

CHAPTER 38

SELECTING MATERIALS FOR MEDICAL PRODUCTS

Sherwin Shang
Baxter Healthcare Corporation
McGaw Park, Illinois

Lecon Woo
Baxter Healthcare Corporation
Round Lake, Illinois

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1 INTRODUCTION

Medical device and medication delivery system products are critical sectors in the medical, pharmaceutical, and health-care industries. Many medical devices and solution drug delivery systems are disposed after a single use. These disposable devices and delivery systems are generally produced from polymeric materials. The disposable materials that host solution drugs or biological agents are recognized as parts of drugs and biological agents. New drug applications (NDA) to the Food and Drug Administration (FDA) and to foreign government regulatory agents are required. In contrast, the materials used in many devices

and disposables that have short solution drug or human contacts require 510K approval.

A new medical product must prove product safety and efficacy to the FDA before market launch. Material toxicology such as testing under U.S. Pharmacopoeia (USP), European Pharmacopoeia (EP), or Japanese Pharmacopoeia XIV (JPXIV) guidelines is used to ensure the safety of the materials for medical product applications. The extractive contents and levels from poststerilized materials indicate the potential impact to solution drug or biological agent quality. Solution stability is used to understand the interactions of polymeric materials with the hosted medication fluids during product shelf life. Examples in Table 1 of medical devices include angioplasty, hemodialyzer, syringe, and oxygenator. Disposable sets and solution containers in medication delivery system include those used to host intravenous (IV) solution, blood components, peritoneal dialysis solutions, parenteral nutritious solutions, and biological agents for infusion and transfusion therapies.

Selecting materials for medical device and disposable products have stringent guidelines. Table 2 lists the FDA International modified ISO 10993-1 test matrix. The materials are tested after exposure to the desired sterilization modes. The biological testing on the materials is dependent on the intended contact duration and body contact. The contact duration is classified as limited (<24 h), prolonged (24 h to 30 days), and permanent (>30 days). The body contact is categorized according to surface devices, external communicating devices, and implant devices.

Regardless of the applications of medical products, the health-care and medical industries always attach a premium to medical product optical clarity. A material's ability to allow unimpeded light transmission is not just a desire to be "clean" but is rather rooted in good clinical practice. For example, in nu-

Table 1 Examples of Medical Products

Medical Product	Product Characteristics
Angioplasty, hemo dialyzer, and oxygenators	Medical device whose materials are compatible to blood and blood vessel tissue.
Intravenous (IV) solution and drug delivery system	Solution drugs stored in a medical container whose materials are suitable to host solution drugs for long shelf life storage without concerns of drug interaction and concentration variation.
Blood collection, processing into red blood cells (RBC), platelets, and plasma, and then storage for blood transfusion	Anticoagulants are stored within blood collection bags to prevent blood agglomeration. A breath container material is a must for red blood cells and platelet storage. Low-temperature ductile impact film for plasma storage at sub-ambient temperatures.
Nutritious solution and peritoneal dialysis (PD) solution containers and their delivery system	Solution drugs stored in medical containers that can be steam sterilized to meet sterility requirements. No drug degradation or harmful extractives from container materials during autoclaving.
Pharmaceutical blister, bottles, and containers	To host solid drug tablets whose packaging materials have good barrier properties of moisture, O ₂ , and CO ₂ , and UV exposure.
Syringe and drug prefilled syringe	Empty is a medical device that requires on 510K approval, but prefilled syringe is a drug product that require New Drug Application (NDA) approval.

Table 2 FDA-Modified ISO 10093-1 Test Matrix

Device Body Contact	Contact Duration ^a	Cytotoxicity	Sensitization	Irritation/ Intracutaneous	Systemic Toxicity	Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Repro./ Devel./ Biolog.
Surface devices												
Skin	Limited Prolonged Permanent	X X X	X X X	X X X								
Mucosal membrane	Limited Prolonged Permanent	X X X	X X X	X X X	o o o	o X	— X	o o	—	o		
Breached or compromised surfaces	Limited Prolonged Permanent	X X X	X X X	X X X	o o o	o X	— X	o o	—	o		
External communicating devices												
Blood path, indirect	Limited Prolonged Permanent	X X X	X X X	X X o	X X X	— o X	— — X	— o	X X X	X X X	X	
Tissue/bone/dentin communicating	Limited Prolonged Permanent	X X X	X X X	o o o	o o o	o o	X X	X X	—	o	X	
Circulating blood	Limited Prolonged Permanent	X X X	X X X	X X X	X X X	— o X	o X X	— o o	X X X	X X X		X
Implant devices												
Tissue/bone	Limited Prolonged Permanent	X X X	X X X	X o o	o o o	o o	X X	X X		X X	X	
Blood	Limited Prolonged Permanent	X X X	X X X	X X X	X X X	— o X	— X X	X X X	X X X	X X X	X	X

Note: X = required; o = option.

^aLimited contact, ≤24 h; prolonged contact, 24 h–30 days; permanent contact, >30 days).

merous primary medical containers, prior to administration of the medical fluid to the patient, the nurse is required to inspect visually for particulate matter (PM) contamination. This inspection is required to protect patients against the danger of exposure to the visible contaminants.

In situations where medications in the powder form need to be mixed or compounded prior to administration, the ability to visually inspect for the completion of dissolution is another important safeguard for patient safety. Recently, transfusion therapies involving harvested, stored, and cultured cellular components became widespread. During the *in vitro* phase, these cellular components frequently need to be manipulated through separation, fractionation, and incubation for diagnostic or therapeutic purposes. In many of the steps, the ability to inspect contents visually or microscopically is crucial to the clinical protocol. These are just a few reasons that optical clarity is a prerequisite criterion for medical material selections.

Another attribute specific to the health-care and medical industries is the need to deliver therapies in a sterile manner. As a consequence, compatibility with common sterilization methods is a must. These methods include steam autoclaving, ethylene oxide (ETO) sterilization, and ionizing radiation (either gamma or electron beam.)^{1,2} Steam autoclaving places a severe burden on the prospective medical material with the use of high temperature (such as 121°C) and pressure. Ethylene oxide is currently being phased out due to worker exposure and environmental concerns, while long-term shelf life stability is an issue for the material postirradiation sterilization.

A third requirement that has received increasing attention is environmental compatibility. As professionals concerned with health care, we obviously cannot, in the course of mending our patients, destroy the environment that we live in and our children will inherit. Of course, the quantitative "environmental score" is quite elusive and often subjected to passionate debate. However, some of the basic tenets are very obvious; progressive companies have already adopted many of the practices in this direction.

All these have urged the medical industry to select safe, clean, and environmentally friendly materials to meet safety, manufacturability, and functionality requirements for medical products. These requirements thus pose the constraints and challenges on the materials selected during product development for medical, pharmaceutical, and health-care industry.

2 CHALLENGES OF MEDICAL PRODUCTS

Medical product challenges faced today are not only from technical advances but also from business competition. Safety is the highest priority. Product clarity, stability, biocompatibility, and low extractives are highly valued. Many medical and health-care products require a specific level of oxygen (O₂), carbon dioxide (CO₂), or water vapor transmission rate (WVTR) at room temperature. These products can be either very rigid or very flexible, and for some drug delivery systems and medical devices superior subambient impact is required. Furthermore, the selected medical materials should be compatible to the desired sterilization mode and render no harmful damage to the packed devices, drugs, and disposable systems.

Polymeric materials are part of the finished medical products. A lowest possible total system cost is used to direct product development and finished product

manufacturing. From a business viewpoint, the lowest system cost guideline has a great impact in determining product design, material selection, and manufacturing processes. The lowest system cost can be achieved when the design, materials, and manufacturing are taken into accounts simultaneously. For example, a lowest system cost is still feasible when employing a costly material that enables to simplify the design and reduce manufacturing cost.

In the managed-care environments, the patient care has been gradually switched from doctor care to insurance provider care. The cost is extensively monitored and supervised. Under this great competition, high medical product quality is expected with no further premium increments. Moreover, home care also gradually becomes popular. This requires the medical manufacturers to design ease-of-use medical products for patients with no specific training in the medical field. The medical design and materials selection can play a critical role to fulfill the patient expectation, meet product functions, and achieve business goals.

3 PRODUCT DEVELOPMENT FUNDAMENTAL FACTORS

The key factors that govern the development of medical products can be categorized into four distinct areas: product design, material selection, manufacturing process, and product performance.^{3,4} The detailed requirements of these four areas are listed in Table 3. Designing user-friendly products, selecting high-performance low-cost materials, establishing cost-effective manufacturing processes, and validating product quality for safety and efficacy are a must. These considerations can greatly restrict a manufacturer's choices for developing a product.

3.1 Product Design

Medical product design is focused on safety and efficacy. Product design begins with concept design, design drawing, and stress analysis and ends with the evaluation of the prototype. Different design iterations are created and materials are selected to build prototypes. The prototype is modified after feedback from clinicians, patients, engineers, and manufacturers. The functionality is tested to confirm the desired efficacy.

