



Homogenous Antimicrobial Thermoplastic Urethanes

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Abstract:

Analysis overview based upon the investigation and development efforts conducted to provide a method for homogeneous distribution of anti-microbial agents in TPUs and the elution dynamics of the active agent, including kill data, where the anti-microbial agent is not deactivated by thermal processing, yet remains homogeneous in extruded applications.

Polyurethanes exhibit versatile characteristics and can be used in a wide array of products for use in many industries. In combination with an anti-microbial agent the material applications are far reaching and can meet many different end-product requirements. The primary focus for this investigation and subsequent development efforts is based upon the medical and biopharmaceutical industries, in association with the widespread incidence of patient infections due to bacterial or bioburden transmissions.

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Antimicrobial Thermoplastic Urethanes

Introduction:

The wide use of polymeric materials in medical devices has been associated with an increasing incidence of patient infections. This phenomenon is particularly common with indwelling catheters, especially when those catheters are used for extended periods of time. ChronoFlex Antimicrobial Polymers have been specifically developed to help reduce the incidence and severity of infections in patients subject to indwelling medical devices.

Bacteria are becoming resistant to organic anti-microbial and antibiotic agents in general, as seen with the current MRSA (Methicillin Resistant Staphylococcus aureus) bacteria. Most MRSA and other infections occur in hospitals and clinics from simple procedures such as catheterizations.

There are a number of technical problems one must consider when designing a TPU for antimicrobial applications, including:

- Thermal stability of the antimicrobial agent.
- Ability to disperse the agent homogeneously in the final product.
- The rate of elution of the active moiety in various environments.
- The effectiveness or activity of the agent across a wide range of microbes.
- Toxicity concerns.
- Availability and cost concerns.

Experimental:

In 2005/6, development was conducted on a novel drug eluting cardiac stent in which a solid drug was eluted through a solid TPU for application as an anti-stenosis agent. This work led directly to the investigation of anti-microbial polymers, beginning with a line of polycarbonate-based aliphatic polyurethane TPUs, where the anti-microbial agent was incorporated homogeneously throughout the TPU. The combination of a hydrolytically stable polycarbonate and a hydrolytically superior diisocyanate produced a biostable and biocompatible TPU for medical devices such as catheters, short-term implantable tubing and similar applications.

Considerable research was done on the available antimicrobial agents that met the following criteria:

- Active agent stability to repeated exposure of 260 to 420 F.
- Limited migration of the agent when in use, as for example in a catheter.
- A wide kill selectivity for microbes.
- The agent is not toxic or harmful in small quantities.
- The active agent elutes an antimicrobial factor, such as metal ions, to the surface of the device in therapeutic amounts over a significant time duration.
- The TPU has an active storage life time over and extended time period.

The antimicrobial TPUs must be capable of being manufactured with standard TPU processing equipment, and the product could be further extruded or injection molded several times and continue to elute an antimicrobial agent at a desired rate.

This essentially limited the choice of an anti-microbial agent to inorganic agents, as the organic antimicrobial agents tend to be volatile and degrade at TPU processing temperatures, typically 280 to 420 F.

Our search for effective and practical antimicrobial agents that fit the thermal stability and elution criteria were therefore inorganic. These included, but were not limited to, iodine, boron, chlorhexidine-silver sulfadiazine, sodium silver hydrogen zirconium phosphate, a mixture of 0.6 % silver, 0.4 % cupric oxide and 0.8 % zinc, a mixture of 95.9 % zinc oxide plus 0.25 % silver and soluble glass compounds containing an antimicrobial agent that could be effectively eluted at the desired rate.

When silver ions, for example, enter microbial cells, they interact with cellular enzymes, this killing the microbes. Some antimicrobial agents are ineffective because they rupture the microbial cell walls.

Independent test analysis was conducted by both US and Japanese labs. All testing was based on JIS Z 2801, which is the Japanese Industrial Standard for evaluating the antimicrobial activity on the surface of antimicrobial products. The antimicrobial activity is measured by comparing the level of bacteria that remains on the surface of the antimicrobial product after a 24 hour exposure time to that which is found on the surface of an untreated control test piece after 24 hours.

A Kirby-Bauer “zone of inhibition” test was also run to show that we had no antimicrobial agents, per se, becoming free of the TPU device and endangering the patient.

Technology:

Antimicrobial agents may be generally classified as either organic or inorganic materials. Organic antimicrobial agents may be complex toxic bactericides which often leach from the polymer causing health concerns. Organic antimicrobial agents also include antibiotic pharmaceutical preparations which may be added to medical devices often as coatings. Organic antibiotic agents are heat labile and readily degraded by humidity and mechanical processing. This makes organic antibiotic agents difficult to incorporate into standard resin processing systems. Microbial antibiotic resistance continues to be a concern with pharmaceutical based materials.

