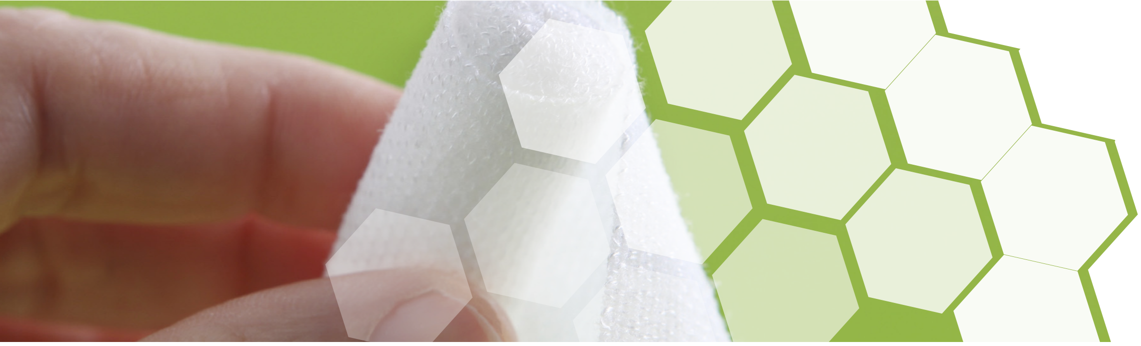

Brief Technology Overview of Anti-Microbial, Infection Control Chemistries for Medical Applications

Introduction

It is well known that antimicrobial materials are useful in neutralizing or reducing the impact of bacterial growth. For example, the main purpose in adding antimicrobials or biocides in plastics, especially in medical applications, was to protect the polymeric materials from deterioration and destruction from microbial attack. Some traditional antimicrobial agents are often actually preservatives, which while effective as antimicrobials are toxic to humans. Certain metals and more specifically the ions released from these metals have also proven effective as antimicrobial agents while also possessing a safe medical profile. From both a cost and safety viewpoint it is however advantageous to minimize the quantity of these metals and ions in use.

It is also well known that bacteria are found on all healthy skin, in soil and on the foods that we eat. Normally such bacteria are benign, but they can become problematic when exposed to a compromised or weakened immune system or allowed to grow and dominate the normal bacterial flora. Under these uncontrolled growth conditions, certain benign colonies become opportunistic and thrive in the compromised environment, often leading to spoilage, odors, infection, and food poisoning that sometimes lead to illness or even death. In several industrial and consumer applications, including medical, metallic based antimicrobial agents, in particular silver, have been well accepted as an infection-control technology in certain medical settings.

Prior to the introduction of silver-ion controlled-release antimicrobial agents, formulators used a wide variety of silver, zinc and/or copper containing compounds, oxides, salts, colloids, proteins and other chemicals. The list is broad and includes but is not limited to: silver acetate, silver azide, silver bromide, silver bromate, silver carbonate, silver carbamate, silver chloride, silver chlorate, silver chlorite, silver chromate, silver nitrate, and many others. Additionally, it is important to list the naturally occurring and biocompatible silver alginate. Several versions of colloidal silver are also known. Further, there are similar lists for copper and zinc also. The agents mentioned above are well known and provide potent kill rates depending on the concentration used. These materials present readily available silver however it can and often is consumed very quickly, often in minutes. It is the ionic species of silver, Ag^{+} that is most effective however it is reactive and short lived.

Alternatively, metallic silver, metal or silver plating is very durable and long-lived however it is a poor antimicrobial as there is very little ionic silver available. One approach to utilize metallic silver but increase its effectiveness it by making a smaller and smaller particle size, all the way down to nano-sized particles of under 50 nm. Improved ionic release is observed based on the greater surface area.

Silver salts and many silver compounds can offer a degree of controlled release especially if they are complexed or entrapped within another material. Zeolite loaded with ionic silver is a well known example as allows release of the positive silver ions when negative ions replace them in the structure. Some other approaches have similar performance although the chemical structure is different.