For example, to maintain product sterility integrity during shelf life, a closed system design is required. In addition to product design for safety and efficacy, the product design also includes device component design such as molding and assembly, particularly for component joining, welding, and bonding. These designs are typically under the constraints of materials availability, cost of materials, materials compatibility for joints, manufacturability, sterilization modes, and product integrity during the shelf life and up to the time of use. Moreover, marketing always prefers to have features beyond safety and efficacy; good product features are usually an excellent vehicle to win patient acceptance.

3.2 Selecting Materials

The process of selecting suitable materials for medical products begins with the creation of a precise and accurate definition of the product's material and functional requirements. Finding the right polymers for medical products requires simultaneous consideration of design, processing, and performance needs.¹ Other critical factors considered at the material selection stage include biocompatibil-

Table 3 Medical Product Development Considerations

Product design	<ul style="list-style-type: none"> Safety and efficacy Product functionality Ease of use Product integrity Design a closed system to ensure sterility integrity Flexibility for medical product design Easy assembly No build-in residual stress in plastic components Bonding/assembly capability among product components Easy quality control by operator vision or instrumental sensor Sterilize/form/fill/seal
Materials selection	<ul style="list-style-type: none"> Meet requirements of safety, design, processing, and performance Material compatibility for product components assembly Drug and solution contact Biocompatibility and chemically inert Leachables and oligomer residues Optical clarity WVTR, O₂, and CO₂ barrier Subambient impact resistance Material aging, particularly after sterilization Additive chemicals and catalyst residue Lot-to-lot consistency from resin supplier Environment friendliness Cost Supplier technical service
Manufacturing processing	<ul style="list-style-type: none"> Extrusion/molding/thermoforming capability Large-scale manufacturability High production output rate Wide processing operation window Compatibility with the plant's existing manufacturing systems Assembly technology Sterilization methods
Product performance	<ul style="list-style-type: none"> Safety, efficacy, and quality Unique features Cost/performance Function oriented Market competition Customer delight User friendly Cosmetic appearance Touching feeling Odor

ity, leachability, drug-plastic interaction, oxygen and moisture barrier protection, optical clarity, ultraviolet (UV) stability, shelf life, the end-use environment, and total system costs. In addition, designers must consider the demands of downstream operations such as component bonding, assembly, shipping, storage, and post-use disposal.

One of the key factors in medical material selections is the sterilization effect to the material properties. Steam sterilization demands that the melting points of materials exceed their autoclaving temperatures. Ethylene oxide (ETO) sterilization needs to vent the residual ethylene oxide from the device fluid path to a minimum level before products can be released. Radiation poses potential materials degradation that could impact the product performance and also its extractives might interact with solution drugs or biological agents.

Gamma Radiation Effect on Medical Materials

Gamma sterilization is becoming popular in the medical device and packaging industry because of convenience and low cost. Concerns of worker exposure to ethylene oxide and temperature limits of medical materials during high steam autoclaving have made gamma sterilization more preferable. This mode of sterilization is a consequence of the high-energy electrons released from the interaction of the gamma-ray photons with materials. These high-energy electrons in turn react with the deoxyribonucleic acid (DNA) sequences in the microbiological burden in medical devices and drug delivery systems and permanently alter their chemical structures to render them innocuous.¹

The high-energy electrons, however, can also initiate ionization events in the material being sterilized. It can create peroxy and hydroperoxy free radicals in the presence of oxygen and start the degradation cascade. Different materials degrade via various mechanisms, leading to different modes of failure such as discoloration, excessive pH shifts and high extractables, and catastrophic failures. Gamma exposure at 20 and 50 kGy (10 kGy = 1 Mrad) is usually used for radiation sterilization. Oxidative induction time (OIT) and yellowness index (YI) are used to identify a material's radiation sterilization compatibility. OIT, a method of thermal analysis measured by differential scanning calorimetry (DSC),^{2,5-8} is used to measure the total stability of a polymer at a given condition. A more stable plastic has a higher OIT value.

Polyvinyl chloride (PVC) thermal stability, measured as OIT in Fig. 1, has been reported to exhibit a rather sharp maximum with respect to the concentration of a primary stabilizer, calcium zinc stearate at about 0.2 phr (part per hundred) or about 0.13% for the system studied.⁵ It was noted that an extremely linear relationship was found for the secondary stabilizer such as epoxidized oil. Combined together, Fig. 2 shows the PVC stability function spanning a three-dimensional design space.

The OIT responses of a PVC formulation at 230°C as a function of the sterilization dose is shown in Fig. 3 with a dose rate of about 6 kGy/h. From the

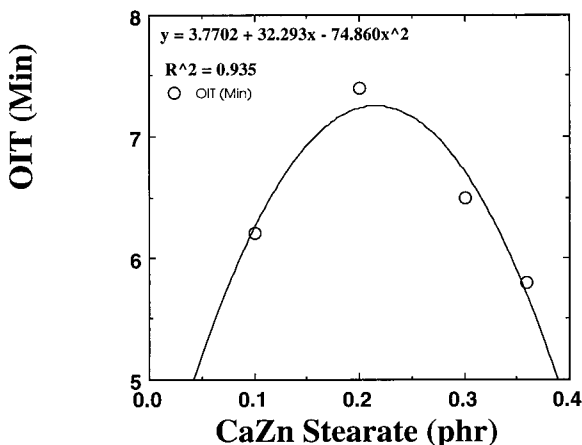


Fig. 1 PVC OIT dependence on CaZn stearate.

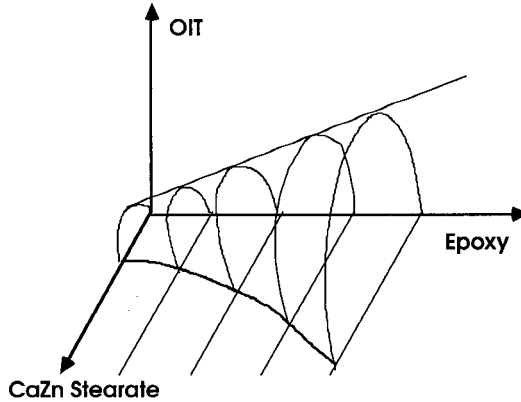


Fig. 2 Three-dimensional schematic of PVC stability.

zero dose OIT of about 9 min, a steady reduction in total stability was seen. In addition, the slope (rate of OIT decrease) appeared to increase from 20 to 40 kGy, indicating a nonlinear response accelerating the degradation reaction at high doses. Figure 3 also indicates that after 40 kGys the formulation loses more than half of the initial total stability. This will limit the maximum dose this particular formulation was capable of sustaining.

Radiation also changes polyolefin stability. In a hindered phenol-stabilized high-density polyethylene (HDPE) film system, the film OIT at 200°C was determined for dose levels of 0, 20, and 40 kGy. Results in Fig. 4 clearly indicated significant annihilation of the antioxidants during the course of the sterilization. It was noted that the OIT was nearly flat at 20–40 kGy. This suggests that the antioxidant in question did not provide additional protection when the radiation dose was reduced from 40 to 20 kGy.

When Figs. 3 and 4 were compared, PVC was noted to have a slower stability reduction than HDPE when subjected to radiation. In addition to the inherently

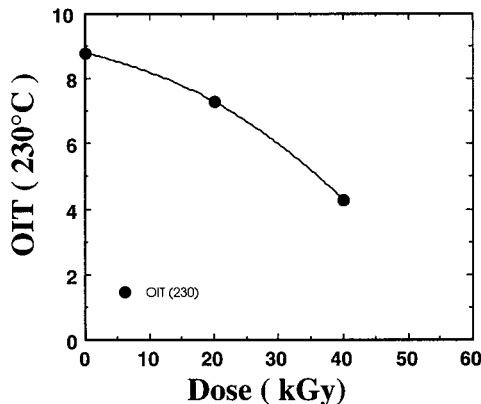


Fig. 3 Effect of radiation dose on PVC stability.

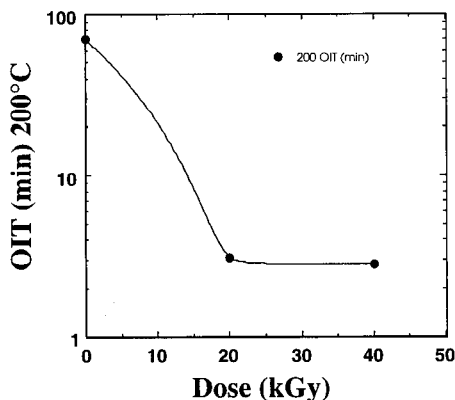


Fig. 4 Effect of radiation dose on HDPE Stability.

more stable of PVC over PE, it can be also due to the higher concentration of secondary stabilizer in PVC, which can be about 10%, as shown in Fig. 5. This may explain why the medical products made from PVC seldom encounter catastrophic failure after radiation.

