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Aliphatic Polycarbonate Polyurethanes with Broad Chemical Resistance for *In Vivo* Medical Devices

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Executive Summary

The use of polyurethanes in medical devices continues to increase, owing to their many desirable characteristics such as high strength, availability in a broad range of durometers, and their good bio- and hemo-compatibility. While the polyurethane family of polymers is often considered homogeneous, there are wide arrays of polyurethane chemistries that dictate both the performance characteristics of each polymer and its individual resistance to degradation by various chemicals. Parker Hannifin has developed a unique aliphatic polycarbonate (ALC) polyurethane which displays characteristic polycarbonate resistance to oxidation and alcohol absorption, but demonstrates expanded resistance to environmental stress cracking.

Medical Device Recalls on the Rise

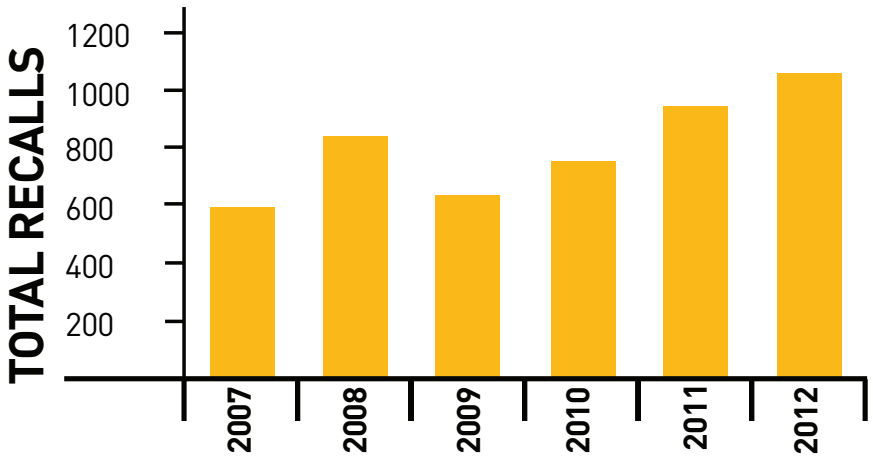
The nature of the medical device manufacturing market requires companies to manage complicated product designs coupled with strict and sometimes burdensome regulatory oversight. Included in this oversight is increasing regulatory scrutiny and low tolerance for medical device failures. In response to this increased scrutiny, the rates of medical device recalls have been steadily rising in the United States (Figure 1).

A CHANGING RECALL ENVIRONMENT

Recalls in the U.S. are on the rise

While many of these failures occur when a device is used according to its instructions for use, manufacturers are still responsible for device failures when they are used off label or exposed to conditions that were not initially anticipated. One of the ways in which medical device manufacturers can improve the robustness of their products is to work with materials that are reliable across a broad spectrum of chemicals that may be encountered during use of the device.

Figure 1. Total FDA Medical Device Recalls



Total FDA medical device class I, II, and III recalls from 2007 to 2012. All data from Elsevier's *The Silver Sheet*.

Major Classes of Polyurethanes for Medical Devices

Polyurethanes are plasticizer-free, segmented polymers comprised of alternating soft and hard segments. In life science applications, the soft segments are typically formed from polyester, polyether, or polycarbonate diols with low glass transition temperatures. It is this soft segment that provides flexibility to the polymers and allows them to forgo plasticizers. The hard segments are composed of high glass transition temperature aliphatic- or aromatic-based diisocyanates, linked by a diol chain extender of low molecular weight, and are responsible for the strength characteristics of polyurethanes.

The first polyurethanes used for medical applications were based around polyester chemistry.[1, 2] The polyester-based urethanes have excellent mechanical properties but are severely limited by their susceptibility to water hydrolysis and esterase degradation. In response to the poor water compatibility of polyester urethanes, polyether-based urethanes became more predominant for medical applications. While the polyether urethanes are much more resistant to hydrolytic cleavage, they were found to be prone to oxidative degradation, resulting in cracking of the polymer when left *in vivo* for prolonged durations.[1, 3]

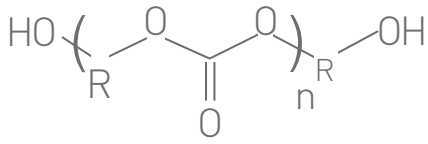
POLYESTER-BASED POLYURETHANES

- 1st Generation TPU for medical applications
- Excellent mechanical properties
- Poor resistance to hydrolysis

