ENGINEERING ADHESIVES FOR REPEATED STERILIZATION

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Introduction

A variety of sterilization methods have been used to condition medical devices over the past forty years. In the 1960s and 1970s, the types of materials which were used for the construction of devices lent themselves to rigorous sterilization methods. Typically, devices were constructed of materials such as metal, glass and rubber. However, as devices became more intricate and higher performing, the types of materials used for their construction were modified. Thermoset and thermoplastics have replaced the materials of a few decades past and the assembly methods used for medical device construction have also been modified.

Earlier medical devices were assembled using methods conducive to the substrates involved, including mechanical fastening, molding or machining. The materials and joining methods of three to four decades ago could easily withstand a variety of sterilization methods, including some of the more rigorous procedures.

Advances in contagious disease coupled with higher performing devices resulted in a shift in the manner in which devices were fabricated and assembled. The introduction of plastics into the device market led to new methods of assembly and new concerns for sterilization resistance. Adhesives became the method of choice for many device manufacturers due to a number of reasons including:

- Ability to bond a variety of substrates
- Ability to bond and seal
- Ability to fill large gaps
- Easily automated

Several classifications of medical devices exist including sterile disposables, non-sterile reusables, and, most recently, sterile reusables and resposables. Sterile disposables include devices such as syringes, oxygenators and catheters. Such devices were fabricated with the intention that they be used one time. As such, sterile disposable devices are typically exposed to one or two sterilization cycles prior to use. Non-sterile reusables are devices which do not come into contact with blood or bodily fluids. Typically, non-sterile reusables have minimal sterilization requirements.

The newest classifications of medical devices – sterile reusables and resposables – have emerged as a result of advances in less invasive surgery as well as a desire by device users to

reduce costs through re-use. Sterile reusables include surgical instruments such as endoscopes and laproscopes, while sterile resposables include devices which were intended for one time use, but are now being considered for re-use. In both cases, repeated sterilization is a requirement. The type of sterilization employed for reusables and resposables, duration of exposure, and maximum number of cycles is expected to vary based on the type of device and use. It is anticipated, however, that methods conducive to quick turn-around and low toxicity will likely be utilized (i.e. autoclaving, hydrogen peroxide, chemical immersion).

Sterilization Methods

Sterilization is defined as the elimination of all living organisms and can be accomplished in a variety of ways. Heat, chemicals and radiation are all methods employed to ensure that medical devices are suitable for human use. Table I provides a list of commonly used sterilization methods along with a brief description, typical temperature exposure and likelihood that the method would be considered for use with reusable/resposable medical devices.

TABLE I: Sterilization Methods

Sterilization Method	Description
Steam Autoclave	• Steam under pressure (15-20 pounds steam pressure) • Temperatures between 110 – 135°C • Estimated 80% of market • Potential effect of adhesive bond strengths • *Potential candidate for use with reusable/resposable devices*
Ethylene Oxide	• Toxic gas which requires 24 hours of aeration following exposure • Temperatures: ~ 55°C • Minimal effect on adhesive bond strengths
Gamma	• Cobalt-60 radiation source • Temperatures: ambient • Minimal effect on adhesive bond strengths
Electron Beam	• Electron accelerator, radiation source • Temperatures: ambient • Minimal effect on adhesive bond strengths
Hydrogen Peroxide	• Typically low temperature plasma • Temperatures: ambient to 50°C (vapor phase temperatures slightly higher) • Minimal effect on adhesive bond strengths • *Potential candidate for use with reusable/resposable devices*
Chemical Immersion	• Liquid sterilant solutions such as glutaraldehyde or peroxyacetic acid • Temperatures: ambient to 50°C • Minimal effect on adhesive bond strengths • *Potential candidate for use with reusable/resposable devices*

Autoclaving, the sterilization method for an estimated 80% of medical devices, presents the greatest challenge to device manufacturers due to the combination of temperature, pressure and moisture. Manufacturers are required to seek substrates and joining methods that are versatile and easy-to-use, yet still hold up in the most rigorous environments. Plastic suppliers have begun to develop materials that offer advanced resistance to rigorous environments such as autoclaving. For example, specialty grades (autoclave resistant) of polycarbonate and polysulfone are commercially available.

Adhesives

Adhesives have been used in the medical market for nearly three decades. Although a number of adhesives are industrially available, not all possess biocompatibility compliance. Cyanoacrylate, light curing cyanoacrylate, light curing acrylic, dual UV/moisture curable silicone, epoxy and urethane adhesives are commonly used for the assembly of medical devices. In general, adhesives offer several benefits over other medical device assembly methods, including the ability to fill large gaps, the ability to bond dissimilar materials, the ability to distribute stress evenly across a bondline, and the ability to form a hermetic seal when confined between two substrates.