Figure 5 also shows that radiation sterilization reduced the PVC secondary stabilizer concentration, as measured by high-pressure liquid chromatography (HPLC). This in turn reduced material stability as evidenced by OIT. Sterilization by radiation was noted to deplete more secondary stabilizer than the subsequent steam autoclaving and pasteurization combined.

In contrast, catastrophic failures have been reported during polypropylene (PP) shelf life storage. Intense investigation came to the following consensus:^{5,9-12} The long-lived free radicals trapped in the crystalline domains migrating toward the crystalline/amorphous interface combining with available oxygen form peroxy and hydroperoxy radicals that initiated degradation near the interface.³ As enough tie molecules between crystallites were cut through the chain

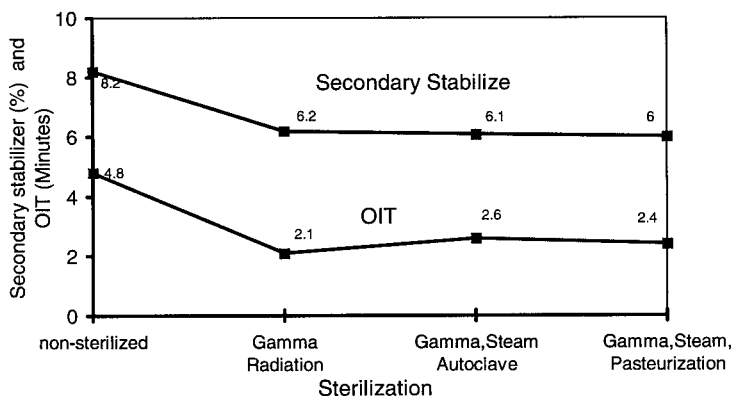


Fig. 5 Change of OIT with secondary stabilizer concentration of PVC.

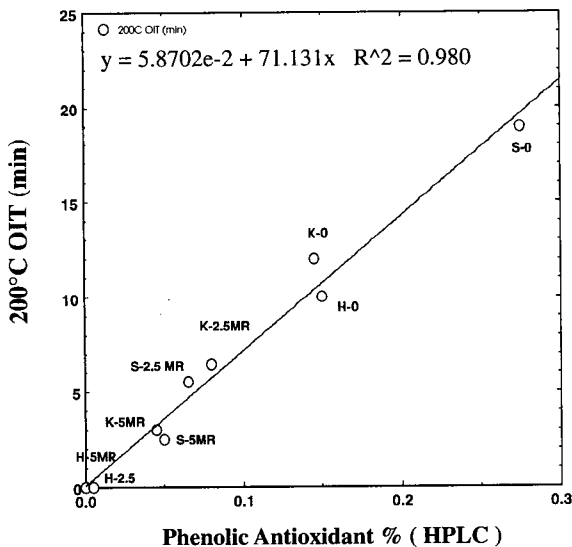


Fig. 7 PP OIT dependence on antioxidant concentration.

from 9 to 4 min., the PVC YI value increased from 20 to 50. The increase in YI can be related to the poly-ene formation in PVC and quinone and hydroquinone formation from phenolic antioxidants due to radiation and thermal exposures.

Without quinone and hydroquinone formation in a proper stabilizer system, the increase in PVC color, measured by YI, is the result of a series of conjugated dienes (poly-enes) in PVC molecule chains formed by cationic dehydrohalogenation of PVC. Since the electrons on these conjugated dienes can freely move over the entire length of the conjugated diene, a one-dimensional electron well resulted. The length of conjugated dienes can be increased due to ineffective

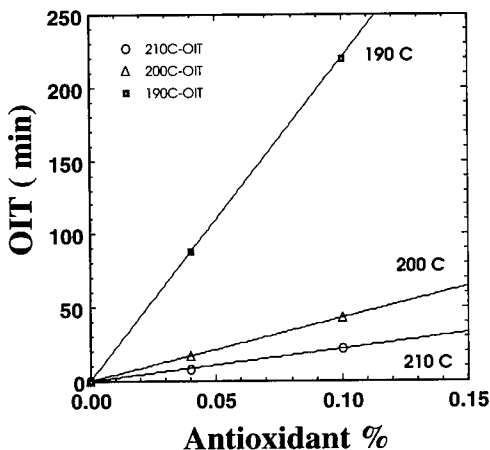


Fig. 8 HDPE OIT dependence on antioxidant concentration.

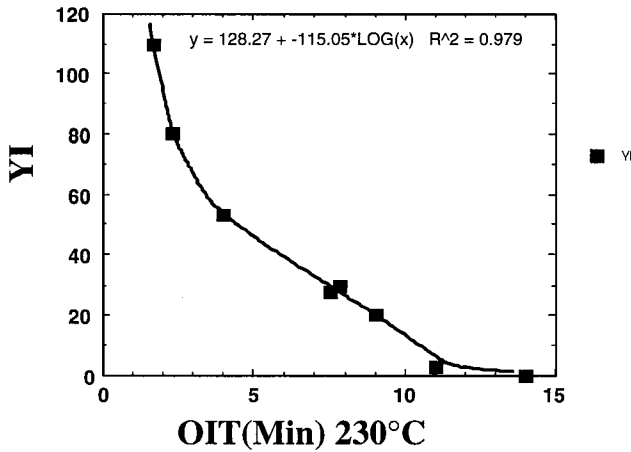


Fig. 9 Correlation of PVC OIT and color YI.

stabilizer protection during radiation sterilization. The energy levels and the absorption spectra of the free electron can thus begin to move from ultraviolet (UV) toward the visible wavelengths. As the absorption spectra increase in intensity from the short wavelength direction, the originally clear PVC film starts to appear yellow to dark yellow, orange, red, and finally black as the degradation progresses.

In PVC medical containers used for drug delivery system, a better quality film material made from a superior stabilizer system is expected to have a higher thermal stability than a standard PVC. The superior stabilizer system has an extra gamma-compatible additive component than the standard stabilizer system. Figure 10 shows that the better-quality PVC has a higher OIT for both sterilized

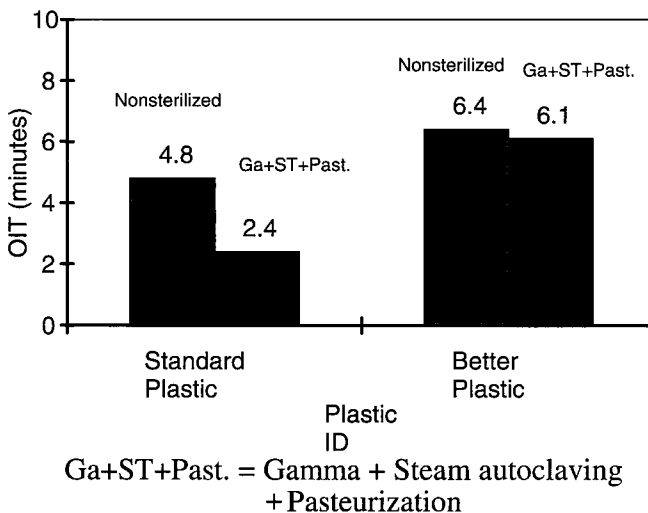


Fig. 10 Effect of stabilizer system on PVC stability.

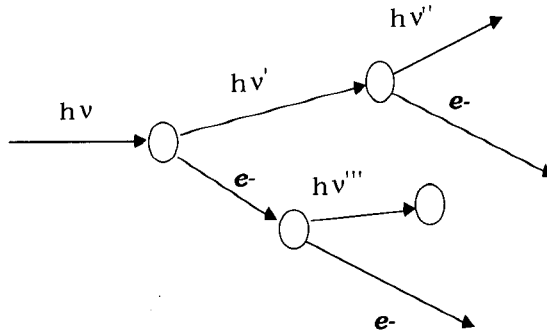


Fig. 11 Compton scattering with matter.

and nonsterilized material. This is because a more effective PVC stabilizer system can minimize both thermal degradation during film extrusion and the subsequent radiation sterilization.

Electron Beam (E-Beam) Radiation Effect on Medical Materials

Recent advances in electron beam technology have made this mode of sterilization a worthy competitor to the traditional gamma processing. Some key factors of E-beam critical to medical industry are the increased available energy, compact design, improved reliability, easy turn on and off, and an effective source without steadily depleting with time.

The primary interaction between gamma radiation and E-beam with matter is known to be different. However, the major interaction is still Compton scattering for both cases. It is mainly the shower of secondary electrons, as seen in Fig. 11, that initiates the ionization events that activate numerous chemical reactions, many of which lead to oxidative degradation.

Although the main interaction with matter is basically the same for gamma and E-beam, minor differences between the two modes remain. The principal differences in Table 4 are the charge and the rest mass.² The absence of both a rest mass and a charge gives gamma radiation far greater penetration power than E-beam, whose penetration is primarily dependent on kinetic energy or the potential difference through which the electrons were accelerated.