POLYETHER-BASED POLYURETHANES

- 2nd generation TPU for medical use
- Dramatically improved resistance to hydrolysis
- Susceptible to oxidative degradation

The 3rd generation of polymers designed for life science applications were the polycarbonate soft segmented polyurethanes. The polycarbonate urethanes combine the best of the characteristics of both polyester and polyether urethanes, with better hydrolytic stability than the polyesters and better oxidative stability than the polyethers.[4]



POLYCARBONATE-BASED POLYURETHANES

- 3rd Generation TPU for medical use
- Better resistance to hydrolysis than polyesters
- Better resistance to oxidative degradation than polyethers

Aromatic hard segmented urethanes are based on diisocyanates with benzene ring structures and possess the best mechanical properties, providing high tensile and burst strength, high melting points, and increased degradation temperatures. However, the aromatic polyurethanes are unstable in light and can yellow over time, giving the visual impression that the device is deteriorating or going bad. There is also concern over the use of aromatic polyurethanes due to the potential formation of carcinogenic compounds upon degradation. When the urethane linkage in aromatic polyurethanes is cleaved, carcinogens such as 4,4' methylene dianiline can be formed.

In response to concerns over the degradation of aromatic polyurethanes, aliphatic polyurethanes have become more prevalent. The aliphatic polyurethanes have lower mechanical properties than their aromatic counterparts but in medical applications, this loss is almost never sufficient to impact the integrity of the device. Additionally, aliphatic polyurethanes degrade to potentially safer end products and do not discolor upon exposure to light. However, along with the decreased mechanical properties, aliphatic polyurethanes are more prone to a physical degradation process termed "environmental stress cracking" (ESC) than their aromatic counterparts.

Environmental Stress Cracking

ESC can occur when a polymer is placed under tensile stress in the presence of an active chemical agent. The stresses can arise from multiple sources, many of which are difficult to identify and to control. Stresses on the polymer may be intrinsic due to arrangement of the hard and soft segments within the polymer, applied to the polymer in use, such as bending or kinking, or incorporated into the polymer during the manufacturing process, due to exposure to large temperature differentials over a short period of time.

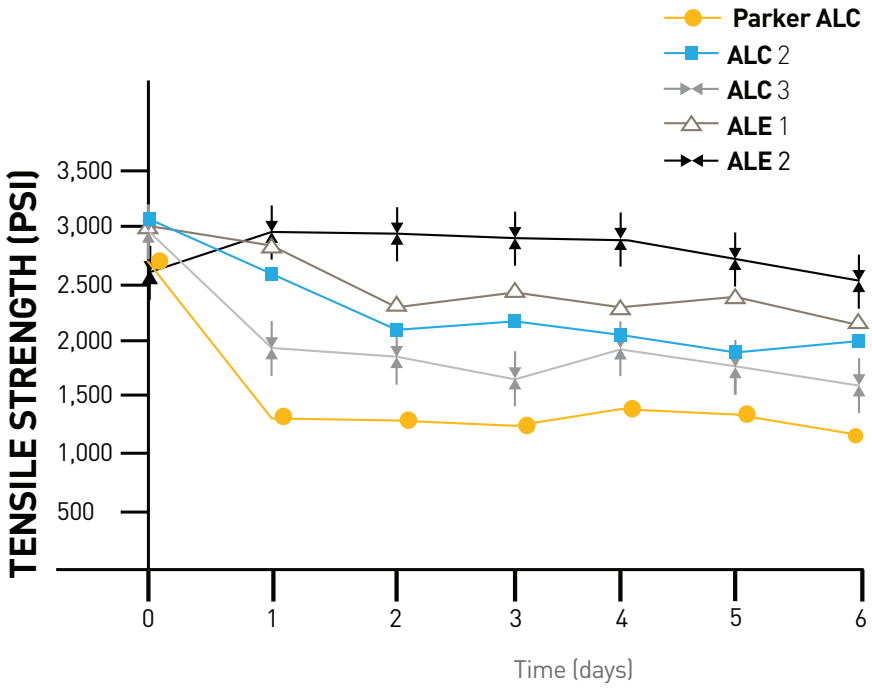
Chemical Degradation of Polyurethanes

Polyurethane polymers undergo degradation by a number of chemical methods with hydrolysis and oxidation acting as the predominant mechanisms of decomposition for *in vivo* applications. We analyzed the performance of several aliphatic polycarbonate (ALC) urethanes, including Parker Hannifin's proprietary formulation and two commercially available formulations. For comparison, we also tested the chemical resistance of two aliphatic polyether (ALE) formulations. The ALC and

ALE urethanes were loaded with 20% barium sulfate and extruded to a 10F outer diameter with a 0.030” wall thickness. These tubes were then kinked to create a stress riser and exposed to acid, alkaline, or saline solutions at elevated temperatures. These conditions were chosen to cover a comprehensive array of chemical exposures that are commonly encountered with *in vivo* use of polyurethane medical devices.