Cyanoacrylate adhesives are polar, linear molecules which undergo an anionic polymerization reaction. A weak base, such as moisture present on essentially all surfaces, triggers the reaction causing the linear chains to form. The products are maintained in their liquid form via the addition of weak acids which act as stabilizers. A wide variety of cyanoacrylate formulations are available with varying viscosities, cure times, strength properties and temperature resistance.

Cyanoacrylates form thermoplastic resins when cured. The initial cyanoacrylate resins, which were first commercially available in the 1950s from Eastman Kodak, possessed several performance limitations which have since been addressed with formulation modifications. Standard unfilled ethyl monomer based cyanoacrylates typically exhibit low impact and peel strengths, low to moderate solvent resistance, and maximum operating temperatures of 160 – 180°F. Specialty formulations are now available to address the initial limitations including rubber toughened cyanoacrylates for enhanced impact and peel strengths, low odor/bloom products for minimized frosting, surface insensitive formulations

for rapid fixture and cure in low humidity/acidic environments, and thermally resistant products with continuous operating temperatures of 250°F.

Besides advancements in ethyl cyanoacrylate technology, there have also been significant advancements in primer and accelerator formulations which not only offer speed of cure but also the ability to bond "hard-to-bond" plastics. The primers are solvent-based systems which deposit reactive species onto otherwise "dead" substrates. Such reactive species allow for significant increases in bond strength for the majority of difficult to bond materials including polyethylene, polypropylene, fluoropolymer, and acetal homopolymer.

Testing of cyanoacrylate adhesives with a number of sterilization methods has yielded varying results. Cyanoacrylate adhesives, in general, have been shown to withstand up to and including fifty (50) cycles of liquid sterilization immersion as well as hydrogen peroxide. In addition, select cyanoacrylate adhesives have exhibited moderate resistance to autoclave exposure – with some specialty ethyl grades maintaining nearly 100% of their initial strengths following exposure to fifty (50) autoclave cycles. A critical factor in maintaining bond strengths with cyanoacrylate adhesives following autoclave exposure lies in the selection of substrates that offer moderate to high initial strengths as well as substrates capable of withstanding the rigorous temperature, pressure and steam environment of the system.

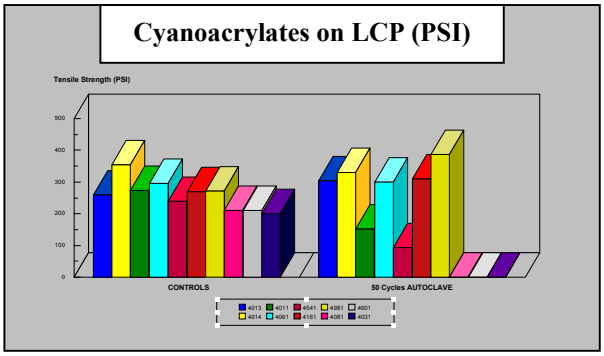

Figure 1: Cyanoacrylates on LCP – 50 Autoclave Cycles

Light curing acrylics cure via a free radical reaction to form thermoset resins when exposed to light of the appropriate wavelength and intensity. Like cyanoacrylates, light curing acrylic adhesives are available in a wide range of viscosities from low (~ 50 cP) to thixotropic gels. In addition, light curing adhesives vary in final cured form from hard, glass-like resins to soft flexible resins.