Doses higher than those employed for sterilization were used to explore and accentuate minor differences. However, doses higher than that of the sterilizing

Table 4 Characteristic Comparison of Electron Beam and Gamma Irradiation

Mode	Electron Beam	Gamma Irradiation (^{60}Co)
Charge	-1	0
Rest mass	$9e^{-28}$ g	0
Energy	0.1-15 MeV	1.17 MeV
Velocity (C, light speed)	0.3-0.99 C	1.0 C

Note: Bond energy = 3-10 eV
UV source = 4-5 eV

dose are commonly encountered in medical device manufacturing. Rework can require a doubling of the radiation doses. Dose variations under a given exposure condition would also increase the upper dose limit to achieve the minimum dose required. Also, biological indicators with more resistant strains would likewise increase the required nominal dose.

A gamma irradiator typically delivers dose at rates approximately between 5 and 20 kGy/h, while for electron accelerators it could deliver dose rates as much as 10,000 times higher. Under such high dose rate conditions, significant thermal effects could arise to modify the material's reaction pathways. Due to the huge dose rate disparity, irradiation exposure times are also vastly different. While it is not uncommon for a gamma facility to deliver the sterilizing dose in several hours, the E-beam would take mere seconds for the same dose delivery. It is known that available oxygen diffusion during the exposure times would constitute another factor on materials degradation.¹³

The OIT conducted at 230°C for the gamma-irradiated flexible PVC in Fig. 12 exhibits a near monotonic reduction from the control. This PVC has a better thermal sterilizer additive packaging than the PVC reported in Fig. 3. Between 60 and 100 kGy, a slight reduction in slope is also apparent. However, when compared with the E-beam samples in Fig. 12, the gamma samples appear to follow a slightly steeper slope, at least for the lower dose exposures.

At or around 60 kGy, both the gamma and E-beam samples exhibited an upward shift in slope, indicating that additional doses have proportionally less degradation effect. This could be due to a secondary stabilizer, epoxidized oils, in the flexible PVC that reduces degradation through secondary reaction pathways. It is also interesting to note that even at 100-kGy dose levels, a significant fraction of stabilizer in the flexible PVC remained. This could be due to the relatively high stabilizer loadings for this medical PVC formulation.

In sharp contrast with the flexible PVC, the medium-density polyethylene (MDPE) film in Fig. 13 underwent a drastic reduction in OIT or antioxidant potency. At a dose of 30 kGy, OIT of MDPE was reduced from almost 900 min of induction time to about 20 minutes at 180°C. Subsequent additional doses resulted in a near linear decline in OIT on the logarithmic scale.

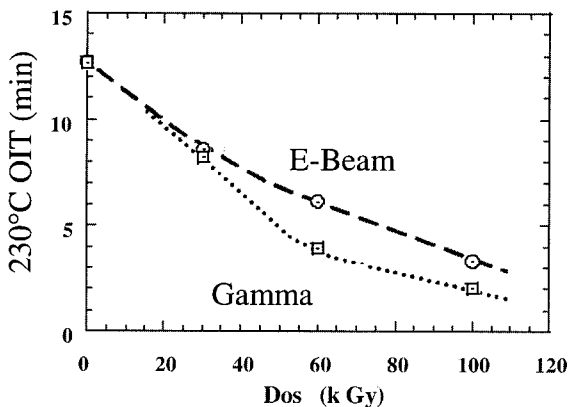


Fig. 12 Comparison of gamma and E-beam irradiation on OIT of PVC.

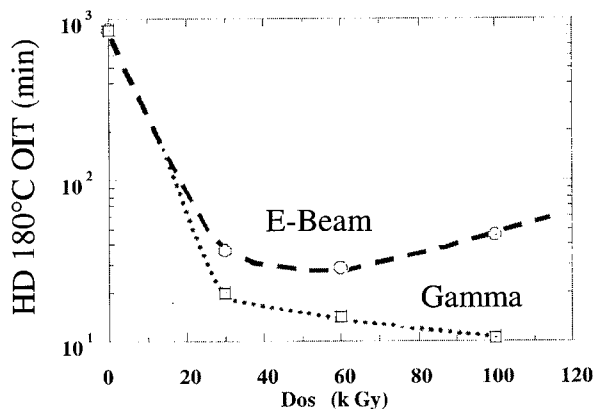


Fig. 13 Comparison of gamma and E-beam irradiation on OIT of MDPE.

This significant reduction in OIT stability was also seen in Fig. 13 in the E-beam samples at 30 kGy, although a slightly better retention of antioxidants is seen with the E-beam. At 30 kGy, the E-beam has about 40 min on OIT as compared with 20 min for gamma. From 60 to 100 kGy in E-beam, a distinct upturn in OIT is plainly evident. This upturn is most likely caused by thermal and exposure time effects under high dose rates from limited oxygen availability and accelerated free radical termination reactions favored at higher temperatures.

For the PP sample, a drastic OIT reduction is evident again, with even greater depletion ratios under gamma irradiation in Fig. 14. Once more, the OIT upturn at higher dose rates are very pronounced under E-beam. Most likely, similar dose-rate-related exposure time and thermal effects are the causes.

The significant departure toward greater overall stability and the upturn at 100 kGy could be rationalized by the extremely high dose rate and the resulting temperature rise. At these high doses, E-beam dose rates of over 200 kGy per second or 720,000 kGy per hour are encountered, or about four orders of magnitude higher than that of the gamma irradiation. In terms of the irradiation time,

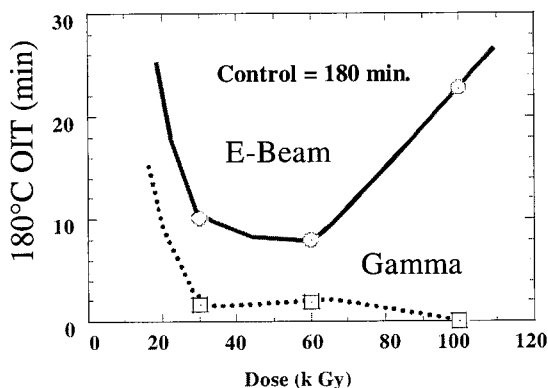


Fig. 14 Comparison of gamma and E-beam on OIT of PP.

instead of nearly 17 h for 100 kGy, it would take 0.5 s for the E-beam. These high dose rates would invariably lead to much higher free radical concentrations during the exposure and much higher recombination reactions discussed earlier.

Using a standard specific heat at room temperature of $1.7 \text{ J}/^\circ\text{C}$ for PP, and assuming no heat loss (adiabatic), temperature rises for PP are shown in Fig. 15. It is seen that particularly for 100 kGy, a temperature over 85°C is reached. At the higher temperatures, the free radical recombination and termination reaction is expected to be much faster than at near 25°C . Less antioxidant consumption and less polymer degradation are predictable. The potential side effect of higher dose rate by E-beam could be surface cosmetic defects on medical devices due to fast melt and cooling.

The E-beam results suggest medical device and medication delivery system made from PP materials could be E-beam sterilized. The concerns of catastrophic failure could be minimized. The OIT indicates that PP has much better thermal stability at the high dosage of E-beam sterilization. This recommendation, however, still requires the confirmation from real-time sample testing, particularly with medical products for up to 2 years of product shelf life.

3.3 Newly Commercially Available Polyolefin-Based Materials

Recent progress in metallocene technology, including the ability to produce inexpensive metallocene catalysts, has led to the development of cost-effective metallocene-based polyolefin and cyclo-olefin materials. Metallocene polyolefins have the potential to achieve much better performance than existing PE and PP formulations. Cyclo-olefin materials give a high clarity for medical applications. Because they have properties similar to many specialty polymers and engineering plastics, metallocene polyolefins have the potential to replace PVC and some expensive engineering plastics, particularly for medical products requiring high clarity and impact strength and ductility at low temperatures. As a result, this polyolefin family is showing great potential for use in the medical and health-care products industries.

The materials used by most of medical device and solution drug delivery systems today are still dominated by PVC materials. To be useful in medical

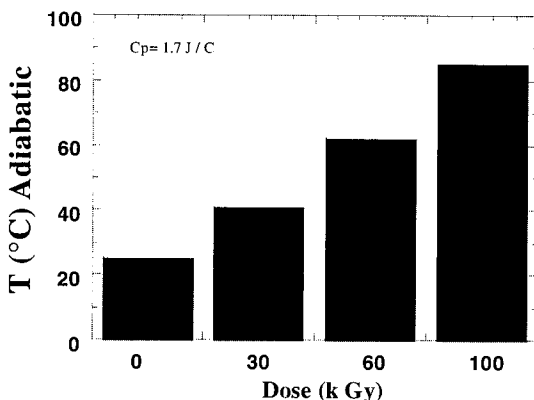


Fig. 15 PP temperatures rise at different E-beam doses.

products, however, metallocene-based polyolefins must also fulfill product design, processing, and performance requirements simultaneously. To meet these criteria with high product quality at the lowest possible cost, it will require a broad spectrum of material characteristics and processing capabilities.