Immersion of stressed tubes in hydrochloric acid revealed that most tubes experienced little decrease in tensile strength over time. Many of the materials softened after immersion, but this softening is expected from hydrated urethanes and can actually serve to improve patient tolerability of medical devices that are implanted or inserted. Most importantly, all tubes from the ALC and ALE classes maintained their mechanical properties well above a range that would be indicate potential device failure in most applications (Figure 2).

Figure 2. Tube Tensile Strength in Acidic HCl



ACID SOAK STABILITY

Acid tube soak in HCl showing good retention of mechanical properties over time.

Most compounds lost some mechanical strength as they became hydrated but did not lose further strength.

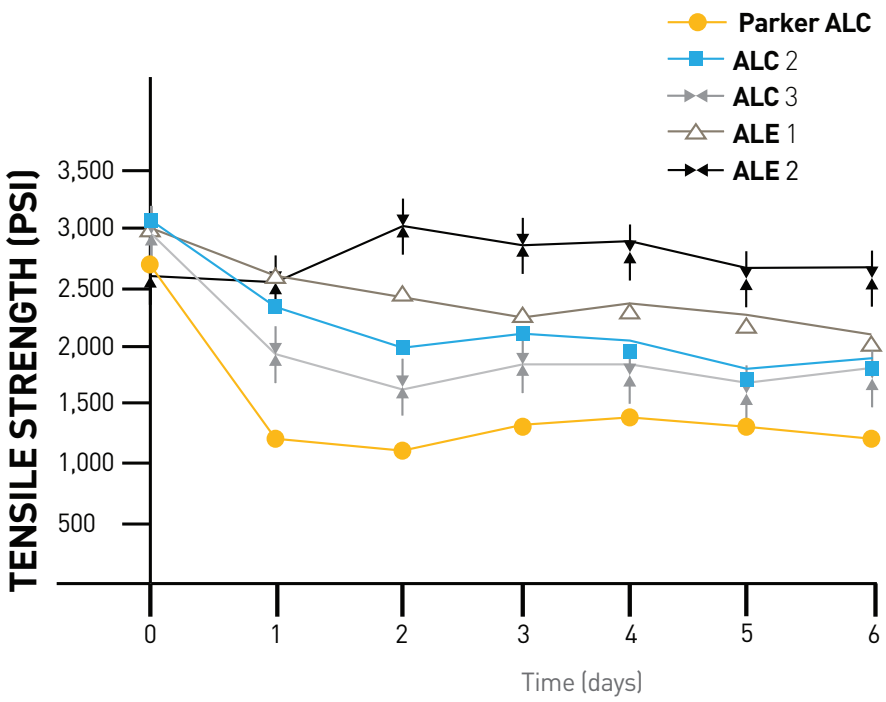
Samples immersed in a neutral saline solution showed similar results to those seen with the tubes exposed to acid. Many of the tubes softened from their initial pull strengths but again maintained tensile strengths well above those required for most devices (Figure 3).

Upon exposure to alkaline conditions, however, shortcomings in ALC compatibility began to manifest. As seen in Figure 4, most ALC urethane tubes are prone to rapid degradation when exposed to alkaline chemicals. Most of the ALC formulations quickly degraded and ultimately failed before 5 and 7 days. Parker Hannifin’s proprietary ALC formulation, however, showed no significant change after initial softening over the course of the testing.

SALINE SOAK STABILITY

Tube soak in neutral saline showing good retention of mechanical properties over time. Similar to the HCl results, most compounds lost some mechanical strength as they became hydrated, but did not lose further strength.