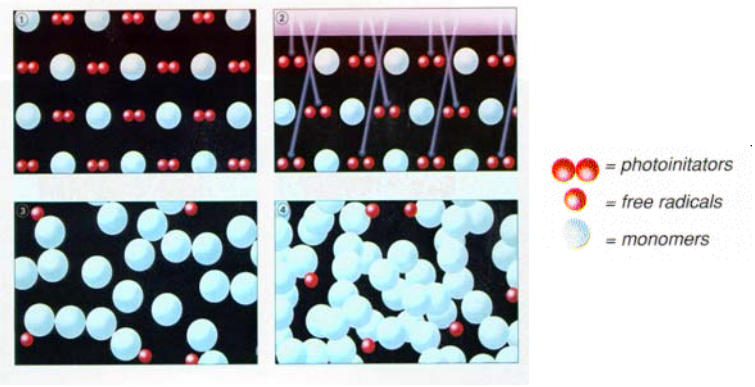

Figure 2: The light cure polymerization reaction

The critical processing key with light curing acrylic adhesives is that light must reach the full bondline in order to cure the adhesive. Adhesive in shadowed areas will not cure. In addition, the maximum depth of cure for the majority of light curing acrylic systems is approximately 0.5". Another consideration when selecting a light cure adhesive is the equipment required for the processing of the product. Light curing adhesives require specific radiant energy (i.e. light energy) in order for the polymerization reaction to occur. It is critical, therefore, that the end user match the adhesive with the appropriate light source. Adhesive manufacturers can recommend the appropriate type of system. Typical low intensity systems can have an average price of $1000 while custom high intensity systems can run into the tens of thousands of dollars.

Light curing acrylic technology offers the significant benefit of rapid fixture and cure (as little as 5 seconds for select joints) following exposure, thus minimizing work in process (WIP). In addition, light curing acrylic formulations have been designed to bond a wide variety of substrates and yield a clear bondline when used in thin sections. Because the final resins are thermoset plastics, thermal, chemical and environmental resistance of light curing acrylics are enhanced versus cyanoacrylate adhesives.

Light cure acrylic adhesives offer widely varying performance following autoclave exposure. As with cyanoacrylate adhesives, light curing acrylics vary in bond strength retention following exposure based on formulation, substrates selected and initial strengths achieved. Testing has indicated that, in general, light curing acrylic adhesives maintain 50% or less of initial strengths following fifty (50) autoclave cycles.

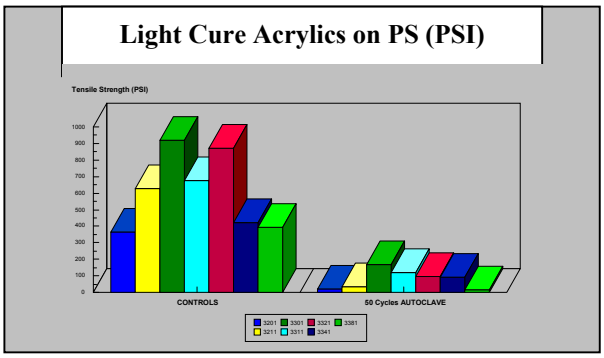

Figure 3: Light Cure Acrylics on Polysulfone– 50 Autoclave Cycles

A new technology introduced in the United States in 1998 combines the benefits of cyanoacrylate technology and light curing acrylic technology. *Light curing cyanoacrylates* are ethyl based products which have photoinitiators added to the formulation. The end result is fast fixturing (like that of a traditional light curing acrylic) *and* cure in shadowed areas. Because the light curing cyanoacrylates are ethyl monomer based, the overall physical performance characteristics are similar to those obtained with a traditional cyanoacrylate. Additional benefits gained with the new technology include minimized blooming/frosting since exposed uncured cyanoacrylate can be immediately cured using ultraviolet and/or visible light; increased depth of cure over the traditional cyanoacrylate cure maximum of 0.010 inches, and compatibility with primers for "hard-to-bond" plastics. Light curing cyanoacrylates would be expected to perform similarly to standard ethyl cyanoacrylates following sterilization exposure including autoclave.

Silicone adhesives are similar to polyurethane adhesives in that they form flexible polymers when cured. Silicones, however, possess no rigid segment and therefore exhibit lower cohesive strengths – the strength of the polymer itself. Silicone adhesives are available in several forms including one part moisture cure, one part heat cure, and one part dual moisture and light cure formulations. Although two part silicone systems do exist industrially, the catalysts used in such materials typically cause the system to fail biocompatibility screening.

The majority of moisture curing silicones have two primary characteristics which limit their use in the medical device market. The evolution of by-products such as acetic acid coupled with the 24 hour cure time often cause device manufacturers to seek alternative, faster fixturing/curing materials. The use of dual curing systems which react initially to light

and subsequently moisture cure provide cure-on-demand fixture strength followed by full cure up to 72 hours later.

The sterilization resistance of silicone adhesives is typically measured on the bulk polymer rather than on assembled specimens due to the low cohesive strength of the polymers. Testing of dual light cure/moisture silicone adhesives following exposure to fifty (50) autoclave cycles indicated a slight effect on the percent elongation of the adhesives, but an approximate 60% drop in tensile strength.