PVC versus Metallocene-Based Polyolefins

Device manufacturers that wish to consider the use of metallocene polyolefins for use in medical devices or medical packaging will need to look at a wide range of characteristics. While the major traits of PVC have been established through a long history of use, those related to metallocenes are still emerging as the technologies develop and improve. Following are some of the key advantages and disadvantages of each, as their respective technologies now stand.

Advantages of PVC. Polyvinyl chloride can be used to produce a variety of medical products ranging from rigid components to flexible sheeting. The type and amount of plasticizer used determine the compound's glass transition temperature (T_g), which in turn defines its flexibility and low-temperature characteristics and thereby establishes its range of suitable applications.

Because rigid and flexible PVC components have the same material structure, they can be easily assembled by solvent bond. The two solvents most commonly used in PVC bonding are cyclohexanone and methyl ethyl ketone (MEK). Rigid parts that have been molded of PVC are suitable for ultrasonic bonding, while flexible extruded or calendered PVC films can be sealed using heat or radio-frequency (RF) sealing.

Medical products made from PVC can be sterilized by steam, ethylene oxide, or gamma radiation. Plasticized PVC can have a T_g as low as -40°C and still be suitable for steam sterilization at 121°C . Additional characteristics that make PVC attractive include its low cost, broad T_g spectrum, wide processing temperature range, high seal strength, thermoplastic elastomer-like material properties, high transparency, wide range of gas permeability, and biocompatibility. Medical products made from PVC have passed critical toxicological, biological, and physiological testing. In sum, PVC is one of the best medical materials in terms of cost and function. No other single material has such broad material latitude.

Disadvantages of PVC. Even though many medical products have been made from PVC, the material continues to receive criticism.¹⁴ The most commonly cited shortcomings involve toxic effluents produced during manufacture and the generation of hydrogen chloride (HCl) during incineration. Because HCl is a component of acid rain, postuse disposal costs for incinerating PVC can be quite high. Other concerns related to PVC depend largely on the type and amount of plasticizers used. For some PVC compounds, there is evidence of plasticizer leaching to medical solutions, chemical interaction with drugs, water vapor loss during long-term storage of medical solutions, and gas permeability.

Although these disadvantages sound challenging, most can be eliminated or managed using existing technologies. For instance, current PVC manufacturing techniques can reduce residual vinyl chloride monomer levels to less than 1 ppm, thus minimizing the toxic effects of the compound. Similarly, modern emission-scrubbing equipment can adequately prevent releases of HCl and other

effluents during incineration disposal. On the other hand, di-2-ethyl-hexyl phthalate (DEHP) is known to enhance red blood cell (RBC) membrane stability that prevents RBC from rupture.

With regard to the leaching of the plasticizer DEHP, however, expert opinion remains divided. California's Safe Drinking Water and Toxic Enforcement Act of 1986 raised concerns about the toxicity of DEHP. But a long-term hemodialysis study that covered more than 7 billion patient-days of exposure resulted in no widely accepted data linking DEHP exposure to carcinogenicity in human beings.¹⁵

Advantages of Metallocenes. The revolution in polyolefin materials spurred by new metallocene catalyst technologies has created a great opportunity for medical and health-care industries. High yield, high clarity, high impact resistance, and low extractables are just a few useful characteristics of this plasticizer-free polyolefin family.

Metallocene PP is one group of compounds for which research has shown great potential.¹⁶⁻¹⁷ Unprecedented control over the microstructure of PP has led to commercial production of syndiotactic PP (s-PP); material scientists are also exploring new elastomeric PP using oscillating catalysts.¹⁸ The material properties of these two new PPs are similar to those of thermoplastic elastomers (TPEs), particularly the oscillating catalyst compound, which requires only a propylene monomer. This is different from current commercial PP elastomers that are based on the monomer C3 but have C2 and C4 as comonomers.

Moreover, metallocene-based cyclo-olefin has been tested for medical syringe applications. The cyclo-olefin materials possess a high clarity for solution drug prefilled syringes that is easy for visual inspection.

Metallocene PE (m-PE), on the other hand, has been targeted for use as a film in the medical container and packaging industry.¹⁹⁻²⁰ Enhanced clarity and reductions in both initial seal temperature and crystallinity certainly create many advantages for the medical industry. Metallocene PE is also expanding into medical packaging applications traditionally dominated by ethylene-propylene-diene monomer and ethylene-propylene rubber.

There are a number of other characteristics that make metallocene-based polyolefins attractive for use in the medical industry. Most important, the TPE-like materials are chemically inert and do not interact with drugs. Their narrow molecular weight distribution (MWD) results in low leaching and extractable levels, and their high thermal stability minimizes the need for stabilizers. The materials accommodate gamma radiation, and impact-resistant s-PP film tolerates steam sterilization. Lastly, the compounds are environmentally sound and can be cleanly incinerated or recycled, thereby reducing disposal costs.

Potential Metallocene Disadvantages. The current formulations of metallocenes have a number of disadvantages that researchers may in time overcome. For instance, concern over metal residues makes researchers' efforts to reduce the use of the cocatalyst methylaluminumoxane (MAO) a matter of some urgency. Fortunately, some of newly commercially available m-PE have significantly reduced cocatalyst levels. The usefulness of some formulations may also be limited by processing concerns: Because of its narrow MWD and long crystallization half-time, for instance, s-PP is difficult to process.

Sealing presents another difficulty. Metallocene polyolefins are suitable for heat sealing but not for solvent bonding or RF sealing, which are required steps in assembling medical device kits. Similarly, metallocene PE can not be autoclaved because of its low melting point (T_m). Finally, metallocene technology must still confront the key challenge of cost reduction to meet market constraints. Although their potential is great, metallocene polyolefins will have to overcome a number of challenges before they gain wide acceptance in the medical and health-care industries. These include concerns in the areas of product safety and resin quality, product design and processing, and product performance.

3.4 Manufacturing Process

In the medical industry, it often takes great efforts and long cycle time to qualify new polymeric materials and to validate their downstream manufacturing processes before products reach the market. It is well understood that the quality and cost of the medical products depend heavily on the manufacturing processes. From medical manufacturing viewpoints, it is highly desirable to extend the applications of the approved materials to other developing products. This strategy can be achieved by maximizing material properties through an expanding process window to fulfill product performance requirements. Better quality, high throughput rate, less development time, and cost-effective products can be achieved if the manufacturing processes are optimized. Some examples of manufacturing process related material properties and product performance are discussed next.

4 MANUFACTURING PROCESS ON MATERIALS PROPERTIES

Polymeric materials suitable for medical application have passed toxicology and biological testing. Medical manufacturers always like to extend the approved materials to other product lines if the existing materials have potential to meet the product requirements. Moreover, the physical properties of materials can vary with the manufacturing processing, such as extrusion, injection molding, and compression molding. For example, the optical properties of sheeting materials, such as haze, gloss, yellowness index (YI), and gel imperfection, can be manipulated by extrusion processing conditions. Some examples are discussed next.

4.1 LLDPE Pelletization Processing on Haze, Gloss, and Gel Counts

The pelletizing conditions of linear low density polyethylene (LLDPE) resin and its blown extrusion conditions are examined simultaneously to optimize film properties. Figure 16 shows the effect of pelletization melt temperature on haze and gloss at a constant throughput rate (18 kg/h). No significant change in haze and gloss is observed as the pelletization temperature is below 250°C.

However, the gel level in the blown films is significantly affected by the output rate and melt temperature of the pelletization process. Figure 17 shows the effects of pelletization melt temperature and output rate at the fixed blown temperature of 202°C. Lower pelletization temperature provides lower gel level. This might be related to the dispersion of the higher-molecular-weight species. Uniform dispersion of the high-molecular-weight species might not be achieved if the shear force is too low due to a low melt viscosity at the high pelletizing temperatures.²¹ The output rate does not show a consistent trend in the gel level

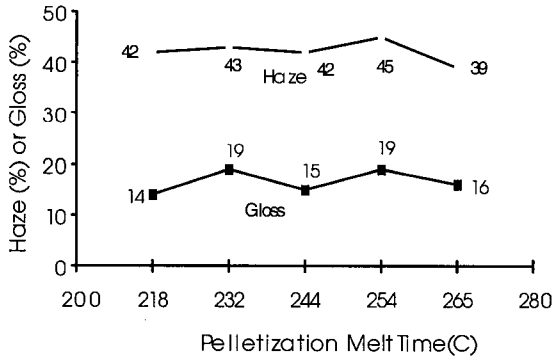


Fig. 16 Haze and gloss of the extruded blown film with different pelletization temperatures. Killion pelletization line was run at 75 rpm and Collin blown line was run at 202°C with 18 kg/h throughput.

of the blown films in Fig. 17. Although, higher shear stresses are provided at higher output rates, high screw speeds could also pass the nondispersed gels through the pelletizing process and result in an initially high gel count in the blown films. The gel level drops dramatically as the pelletization melt temperature decreases to 244–255°C, regardless of the throughput rate of pelletization.