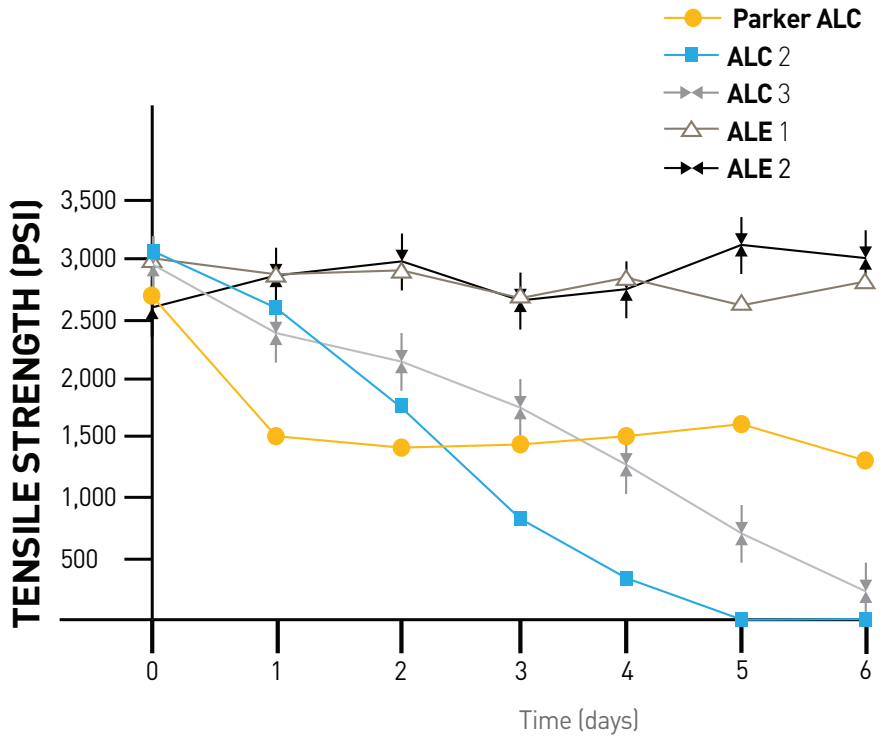
Figure 3. Tube Tensile Strength in Neutral Saline



ALKALINE SOAK STABILITY

Tube soak in alkaline KOH solution showing rapid loss of mechanical properties in most ALC formulations. The ALE formulations remain unaffected by high pH.

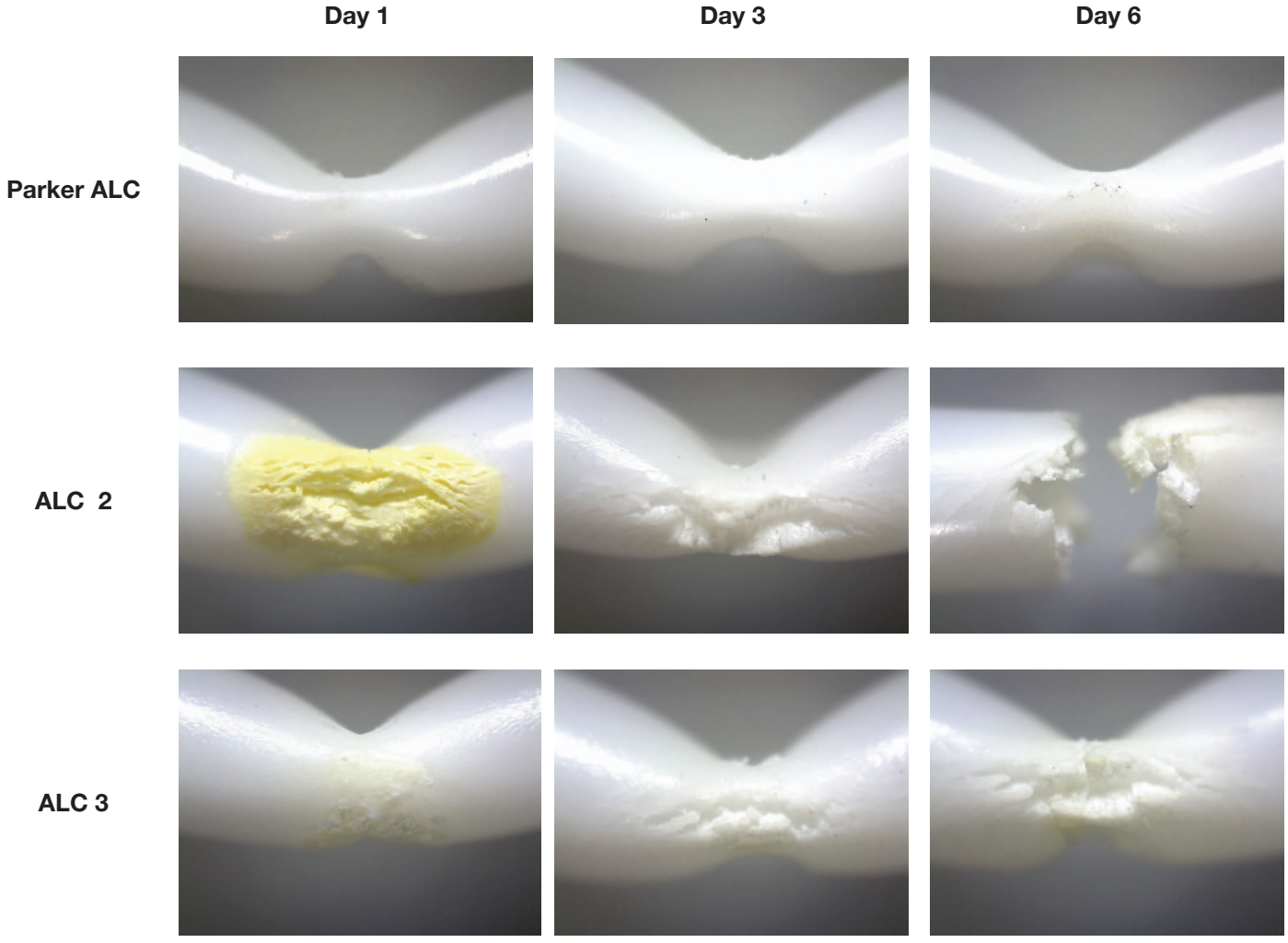
Figure 4. Tube Tensile Strength in Alkaline KOH