TABLE 2: Strength Retention of Dual Curing Silicone Adhesives Following Autoclave Exposure

	Tensile Strength (in PSI)	% Elongation
Control	600	310
50 Autoclave Cycles	250	250

Epoxy adhesives, like the previously mentioned light curing acrylic adhesives, cure to form thermoset plastics. The polymerization reaction occurs via ring opening of an epoxide group initiated by a catalyst such as an amine or mercaptan. Room temperature and heat curing one and two part systems are available. Due to their ability to crosslink, epoxies offer superior chemical, environmental and thermal resistance. The ability to bond a wide variety of substrates as well as their large gap filling capabilities make epoxies useful for deep section potting of medical components and needle assembly.

Because epoxies cure via an exothermic reaction (giving off heat during cure), their use on temperature sensitive components must be closely monitored. A second potential drawback to epoxy use is their rigid nature when cured, which typically results in low peel strengths.

Polyurethane adhesives are similar to epoxies in that one and two part formulations are available. A urethane linkage is formed when the two main formulation components – the polyol and isocyanate – react to form hard and soft segments in the resultant polymer. Such segments contribute to the uniquely flexible yet tough cured material. Like several previously mentioned chemistries, polyurethane adhesives form thermoset resins when cured, thus exhibiting good chemical and environmental resistance. It is important to note, however, that the overall thermal resistance of cured polyurethanes is less than that of cured epoxies.

Polyurethane adhesives are substrate versatile but do, on occasion, require the use of a surface primer to increase the reactivity of the surface to be bonded. Many of the primers require long on part times in order to effectively prepare the surface for the adhesive. A second potential drawback to the use of polyurethane adhesives is their inherent moisture sensitivity. Excess moisture on a part or in one of the constituents can cause a reaction resulting in the evolution of carbon dioxide, which leads to bubbles in the finished component.

Epoxy and urethane adhesives are often selected for applications due to their enhanced chemical and thermal properties. Such resistance makes the adhesives suitable candidates for the new classes of medical devices: sterile reusables and resposables. With the potential of repeated autoclaving exposure, it is critical that reusable/resposable device manufacturers select adhesives which have the ability to withstand high temperatures and high steam pressure conditions.

Autoclave Resistant Epoxy & Polyurethane Adhesives

The typical adhesives selected for the assembly of disposable and reusable medical devices, particularly cyanoacrylates and light curing acrylics, were found to exhibit low to moderate resistance to autoclaving. The goal of a developmental study recently undertaken, therefore, was to identify adhesives which could be used for repeated autoclave cycles while still offering the benefits of ease of use, substrate versatility and high performance.

Five adhesives were selected for evaluation as potential candidates for applications requiring repeated autoclave exposure: three epoxy-based products and two polyurethane-based products. Table 3 provides a summary of the products as well as key product characteristics. The study involved evaluation of the adhesives on five (5) substrates including polycarbonate (PC), stainless steel (S/S), glass, polyvinyl chloride (PVC) and polyetherimide (PEI). All substrates, with the exception of PC, were used for assemblies exposed to ten (10) and twenty-five (25) repeated autoclave cycles. The sterilization exposure parameters utilized included six (6) minutes of prevac sterilization at 132°C with a three (3) minute dry time between cycles.

TABLE 3: Epoxy & Polyurethane Adhesives for Repeated Autoclave Exposure	
Product	**Product Characteristics**
Low Viscosity Epoxy (LV Epoxy)	• Clear • 30 minute work-life, 160 minute tack-free time • Enhanced impact strength • Tensile strength = 8000 PSI
Medium Viscosity Epoxy (MV Epoxy)	• Off-white • 20 minute work-life, 40 minute tack-free time • Enhanced peel and impact strength • Tensile strength = 5700 PSI
High Viscosity Epoxy (HV Epoxy)	• Amber/beige • 120 minute work-life, 140 minute tack-free time • Enhanced peel and impact strength, superior thermal shock resistance • Tensile strength = 5900 PSI
Low Viscosity Urethane (LV Urethane)	• Ultra clear • 10 minute work-life, 180 minute tack-free time • High flexibility with enhanced peel strength • Tensile strength = 490 PSI
Medium Viscosity Urethane (MV Urethane)	• Off-white • 5 minute work-life, 160 minute tack-free time • High flexibility with enhanced peel strength • Tensile strength = 1300 PSI

Figures 4 through 8 provide the results of the repeated sterilization testing for the five (5) adhesives and five (5) substrates. The results, presented graphically, provide an indication of strength performance following exposure as well as failure modes.