4.2 LLDPE Blown-Film Processing on Mechanical, Haze, Gloss, and Gel Counts

Table 5 shows the data of the selected film properties obtained from the extrusion of LLDPE on the blown-film line at isothermal 190, 218, and 246°C temperature profiles. Ultimate tensile strengths on both machine and transverse directions are reduced at a higher blown temperature. This implies less orientation imparted to the blown films on both machine and transverse directions at a higher blown temperature. The higher blown temperature does essentially no harm to the mechanical properties of the films. The gel level remains at the same level, regardless of change in the blown film melt temperature. From the above study, we conclude that the gel level is only affected by pelletizing temperatures.

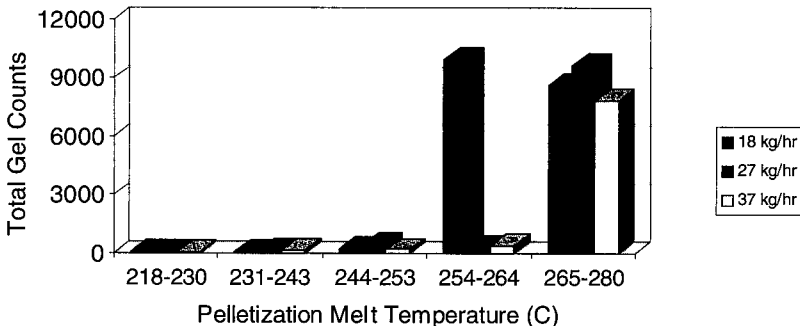


Fig. 17 Total gel count of LLDPE blown films, a different pelletization melt temperature, and different output rates.

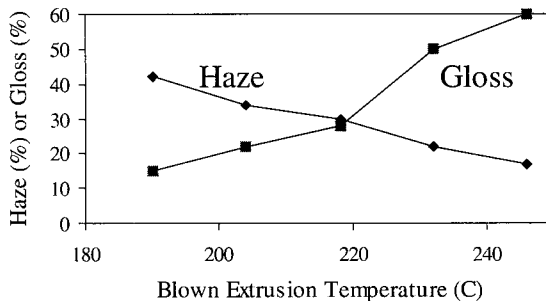
Table 5 Effect of Blown Extrusion Temperature on LLDPE Film Properties

Blown Film Temperature Profile	190°C Profile	218°C Profile	246°C Profile
Haze (%)	57.5	45.8	16.8
Gloss (%)	7.6	15.6	62.6
Ultimate tensile strength (MPa) MD/TD	58/50	58/48	42/46
Ultimate tensile elongation (%) MD/TD	902/1002	860/960	840/950
Elemendorf tear (g) MD/TD	3.3/4.8	3.4/4.8	3.5/4.5
Gel counts			
0.2–0.5 mm	68	50	70
0.51–0.7 mm	4	2	2
0.71–1.5 mm	0	0	0
>1.5 mm	0	0	0

MD = machine direction.

TD = traverse direction.

Figure 18 shows the haze of the films processed at different blown-film melt temperatures. The haze decreases from 42 to 17% as the blown temperature increases from 190 to 246°C. Reduction of haze with increasing blowing film temperature can be related to the mechanical deformation of the melt that reduces both melt elasticity and haze. Studies²² on blown LDPE films suggested that the haze observed in blown-film operations was from melt flow disturbances on the film surfaces at the die exit and crystallization in both surface and bulk. The surface haze moiety or surface roughness from melt flow disturbances could be minimized by reducing melt elasticity through “shear refining” or higher melt temperatures.²³ In Fig. 18, gloss of the blown films increases from 15 to 60% as the blown extrusion temperature increases from 190 to 246°C. Gloss has an inverse relationship with surface roughness.²⁴ It is believed that the surface roughness of the LLDPE blown films is reduced at a higher blown extrusion temperature just like the responses from the study of low-density polyethylene (LDPE) films.¹⁸ Therefore, an ideal LLDPE film with fewer gels, lower haze, and higher gloss can be obtained by pelletizing the resin at a low-temperature profile, and then blown extruding the pellets at a higher temperature profile. However, the potential challenges could be extrusion stability due to low viscosity from high-temperature extrusions.

**Fig. 18** Haze and gloss on LLDPE blown films with different blown extrusion temperatures.

4.3 Metallocene ULDPE Tubing Extrusion Throughput Rate Improvement

Metallocene polyolefins have narrower molecular weight distribution (MWD) than their corresponding Ziegler–Natta polyolefins due to their catalyst characteristics. Lack of lower-molecular-weight species for a metallocene polyolefin generates manufacturing challenges, such as shark-skin appearance and lower throughput rate. It is desirable to maintain the superior material properties of metallocene polyolefins and improve their extrusion processes by broadening their MWD. Blending a minor amount of a second polyolefin is commonly used to broaden the MWD of a metallocene polyolefin.

As we process the metallocene-ultra low density polyethylene (m-ULDPE) resins, the melt pressures become higher as throughput approaches their maximum at a given processing condition. The melt pressure can be reduced by introducing a thixotropic species, such as a lubricant or the other polyolefins with lower molecular weight. Several secondary polyolefins are blended with the base m-ULDPE to address this challenge. Melt pressure becomes a suitable indicator for throughput enhancement in the tubing extrusion process. A lower melt pressure generally yields a higher extrusion rate.

Figure 19 shows the melt pressure of 1.0 melt index (MI) m-ULDPE tubing extrusion, which gradually drops as the weight percentage of 30 MI m-ULDPE increases. The melt pressure decreases to its original 65% level as the 30 MI resin increases to 25% of the blend. The same resin blend has been run in the commercial-scale extruder and the throughput rate was noted to double that of the base resin. It is believed that 30 MI m-ULLDPE resin enhances the extrusion throughput by broadening the MWD, in addition to its lubricant effect.

The throughput rate increased through the blending approach is also confirmed by the other secondary 18 MI m-ULDPE. Figure 20 shows a similar trend with a slightly less throughput rate increase than 30 MI. This suggests that with similar molecular structure, the secondary resin with a higher MI acts like an effective lubricant that changes the rheological properties of the melt.

Figure 21 shows the extrusion melt pressure of the same base resin that is blended with a 20 MI LDPE resin. A similar trend of extrusion melt pressure is observed as the percent of LDPE increases. The melt pressure of the blend with 25% LDPE decreases to 70% of its original value. LDPE is generally known as a broad MWD resin that is easy for common extrusion processing. It

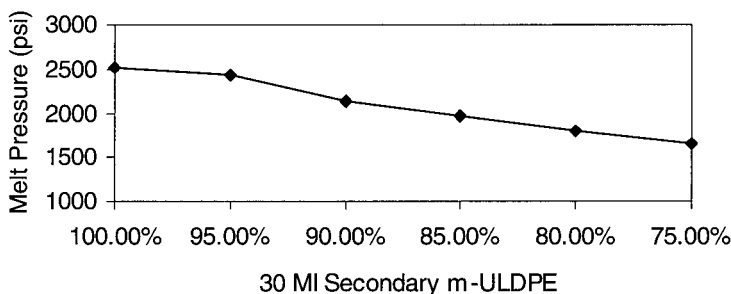


Fig. 19 Melt pressure of 1.0 MI (primary) and 30 MI (secondary) m-ULDPE blends.

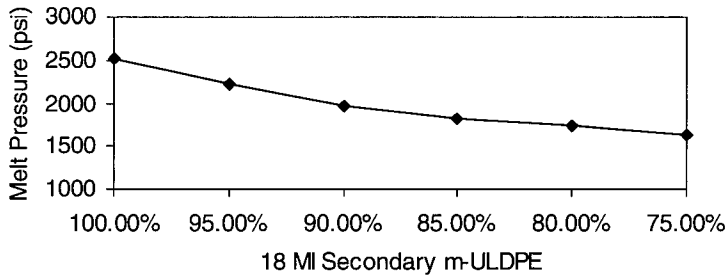


Fig. 20 Melt pressure of 1.0 MI (primary) and 18 MI (secondary) m-ULDPE blends.

is believed that the effect of broadening MWD by LDPE is similar to that by high MI m-ULDPEs.

It is interesting to note in Fig. 22 that a 3.6 MI Ziegler–Natta ULDPE resin does not achieve the similar result. Throughput rate of the blends does not increase even if the composition of the secondary resin increases to 25%. It suggests that broadening the MWD alone is not enough to lower the extrusion melt pressure. The rheological properties of the secondary resin also play major roles in improving the extrusion throughput rate. A typical rheological indicator, such as melt index (MI) number, can be used for this purpose. For the tubing extrusion of 1.0 MI m-ULDPE, an ideal extrusion throughput rate relies on higher MI of the secondary ULDPE or LDPE resins.