Visual inspection of the competitive ALC tubes revealed that stress cracks formed as early as 24 hrs after exposure to potassium hydroxide (Figure 5). Environmental stress cracks, once formed, are known to propagate rapidly if the tube remains exposed to the active chemical environment. As is evident from the photos, even a small amount of cracking can result in loss of material. Depending of the application of the device, the loss of this material while the device is in a patient could result in serious complications. While the other ALC polyurethanes begin degrading under alkaline conditions immediately, Parker's proprietary ALC polyurethane withstood the exposure far past the competition, showing no major stress cracking over the duration of the test.

VISUAL INSPECTION OF ALC STRESS CRACKING

Figure 5.



As expected under conditions where hydrolytic degradation predominates, the polyether ALEs showed no significant decrease in tensile strength in any of the solutions tested. However, in the potassium hydroxide solution, discoloration and yellowing of the tubes was observed (Figure 6).

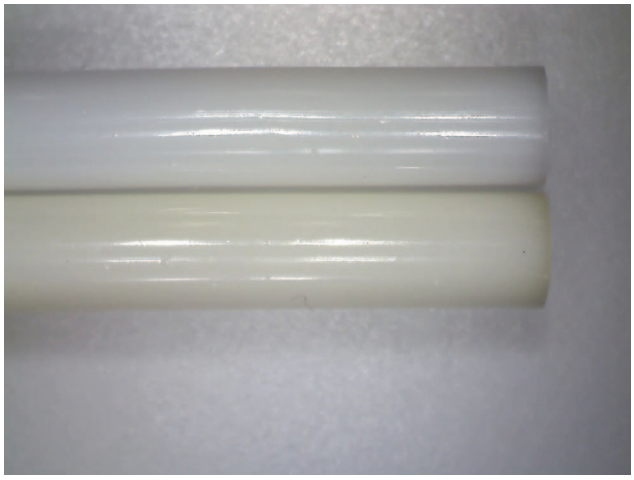
While the relative resistance of polyethers to hydrolysis is well known, their degradation under oxidative conditions can be a limiting factor for *in vivo* applications. In addition to this potential limitation to their use, polyether urethanes are also less compatible with alcohols than their polycarbonate counterparts.

