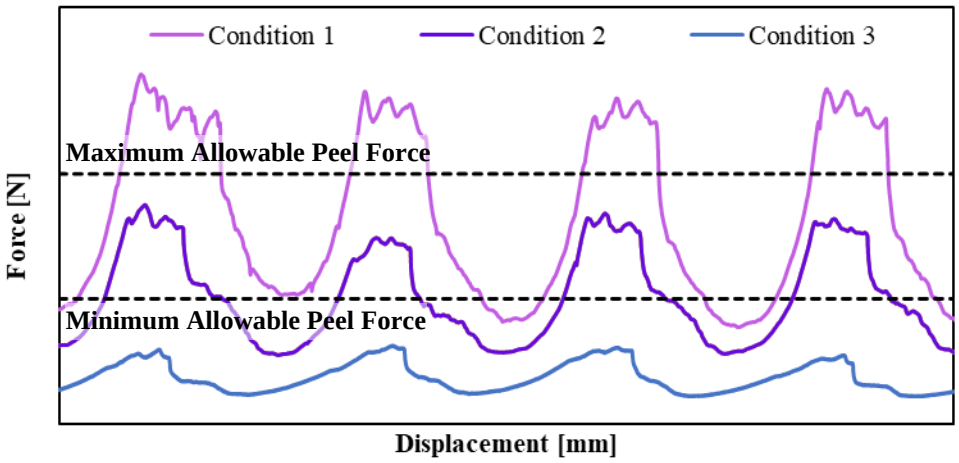

Figure 2: Peel force measurements for four consecutive peel segments for packaging seals manufactured with various welding conditions.

Condition 1 exceeded the peel force requirement and provided an unsatisfactory user experience.

Condition 3 did not meet the minimum peel force requirement and was therefore susceptible to premature opening.

Condition 2 met the peel force requirements and was selected for continued manufacture.

Package Testing

The ability of packaging materials to achieve and maintain the necessary performance characteristics is evaluated as-manufactured and after shelf aging through the life of the product. To accelerate testing timelines, accelerated aging methods such as ASTM F1980 *Standard Test Method for Accelerated Aging of Sterile Barrier Systems for Medical Devices* are employed. Accelerated aging typically involves storing the materials at elevated temperatures, though other potential accelerating factors, such as humidity, light, pH, etc., must also be considered during design of the stability plan. An acceleration factor, known as a Q_{10} value, defines the degree of acceleration achieved by increasing the temperature relative to standard storage conditions. The acceleration factor may be assumed using conservative values outlined in the standard method or literature, or it may be determined experimentally. In either case, data collected after accelerated aging must ultimately be supported by real-time aging data.

CPG can also measure oxygen content in packaging to determine if the oxygen barrier properties are doing their job.

Conclusions

Improper selection of packaging materials for medical devices and pharmaceuticals could lead to costly circumstances resulting from reduced shelf life or sub-optimal product performance. Beyond appearance, packaging design must consider interactions with the product as well as performance stability through manufacturing, sterilization, and shelf aging processes. A deep understanding of materials science is critical when selecting packaging materials.

CPG Packaging Services

Contact Cambridge Polymer Group for help with your packaging selection or characterization needs.

- Material Selection
- Deformulation/Identification
- Chemical characterization/ISO 10993-18
- Oxygen Content
- Water Vapor Transmission Rate (WVTR)
- Fourier Transform Infrared Spectroscopy (FTIR)
- Raman Spectroscopy
- Differential Scanning Calorimetry (DSC)
- Accelerated Aging
- Optical Microscopy
- Scanning Electron Microscopy (SEM)
- Energy Dispersive Spectroscopy (EDS)
- Tensile Strength
- Peel Force
- Tear Strength

About Jaimee Robertson

As Director of Consulting Services at Cambridge Polymer Group, Jaimee Robertson develops new medical devices from initial specifications through concept refinement and product manufacturing, helping clients turn their product visions into reality. Drawing on her years of experience in medical device innovation, she develops custom analytical techniques to characterize polymeric materials, including in-vitro test assays for screening product performance in simulated end-use conditions. Jaimee performs root-cause analysis on medical devices to assess potential and actual failure modes. She received her B.S. in Chemical Engineering and Mathematics and her M.S. in Chemical Engineering at Syracuse University.

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