Figure 4 provides the results for the five (5) adhesives tested on stainless steel lapshear specimens. As indicated, the medium and low viscosity epoxy adhesives performed well following ten (10) and twenty-five (25) autoclave cycles, maintaining close to initial strengths. The medium and low viscosity polyurethane adhesives also exhibited strengths comparable to initial values obtained. The majority of assemblies involving stainless steel exhibited adhesive failure.

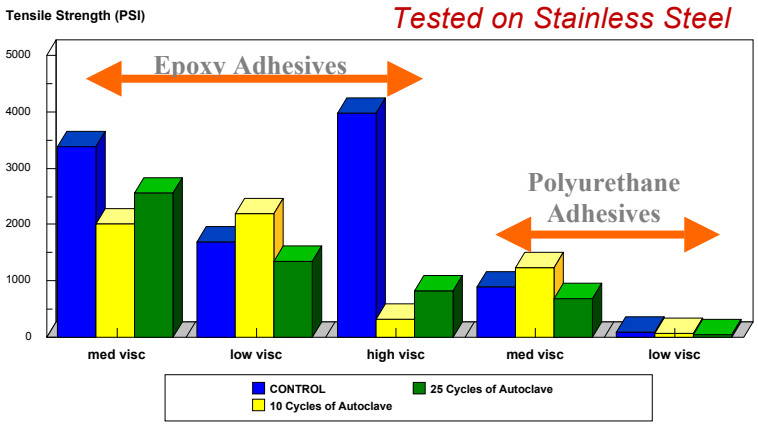

Figure 4: Performance of Adhesives on SS Following Autoclave Exposure

Figure 5 provides the results for the five (5) adhesives tested on glass lapshear specimens. As indicated, all three of the epoxy adhesives performed well following twenty-five (25) autoclave cycles, maintaining close to initial strengths. The medium and low viscosity polyurethane adhesives exhibited a significant decrease in strengths following autoclave exposure. The majority of assemblies involving the epoxy adhesives exhibited failure of the substrate, while the urethane assemblies exhibited a combination of adhesive and cohesive failure.

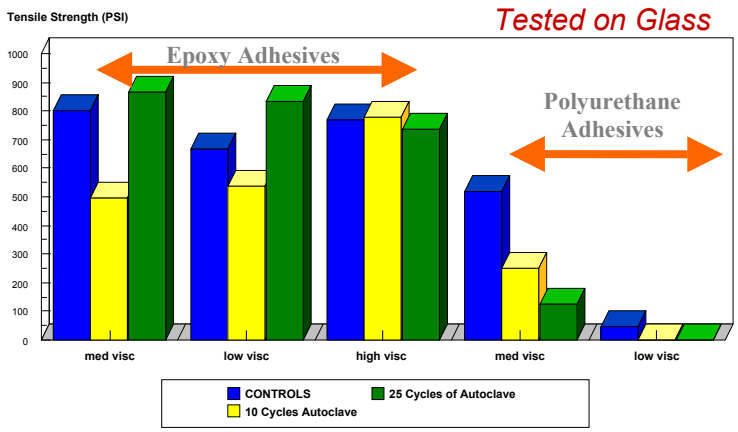

Figure 5: Performance of Adhesives on Glass Following Autoclave Exposure

Figure 6 provides the results for the five (5) adhesives tested on PC lapshear specimens. Testing with PC was limited to a maximum of ten (10) autoclave cycles due to an inherent limitation of the grade of plastic used. As indicated by Figure 6, the low viscosity epoxy and the two urethane adhesives maintained strengths comparable to initial strengths following ten repeated autoclave cycles, with the majority of assemblies exhibiting strengths

in excess of the substrate. The remaining adhesives exhibited a significant loss of strength following sterilization and adhesive failure.