VISUAL INSPECTION OF ALE DISCOLORATION

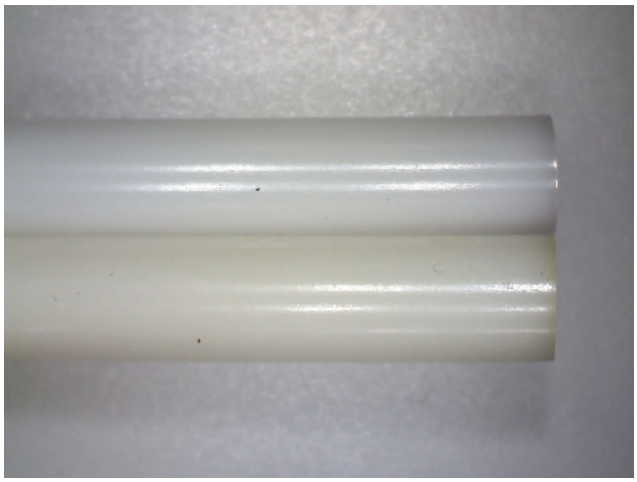
Figure 6.

Day 0 (top tube) / Day 6 (bottom tube)

ALE 1



ALE 2

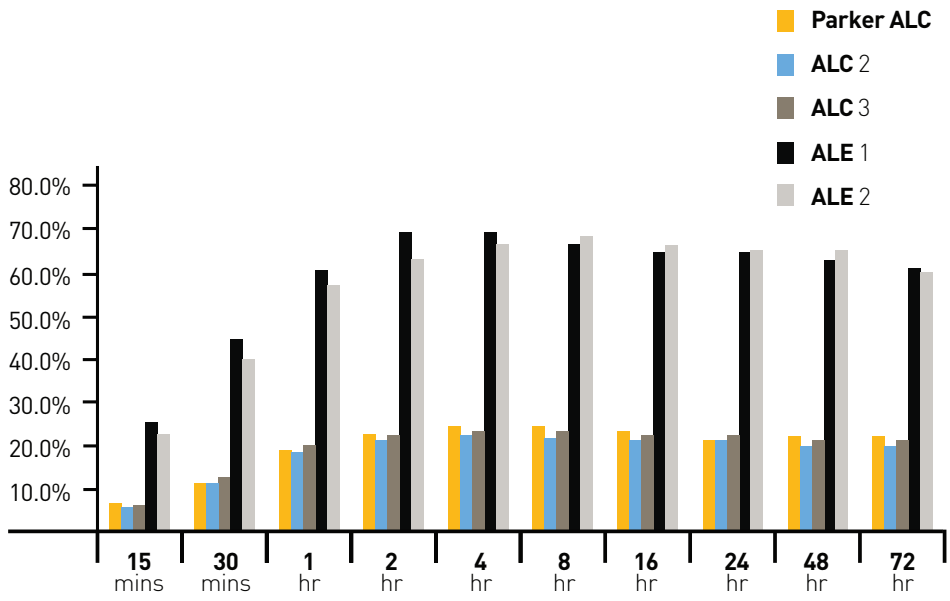


Swelling of Polyurethanes Due to Alcohol Exposure

Polyurethane medical devices can be exposed to alcohols in day to day use. This exposure can be short such as through simple wipe down or can be prolonged such as with complete immersion. Many hospitals are now recommending the use of ethanol locks with central venous and peripherally inserted central catheter (PICC) lines to prevent catheter-related bloodstream infections. To perform an ethanol lock, a 70% or higher solution of ethanol is introduced throughout the entire length of the catheter and allowed to dwell for times which can exceed 2 hrs. Ethanol locks are gaining in popularity due to their simplicity, effectiveness, and the dual antimicrobial and fibrinolytic protection they provide for catheters. Performing an ethanol lock is an especially harsh exposure for polyurethanes as the entire length of the catheter is submersed in a highly concentrated ethanol solution at 37 °C. Certain polyurethanes are more susceptible to swelling when submersed in alcohols. Polyether polyurethanes absorb alcohols quickly and significantly when compared to polycarbonate soft segment urethanes (Figure 7). This rapid absorption also results in swelling of the device both radially and longitudinally.