Inorganic antimicrobial agents include metal ions, e.g. Ag^+ , Cu^{++} , Zn^{++} . ChronoFlex Antimicrobial Polymers contain silver ions (Ag^+) which are preferred as they possess a wide spectrum of antimicrobial activity, safety and heat stability. [See generally Guggenbichler *et al.*, 1999 Infection 27 Suppl. 1, S16-S23].

The broad spectrum of biocidal activity of silver ions includes anti-bacterial, anti-fungal and anti-viral activity. *Id.* The silver ions bind to sulfhydryl groups in enzyme systems and interfere with the transmembrane energy transfer and electron transport in bacterial microorganisms. *Id.* Silver ions also bind to the DNA of bacterial and fungi thereby increasing the stability of the bacterial double helix and inhibiting proliferation. *Id.* There is no microbial resistance to silver ions and no cross resistance with antibiotics. *Id.*

The soluble glass type of antimicrobial offers a number of advantages, namely:

- Effective at low concentration.
- The overall rate of elution.
- Thermally stable to at least 900 F.
- Color stable against UV radiation.
- Long term stability and activity.
- Little or no effect on the physical properties of plastics and elastomers.

ChronoFlex Antimicrobial Polymers may be processed by conventional extrusion and injection molding techniques while maintaining the desired antimicrobial properties.

The antimicrobial additive is incorporated into the polymer structure during the synthesis reaction thus providing a highly uniform dispersion throughout the material. By incorporating the additive during polymer synthesis the requirement for a secondary compounding step is eliminated thus reducing cost and

complexity. Similarly due to the antimicrobial agent being dispersed throughout the polymer capital intensive surface coating and application techniques are not required

Techniques:

Prior to this study, it is our belief that there were only two basic methods for incorporating antimicrobial additives in resin systems currently in use;

- In the first method, the antimicrobial agent is added to the finished resin by compounding or kneading the additive into the resin as a secondary processing step. This is often accomplished using melt extrusion and pelletizing equipment and requires the additive to be heat stable for extended periods. Uniformity of dispersion is often difficult to achieve with this technique.
- The second method involves coating the polymeric product with an agent containing the antimicrobial additive. This method results in an antimicrobial coating which, in many instances, is susceptible to mechanical damage and ultimate loss of the coating and its antimicrobial properties.

Each of these methods are performed with prefabricated resin or on fabricated medical devices or device components. The incorporation of the antimicrobial agent is accomplished as one or a series of secondary steps which add cost and complexity to the manufacturing process.

ChronoFlex Antimicrobial Polymers uses neither of the techniques described above. The Silver containing additive used in ChronoFlex Antimicrobial Polymers is uniquely incorporated into the polymer structure during the polymerization sequence thus ensuring uniform dispersion throughout the resulting polymer.

The active silver ions incorporated in ChronoFlex Antimicrobial Polymers are stabilized by their association with a carrier, such as a phosphate (particularly zirconium phosphate), water soluble silicate powder, zeolite and ion exchange resin. Additional additives may also be incorporated in ChronoFlex Antimicrobial Polymers such as antioxidants, mold release agents, color stabilizers and radiopacifiers (e.g. barium sulfate).

Results:

While the initial R&D and testing was done with lab-size R&D batches, production size batches of antimicrobial TPUs were made for validation. In addition, production batches of anti-microbial TPUs have been made which also contain 20 % of a radiopaque additive.

Physical property testing has shown that there are no significant differences in tensile strength, modulus or elongation of the anti-microbial TPU vs. the standard non-anti-microbial polymer. Therefore, there are no significant machine settings changes required to switch from a non-anti-microbial polymer to the same polymer which contains the active agent in extrusion or injection molding product, for example.

In independent laboratory testing, ChronoFlex Antimicrobial Polymers have been shown to kill both gram positive and gram negative bacteria including *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Escherichia coli* (E-Coli) and methicillin-resistant *Staphylococcus aureus* (MRSA). Using AATCC Method 100 (modified), a >99% reduction in colony forming units (CFU) was observed with ChronoFlex Antimicrobial Polymer samples after 24 hours contact time.

Sample	<i>S.aureus</i> (MRSA)	<i>Escherichia coli</i> (E-Coli)	<i>P. aeruginosa</i>	<i>S. epidermidis</i>
CFAL	> 99.97%	> 99.99%	> 99.79%	> 99.95%

Intellectual Property:

Domestic and international patent applications have been submitted, which provide broad protection for this unique antimicrobial family of biomaterials.

Conclusion:

Initial microbiological laboratory testing has been completed. Additional mechanical and molecular testing is in process. Dose optimization is ongoing using two different silver ion carrier systems. Pilot production and production scale-up is progressing. Our antimicrobial technology is being applied to many product families within our core and in-process development product platforms, with positive results. Additional testing is underway to confirm extended duration elution profiles and kill rates. ChronoFlex Antimicrobial Polymers can be manufactured in a range of hardnesses, mechanical properties and with specific additive packages. They may be readily customized to meet specific customer or applicational requirements.

References:

Guggenbichler *et al.*, 1999 *Infection* 27 Suppl. 1, S16-S23