4.4 PP Injection-Molding Processing on Medical Product Clarity

The effect of molding temperature on the clarity of medical products made from PP pellets is shown in Fig. 23. Plaques were molded at different temperatures from the pellets having identical melt flow rate and additive packaging, but various catalyst systems. As the injection temperature varied from 184 to 232°C, the YI of the first sample decreased from 10 to 1.0, and that of the second sample from 5.7 to 3.1. This decrease in YI, or improved clarity, that takes place as the temperature increase can be related to resin morphology changes brought on by fast quench from high molding temperatures.²⁵

In general, the YI of medical PP suitable for medical product applications is typically expected to be less than 8.0. The variation in YI with molding tem-

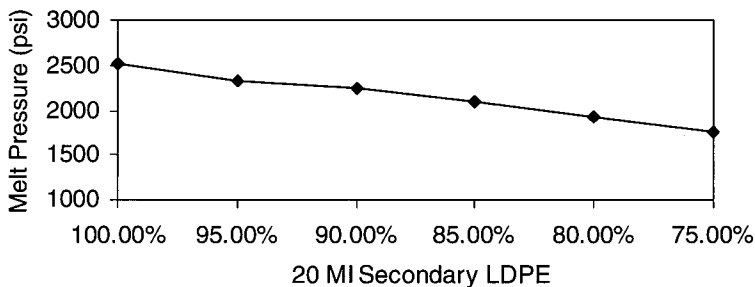


Fig. 21 Melt pressure of 1.0 MI m-ULDPE and 20 MI LDPE blends.

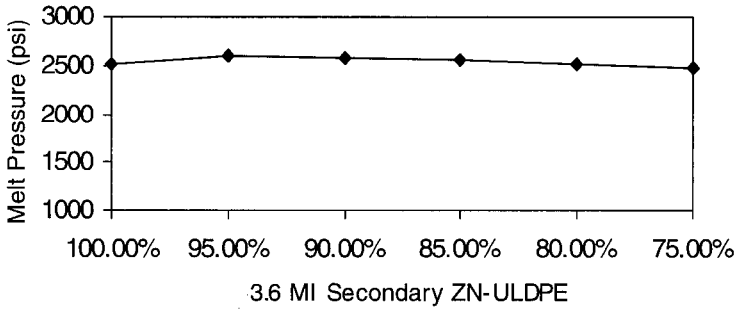


Fig. 22 Melt pressure of 1.0 MI m-ULDPE and 3.6 MI ZN ULDP blends.

perature for different pellets reflects the different catalyst systems used to polymerize the PP flakes. The various levels of catalyst residues introduce different lamellae structures during the cooling process, which in turn results in various degrees of YI reduction.

Figure 24 shows that the YI of plaques molded of PP flakes was essentially independent of the injection-molding temperature. The plaques were molded from flakes that had been pelletized without any additives. Figure 24 indicates that the catalyst residue alone does not cause PP flakes to change in clarity as molding temperature increases. However, the previously mentioned differences in YI between samples when the additives were involved suggest that the metal residues interact with the additives package, and that the effect of their interaction on resin color depends on the molding temperature.

4.5 PP Compression-Molding Processing on Medical Product Clarity

For medical products made by compression molding, temperature again plays a very important role in influencing clarity. Figure 25 shows that a lower YI was observed when medical products were compression molded at 246°C versus at 218°C. In addition, longer compression-molding process produced a lower YI, at both temperatures. PP plaques preheated for 3 min without pressure and followed by 1 or 3 min with pressure generally had higher YI values than those

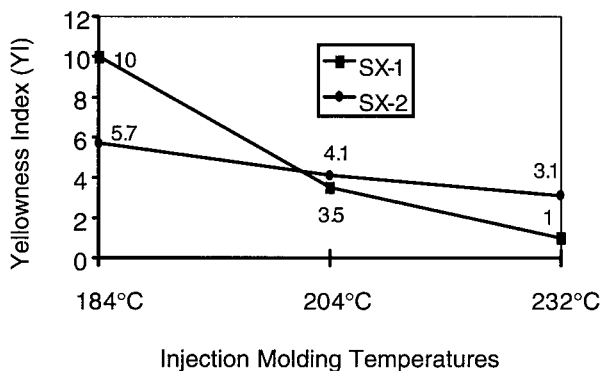


Fig. 23 Clarity of PP pellets improves (YI) as injection-molding temperature increases.

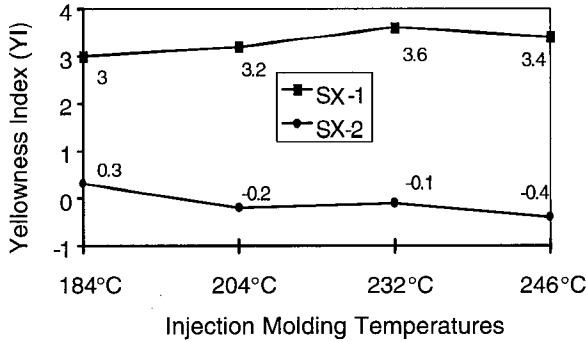


Fig. 24 Clarity of PP flakes is essentially independent of injection-molding temperature.

molded with the corresponding time and pressure continuously applied. The degree of compression pressure, however—observed at either 500 or 1000 psi—has much less influence on the YI of plaque than temperature and molding time. Accordingly, for a given additive packaging, the YI of medical products made from PP pellets can be as high as 10.5 or as low as 0.8, depending on how the product is compression molded.

5 PRODUCT PERFORMANCE

Safety, efficacy, quality, integrity, functionality, and cost are the key factors that determine a medical product’s success in a competitive market. A high-quality product performance associated with a low product cost is the ultimate goal of medical manufacturers throughout the world. To achieve this goal, medical manufacturers must carefully select materials to fulfill product safety and efficacy, ensure product integrity, prevent material–drug interactions, maintain strict quality control, and prohibit dose concentration change.

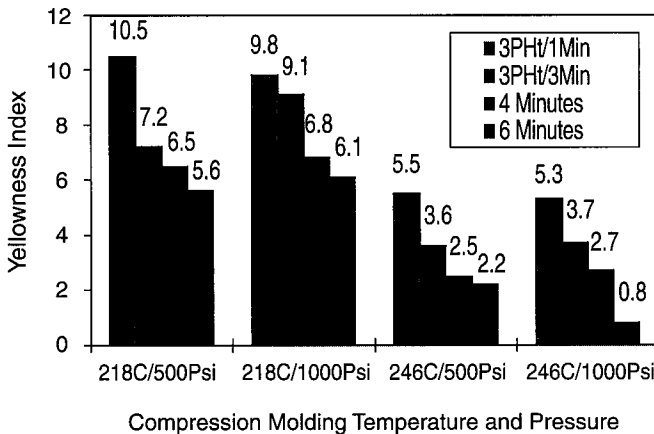


Fig. 25 Compression-molding temperature, pressure, and time on PP clarity (3 Pht/1 min = preheating 3 min then molding for 1 min).

5.1 Correlating Product Performance to Materials Characteristics

Numerous medical products, such as containers and tubing used in the device and medication delivery system, are made from flexible plastics such as plasticized PVC. This is due to its wide formulation latitude, ease of processing, clarity for contamination inspections, and low cost. In many instances these devices and delivery systems are subjected to the simultaneous conditions of subambient temperatures and mechanical stress. For example, near freezing conditions can be expected during winter shipping. Blood components are frequently handled and centrifuge processed at near 4°C. Certain drugs in premixed solutions are often stored and shipped frozen at about -20 to -30°C to enhance the chemical stability. Dry ice storage and transportation calls for temperatures of about -78°C, and in cryo-preservation liquid nitrogen at -196°C is commonly used. Since many products need to be stored in subambient temperatures, low-temperature toughness is needed.^{26,27} And yet since many medical products require terminal sterilization by steam, high-temperature survival is a must.

Early studies by Schmieder and Wolf²⁸ shown in Fig. 26 that glass transitions of plasticized PVC followed a predictable functional relationship with the plasticizer type and content. As expected, the higher content plasticizer samples had lower glass transition temperatures (T_g).

Figure 27 presents the product failure rate in a standardized test conducted at -20°C as a function of the glass transition T_g . Failure rate percent is increased as PVC T_g is higher. This data indicated that the primary variable for the low-temperature performance for flexible PVC is the location of the T_g . This also clearly indicates that the inherent properties of selected materials have a great impact to the product performance.