EtOH ABSORPTION

Figure 7. % Weight Gain in EtOH at 37 °C



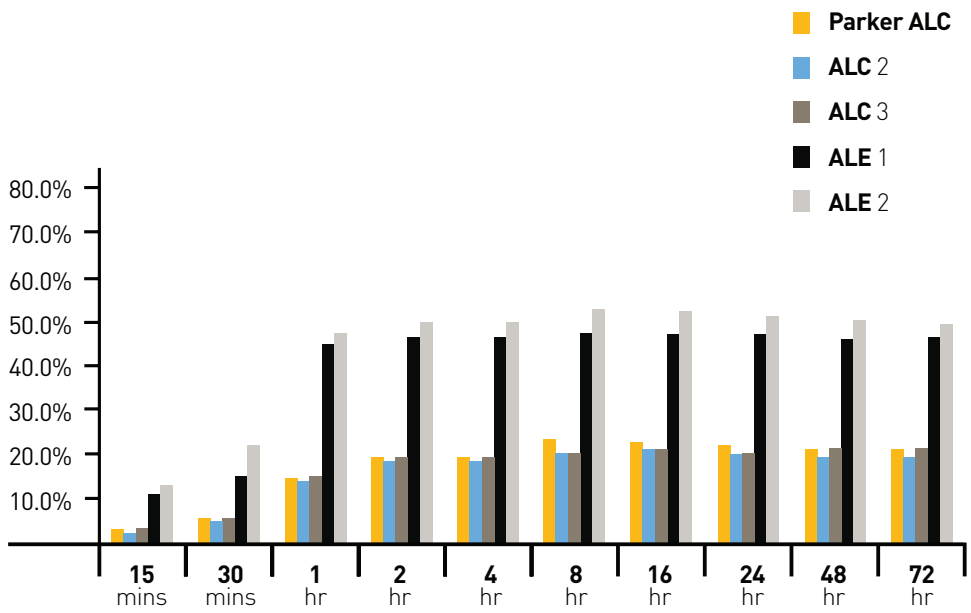
As seen in Figure 7, the polyether-based ALE-based urethanes absorb ethanol much more rapidly and to a greater extent than do the aliphatic polycarbonate-based urethanes. Within 1 hr, polyether urethanes absorb approximately 60% of their weight in ethanol and almost 70% by 2 hrs. Conversely, the polycarbonate urethanes absorb only approximately 20% of their weight at both 1 and 2 hrs. After the 2-hour time point, both the ALC and ALE urethanes did not absorb much more alcohol through 72 hrs. Reaching this peak absorption at 2 hrs is particularly noteworthy for venous catheter applications as this is a commonly recommended ethanol lock dwell time in hospitals.

Direct exposure to isopropyl alcohol (IPA) by submersion is rare, but IPA is one of the more common cleaning agents used to sanitize medical devices. The polyether urethanes again swell much faster and absorb IPA faster than the polycarbonate urethanes (Figure 8).

In only 15 minutes, over 10% IPA by weight is absorbed into the ALE polymer. Care should be exercised in choosing a urethane when it is known that the device will be exposed to IPA, especially when devices will be exposed to IPA over multiple cleaning sessions.

IPA ABSORPTION

Figure 8. %Weight Gain in IPA at 37 °C



Conclusions

Deciding which polyurethane formulation to use for a medical application is a multi-faceted problem and requires consideration of many factors. Details such as the desired mechanical properties of the end polymer to the chemicals that the device will encounter should be taken into account to ensure the product will perform its intended function over its entire lifespan. In addition to these factors, the inherent stresses within the material and external stresses which may be placed upon the material during use, may also factor into the material considerations. In order to give medical device manufacturers the confidence that their products will perform as designed, Parker Hannifin has developed a novel aliphatic polycarbonate polyurethane. Our proprietary formulation delivers consistent performance through a wide range of chemical exposures and provides improved stability when the material is placed under external stress.

Materials and Methods

Polyurethane tubing was loaded with 20% $BaSO_4$ by weight, extruded with a 10F outer diameter and a 0.030” wall thickness and cut to 4” lengths. A single 0.0625” hole was cut through one wall into the lumen at the mid-point of the tube and the tubing was bent in half with the hole on the outside of the bend. The folded tube was then inserted into a 0.5” long glass tube with a 0.03125” inner diameter to hold the bend in place.

Once secured, the tubes were immersed into 3 aqueous solutions at 50 °C: basic 8M KOH, acidic 2M HCl, or neutrally-buffered saline. The tubes were removed at 24-hr intervals, rinsed in distilled water, and allowed to dry for 24 hrs before testing mechanical properties on an Instron Universal Material Tester.

Straight 4” lengths of tubing were also submersed into 100% isopropyl alcohol or ethanol at 37 °C. The tubes were then removed from the alcohol solutions at the indicated time points and weighed after blowing the alcohol from the surface and lumen of the tube.

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