Every medical application has unique needs and challenges. For example, within an infected wound, it can be argued that a large initial release of silver is desired as a means to counteract the infection rapidly. As bacteria can multiply very rapidly it is also however desirable to maintain a medium term and longer term degree of performance which provides ongoing efficacy to maintain control over the bacterial population.

When exposed to metals and metallic ions, in addition to microbes, algae, bacteria, mold, yeast, fungi and viruses are all denatured. There are several theories surrounding this observation, most involve the attachment to or penetration of the cell wall by the metallic ions and either killing of the cell or prevention of reproduction. Silver in particular, forms strong bonds or ligands with sulfur containing materials, proteins in this case, and effectively disrupts cell activity and prevents reproduction. Similarly, this antimicrobial effect is shown by ions of: mercury, copper, iron, lead, zinc, bismuth, gold, aluminum and other metals. Toxicity and/or bioaccumulation is observed with several of these metals, however, silver, zinc and copper are recognized as having little or no toxic effects on mammals.

Challenges with Current Approaches

It is possible to apply a coating to the surface of the substrate material (or to the fibers of the fabric if it is a woven or nonwoven material in wound care applications). There are many coatings that are available for this purpose and with careful processing, an antimicrobial 'active" can be incorporated such coatings. However, challenges are often encountered with this technique including a lack of durability, difficulty in obtaining a uniform coating, color changes over time and limited performance related to a limited quantity of coating add-on. It can be fairly stated that because of these limitations, surface coatings are considered semi-durable and are targeted for applications where they limitations are well-understood and accepted.

In the case of medical applications where woven or nonwoven materials are under consideration, while there are a number of antimicrobial fibers and textile products, both the in-fiber and coated-fiber methodologies have their pros and cons. Some methods involve very expensive metal ion additives to custom fibers, which may add expense to the finished product. The expense of the additives and the volumes involved in these products necessitate small production runs. In addition, the small production runs of fiber are then used to construct small production runs of textile web. The result is a significant work loss at each step of the manufacturing process, as well as a significant cost mark-up at each stage. The resulting antimicrobial fabrics can cost many times what a conventional fabric would cost. In addition, anyone who desires to use one of these antimicrobial fabrics in a product is restricted to a very small selection of available styles and performance characteristics due to the multiple steps involved in creating an end product. Lastly, production runs of unique antimicrobial materials can involve very significant minimum quantities and there drive up pricing.

Other challenges include that fibers can be coarse to the touch due to the fact that the surface of the fibers has been significantly impacted by the silver plating adhered to the surface. These fibers also have a specific appearance color that may or may not be desirable in all applications. When efforts have been directed at incorporating silver within fiber without affecting the fiber properties as significantly via the incorporation of a nanoparticles of silver into fibers , due to the small particle size of the nano silver, there is a risk of much less significant effect on the fiber characteristics. This process, however, still leaves a large amount of the expensive nanoparticles embedded within the fiber where they can do no good from an antimicrobial standpoint. Since the nanoparticles are even more expensive per pound than standard formulations, the final cost of the end-product may not be optimized to a satisfactory level.

In an attempt to deal with the limitations of adding antimicrobial actives to the material substrate, solutions have been tried to provide the antimicrobial actives as an add-on to the material. Examples of such add on methods of applying antimicrobial actives include specially formulated sprays or other post-treatments. However, careful process and quality control needs to be established and exercised because of the inherent risk of lack of durability and accuracy in the post-treatment add-on products is present.

Biovation Approach to Infection Control Chemistries

Biovation is chemical technology agnostic; meaning, Biovation does not limit itself to any particular set of chemical platforms available in the commercial market. Rather, based on decades of research and development of formulations, it compounds and formulates customized and unique solutions for targeted specific applications in the medical sector.