5.2 Optimizing Product Performance

Product performance can be optimized through the combined synergetic effect of the product design, materials selection, and manufacturing processes. One key element is to define clear and complete product requirements at the very begin-

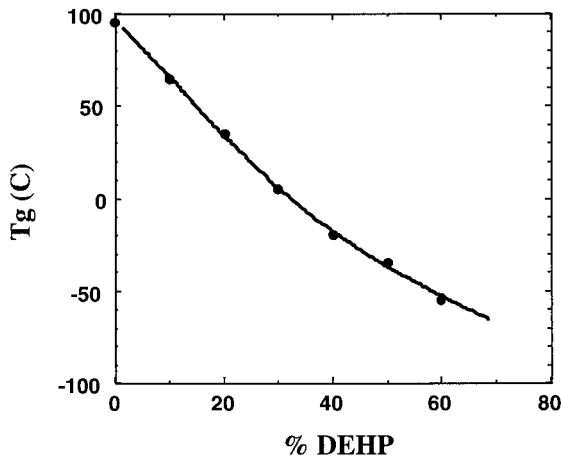


Fig. 26 PVC T_g vs. plasticizer content.

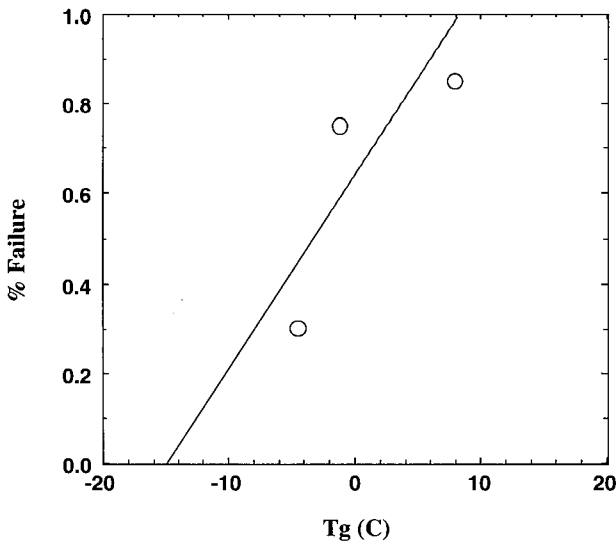


Fig. 27 -20°C product failure rates vs. T_g .

ning of product development. Based on the product requirements, product designers, materials scientists, and manufacturing engineers can create synergy to build a low-cost, high-performance medical product.

6 CONCLUSIONS

Polymeric materials have played a very critical role to enhance medical therapy and product quality, particularly for the medical device and disposable product sectors. Demonstration of product safety and efficacy are required prior to regulatory approval and product launch. Polymeric materials offer flexibility to product design, easy manufacturing, and sterility integrity.

A good materials selection strategy for a specific medical product is to take into account the material functional requirements with product design, manufacturing processes, and product performance simultaneously. The selected materials need to be compatible to the preferred sterilization method of steam autoclaving, ethylene oxide, or ionizing radiation. High-performance low-cost medical products are feasible as the selected materials are suitable for large-scale production by automation processes.

PVC materials have been used for medical products for over 40 years because of broad spectra of physical properties, sterilization compatibility, cost performance ratio, and meeting medical regulatory requirements. Recently, developments in metallocene polyolefins have many unique features that have potential to replace PVC for medical applications.

In addition to product safety and efficacy, the selected materials need to fulfill product functionality, integrity, manufacturability, and cost constraints. Validation of the materials for specific product applications to the desired product shelf is required. The validation includes functionality, stability, and extractives, with focus on the toxicological and biological interactions of the selected polymeric materials with the medication drugs and biological agents.

REFERENCES

1. S. Shang, M. T. K. Ling, S. P. Westphal, and L. Woo, "Radiation Sterilization Compatibility of Medical Packaging Materials," *J. Vinyl & Addit. Technol.*, **4**(1), 60 (1998).
2. S. Shang, T. Yang, C. Sandford, M. T. K. Ling, and L. Woo, "Comparison Electron Beam and Gamma Irradiation on Medical Packaging Materials," Proceedings of the Society of Plastics Engineers, ANTEC, 2740 (2000).
3. R. Carmen, "The Selection of Plastic Materials for Blood Bags," *Transfusion Med. Rev.*, **7**(1), 1 (1993).
4. S. Shang and L. Woo "Selecting Materials for Medical Products," *Medical Device and Diagnostic Industry*, **18**(10), 132 (1996).
5. L. Woo, M. T. K. Ling, and E. Chan, "Application of the Oxidative Induction Test to Medical Polymers," *Thermochimica Acta*, **192**, 209 (1991).
6. ASTM Standard: D3895-92.
7. G. N. Foster in *Oxidation Inhibition in Organic Materials*, Vol. 2, J. Pospisil and P. Klemchuk (eds.), CRC Press, Boca Raton, FL, 1989.
8. H. E. Bair, *Thermal Characterization of Polymeric Materials*, E. Turi (ed.), Academic, New York, 1981, p. 869.
9. Encyclopedia of Polymer Science and Engineering, Radiation-Resistant Polymer, 2nd ed., J. I. Kroschwitz, (ed.), Wiley, New York, 1988, Vol. 13, p. 687.
10. R. J. Rolando, "Radiation Resistant Polypropylene: New Development," *J. Plast. Film & Sheet-ing*, **9**(4), 326 (1993).
11. L. Woo, J. Palomo, M. T. K. Ling, E. Chan, and C. Sandford, "Shelf-Life Prediction Methods and Applications," *Med. Plast. Biomat.*, **3**(2), 36 (1996).
12. L. Matisova-Rychla and J. Rychly, in *Polymer Durability*, R. Clough, N. Billingham, and K. Gillen (eds.), Am. Chem. Soc., Washington, DC, 1996.
13. K. Gillen and R. Clough, in *Irradiation Effects on Polymers*, D. W. Clegg and A. A. Collyer (eds.), Elsevier Applied Science, New York, 1991.
14. D. Goodman, "Global Markets for Chlorine and PVC: Potential Impacts of Greenpeace Attacks," *J. Vinyl Technol.*, **16**(3), 156 (1994).
15. D. C. Finney and R. M. David, "The Carcinogenic Potential of DEHP in Humans: A Review of the Literature," *Med. Plast. Biomat.*, **2**(1), 48 (1994).
16. E. S. Shamshoum, L. Sun, B. R. Reddy, and D. Turner, "Properties and Applications of Low Density Syndiotactic Polypropylene," in *Proceedings of the Worldwide Metallocene Conference, Metcon '94*, Spring House, PA, Catalyst Consultants, **1**, 30 (1994).
17. E. S. Shamshoum, "Syndiotactic Polypropylene Catalyst: Properties and Possible Applications," in *Proceedings of the Second International Business Forum of Specialty Polyolefins*, SPO '92, Brookfield, CT, Society of Plastics Engineers, **1**, 199 (1992).
18. S. Borman, "Elastomeric Polypropylene: Oscillating Catalyst Control Microstructure," *C&EN*, January 16, 6 (1995).
19. J. J. McAlpin, and G. A. Stahl, "Applications Potential of Exxpol Metallocene-Based Polypropylene," in *Proceedings of the Worldwide Metallocene Conference, Metcon '94*, Spring House, PA, Catalyst Consultants, 1994, p. 7.
20. G. W. Knight, and S. Lai, "Constrained Geometry Catalyst Technology: New Rules for Ethylene Alpha-Olefin Interpolymers—Unique Structure and Property Relationships," *Polyolefins*, Vol VIII, Society of Plastics Engineers, Brookfield, CT, 1993, p. 226.
21. S. Shang and R. Kamla, "Influence of Processing Conditions on the Physical Properties of LLDPE Blown Film," *J. Plast. Film & Sheet-ing*, **11**(1), 21 (1995).
22. F. Stehling, C. Speed, and L. Westerman, "Causes of Haze of Low-Density Polyethylene Blown Films," *Macromolecules*, **14**, 698 (1981).
23. M. Rokudai, "Influence of Shearing History on the Rheological Properties and Processability of Branched Polymers. I," *J. Appl. Polym. Sci.*, **23**, 463 (1997).
24. Yang, T., "Surface Roughness and Gloss of Latex Coated Paper," Pittcon '97, Atlanta, GA, 1997, p. 172.
25. S. Shang, "What Makes Clear Polypropylene Discolor?" *Med Plast Biomat*, **2**(4), 16 (1995).
26. S. Shang, M. T. K. Ling, S. P. Westphal, and L. Woo, "Correlating Resin Properties to the Cryogenic Impact Performance of Medical Containers," Proceedings of Soc. of Plastics Engineers, ANTEC, 2862, (1996).
27. L. Woo, S. W. Shang, and S. P. Westphal, "Development High Heat, Metallocene Toughened Polymers—A User's Perspective," in *Proceedings of the Worldwide Metallocene Conference, Metcon '94*, Spring House, PA, Catalyst Consultants, 1997.
28. K. Schmieder and K. Wolf, *Kunststoffe*, **41**, 89 (1951).