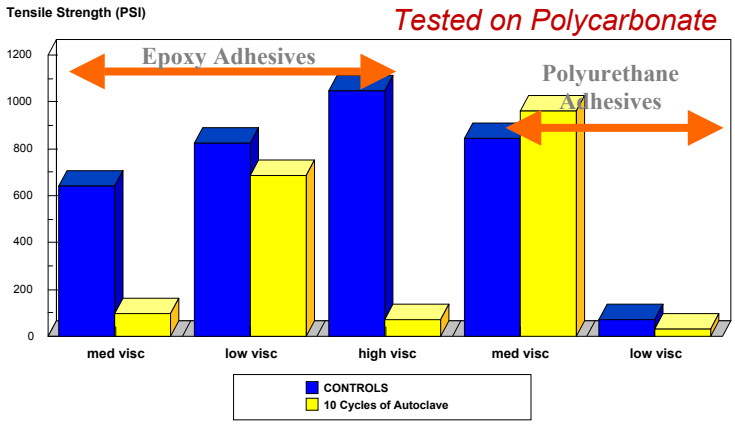

Figure 6: Performance of Adhesives on PC Following Autoclave Exposure

Figure 7 provides the results for the five (5) adhesives tested on PVC lapshear specimens. The majority of assemblies exhibited 100 – 350% retention of strengths following autoclave exposure. In addition, all autoclaved specimens exhibited severe elongation of the substrate during test. Such deformation of the substrate is likely attributed to a slight melting of the plastic since some grades of PVC have reported melt temperatures as low as 132°C.

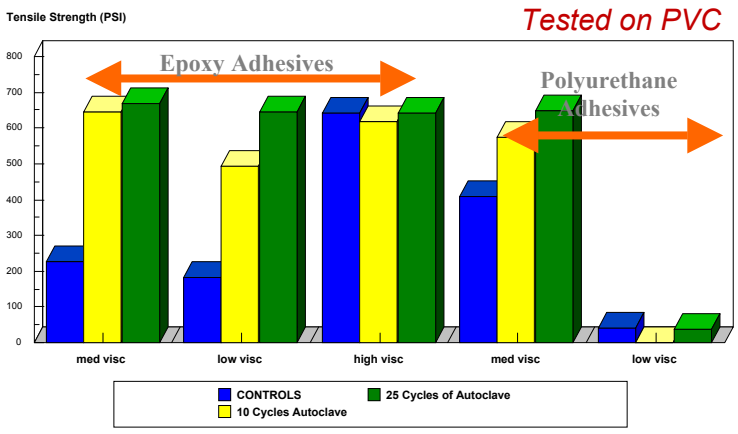

Figure 7: Performance of Adhesives on PVC Following Autoclave Exposure

Figure 8 provides the results for the five (5) adhesives tested on PEI lapshear specimens. Although a number of the epoxy assemblies exhibited substrate failure following autoclave exposure, the low viscosity material was the only product to maintain strength

values close to the initial values. The medium viscosity urethane adhesive also maintained strengths comparable to or in excess of initial strength values. The assemblies involving the urethane adhesives exhibited a combination of adhesive and cohesive failure modes.

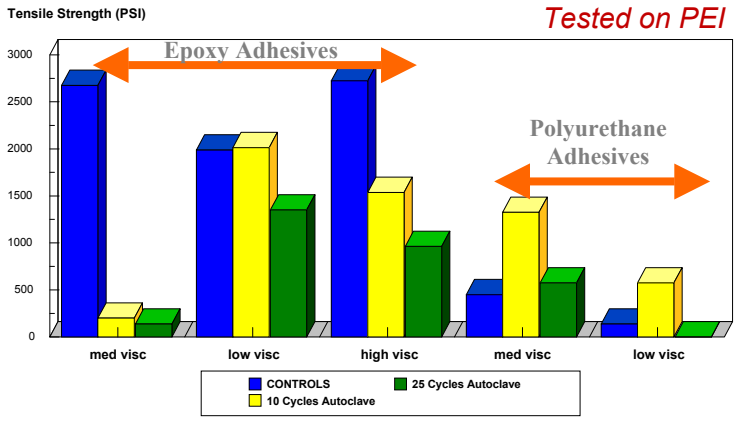

Figure 8: Performance of Adhesives on PEI Following Autoclave Exposure

Summary

Adhesive resistance to repeated autoclave cycles was found to vary based on the adhesive formulation and the substrate selected. In general, however, it was found that several of the epoxy and urethane adhesives evaluated are capable of withstanding up to twenty-five (25) repeated autoclave cycles on a variety of substrates including glass, metal and plastic. In particular, the clear, low viscosity epoxy and the off-white, medium viscosity urethane adhesives offered strengths following up to twenty-five autoclave cycles of a minimum of 70% of initial strengths or strengths in excess of the substrates. Because adhesive performance can vary based on substrate, it is recommended that each application be fully evaluated to ensure that the combination of adhesive and substrate are compatible with the repeated sterilization environments – the most rigorous being autoclave.

Substrates such as glass, PC, and PVC need to be screened carefully to ensure that they are capable of withstanding the environment imposed by repeated autoclave sterilization. Deformation and/or weakening of the substrate should be monitored closely or reviewed with the substrate supplier prior to use for a reusable or resposable device.