The use of certain noble or transition metals in metallic or ionic states is an accepted antimicrobial approach in many plastics and coatings. Silver, Zinc and/or Copper are offered commercially for use in plastics including; metallic plating, zeolite and zirconium matrices, colloidal suspensions and nano-particulates, silver salts in solid or dissolved formats and others; Biovation takes advantage of this commercial availability. Each metallic system exhibits a certain speed and rate of ionic release profile which is rather inflexible and is largely surface-area driven. An example is when silver oxidizes or tarnishes thereby releasing antimicrobial Ag^{+} ions when exposed to ozone, hydrogen sulfide, or air containing sulfur. Further, each species or version of a metal containing "active" performs in a specific manner. This performance is measured via elution or release of silver, copper or zinc ions into the local environment. This elution is what comprises the basic antimicrobial activity and without elution of metallic ions, there is no beneficial effect. The elution is governed by many factors including but not limited to surface area, dissolution speed, and construction of the particle i.e., zeolite "cage" or solid metallic particle for example.

Through exhaustive and detailed evaluation, the performance characteristics of many antimicrobial "actives" have been determined. It is then possible to identify the desired rate-of-release and mechanism-of-release which combined determine the antimicrobial elution, properties of each "active" and via blending or compounding of multiple "actives" obtain an optimized solution. This optimization can take into account many factors strictly depending on the final product and desired performance. The overall cost, speed of ionic release, duration of ionic release, color change properties, particle size and the ratio of ions of multiple metals are therefore within the control of the formulator. The attained results have been obtained via this investigative process and form the basis of Biovation's approach to creating and implementing formulation solutions for end-customers.

Numerous iterations of formulation and analysis results in the construction of "actives" which allow different rates of release and mechanisms of silver ion release; it is an activity that Biovation engages with for its customer projects. The creation of various formulations provides a convenient mechanism with which to tailor the "actives" in composition and quantity by using a combination of masterbatch concentrates.

For example, to obtain rapid silver release, several conditions must be met; the silver must be contained in a readily accessible place and in a rapid-release format. In some of the projects we have done for our customer partners, the surface of the fibers used to make the absorbent pad can be treated to include a coating and the "actives" can be contained within such a coating. It is clear that a surface coating of fibers offers a very high surface area and we have used this to our advantage.

In the event of surface coating, the coating must be flexible and soft enough to not break and shed particles when flexed. The coating must also be biocompatible as it will be in direct contact of a breached skin surface and bodily fluids. Any number of polymeric dispersions or emulsions can be used for the coating, including polyurethanes and acrylics, each will simply dry or crosslink upon drying, sometimes with a catalyst required. Certain silicones will also serve well in this function. Acrylics and copolymers can be used as super absorbents and these materials have also been evaluated in coatings.

Additionally, a solvent coating and UV cure and reactive urethane chemistries functions well also. The aqueous route is chosen simply for lower cost and ease of processing. There is always the question of entrapped solvent when that system is used, unreacted UV initiator , cross-liners or ioscyanates in a urethane system. The aqueous approach certainly is the cleanest. A thickening agent or film-former is optional. Cellulose or starch is a suitable thickener as are many acrylics. These materials are dispersed in water and applied to the nonwoven pad in a dip/nip/dry process. The consistency of coating is very good.

It is obvious that silver cannot be entrapped within in a slow dissolving compound or in an slow-reacting ionic exchange medium and still release rapidly. The silver ions must be very readily available and with small particle size, nano scale or molecular level, when possible. Certain nano-scale metallic silvers are available however they are very expensive, tend to clump and agglomerate and are sometimes difficult to handle. It must be noted that pure nano silver is actually a very slow release mechanism; as particles are metallic silver, ions are only released from the surface via oxidation. Metallic silver is a very poor antimicrobial as the limited surface area limit availability of silver to release the desired silver ions. Placing the silver in smaller and smaller nano-particles effectively increase surface area speed the release of silver ion via oxidation; however, research is on-going by institutions to determine if nano-particles present any health risks due to a possibility of ending up in unintended areas of the human body.

It is difficult to formulate the exceptionally rapid and powerful performance of product with fast initial response while maintaining long-term efficacy all with minimal cytotoxixity. Such requirements are familiar to Biovation and have resulted in formulation options and directions to assist our customer partners in multiple end-uses for medical applications.

Contact Us

Biovation's expertise is in infection control formulations and we look forward to partnering up with you. We invite you to contact us solutions@biovation.com to discuss how Biovation can help you with our portfolio of technologies and solutions.

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