Technical White Paper

Functionalized Triclosan for Controlled Release Applications

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Abstract: *This white paper is intended to provide readers with an overview of novel hydrolysable Triclosan-based compounds and macromers. These hydrolysable Triclosan compounds and macromers were prepared by functionalization of Triclosan with safe and biocompatible molecules such as glycolic acid, lactic acid, p-dioxanone, and/or caprolactone monomers. These monomers are the key components of a majority of absorbable medical devices. This functionalization enhances the native value of Triclosan and allows for the controlled release of Triclosan at the site of action over desired time period along with increased solubility. Furthermore, these hydrolysable Triclosan compounds and macromers have improved bioavailability, improved efficacy and are also anticipated to degrade into safe and biocompatible molecules. Moreover, these macromers will provide extended antimicrobial properties to the substrate when incorporated in a bulk material or applied as part of a coating. These functionalized hydrolysable Triclosan compounds have potential applications in the same or similar areas as the non-functionalized Triclosan compounds, since the compounds retain the innate properties of the active Triclosan. Hence, they may find applications as anti-microbial agents, medical device coatings, cosmetics and controlled release applications, surgical sutures and implantable medical devices.*

1.0 Triclosan

Triclosan is a chlorinated aromatic compound containing an ether and phenol group as shown in **Figure 1**. The anti-bacterial property of Triclosan has led to its widespread use in a number of medical devices and consumer product applications. Besides being used in soaps, cleaning agent formulations, anti-microbial fabrics and other consumer articles, where it has been shown to be effective in reducing and controlling bacterial contamination on hands and treated articles, formulations containing Triclosan have also been used in a number of medical devices including sutures incorporated for extended anti-microbial activity. More recently, showering or bathing with 2% Triclosan has become a recommended regime for the decolonization of patients whose skin is carrying methicillin resistant *staphylococcus* aureus (MRSA) following the successful control of MRSA outbreaks in several clinical settings.

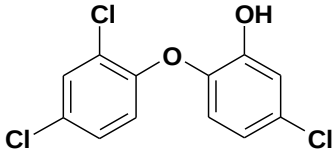

Figure 1. Triclosan

Inspite of its widespread applications and beneficial anti-microbial properties, the limited solubility of Triclosan and related compounds in water renders them non-hydrolysable. This reduces their circulation time and hence efficacy at the site of action. Furthermore, it is very difficult to polymerize Triclosan in its phenolic form. This prevents the beneficial attributes of Triclosan and Triclosan containing compounds from being used to their full potential. Hence, it is desirable to enhance the native value of Triclosan by, for example, providing functionalized Triclosan and Triclosan containing compounds with a specific controlled degradation profile or range, enabling controlled release of Triclosan over an extended period of time while retaining its inherent antimicrobial activity.

2.0 ***Functionalized Triclosan Compounds, Macromers and Triclosan end capped Polymers***

In order to enhance the native value of Triclosan while retaining its anti-microbial properties, we at Bezwada Biomedical, LLC have developed novel functionalized triclosan compounds and macromers. These functionalized Triclosan compounds are prepared by functionalization of the phenolic hydroxyl group of Triclosan with hydroxy acid such as glycolic acid, lactic acid, open chain caprolactone and open chain p-dioxanone, via Williamson etherification as shown in **Figure 2**. These hydroxy acids are the base materials of a range of absorbable and biocompatible polymers and copolymers, such as poly (lactide) (PLA), poly(glycolide) (PGA), poly(caprolactone) (PCL), poly(p-dioxanone) (PDS), poly(lactide-co-glycolide) and poly(glycolide-co-caprolactone). These polymers and copolymers are the key components of a majority of absorbable medical devices ranging from sutures, staples, orthopedic screws and implantable surgical devices to tissue engineering scaffolds.

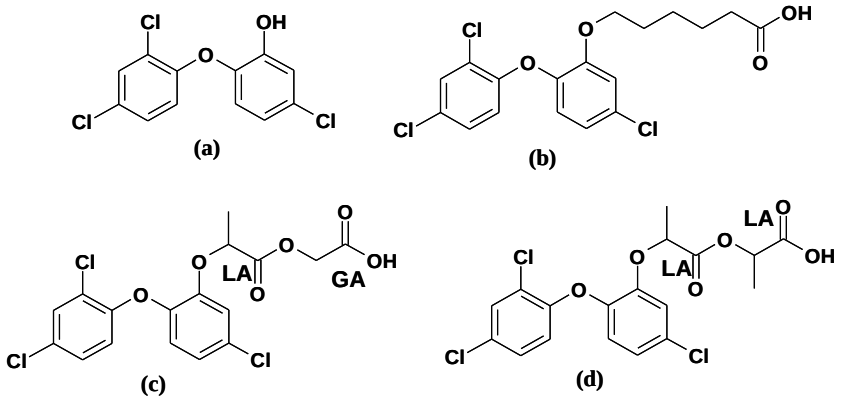

Figure 2 Functionalized Triclosan Compounds: (a) Triclosan; (b) Caprolactone Functionalized; (c) GA+LA Functionalized; (d) LA+LA Functionalized Triclosan, where GA is Glycolic Acid and LA is Lactic Acid.

Functionalized Triclosan compounds prepared as shown in **Figure 2(b)-(d),** were then covalently attached to another Triclosan molecule via esterification as shown in **Figure**

3(a)-(b) to provide dimers with different hydrolysis profiles. For example, dimer with structure **3(a)** will hydrolyze faster than dimer with structure **3(b).** Furthermore, Triclosan compounds shown in **Figure 2(b)-(d)** can be covalently attached to the biodegradable polymer backbone or were condensed with diols/polyols or polyethylene glycols to form oligomers and Triclosan end-capped polyesters.

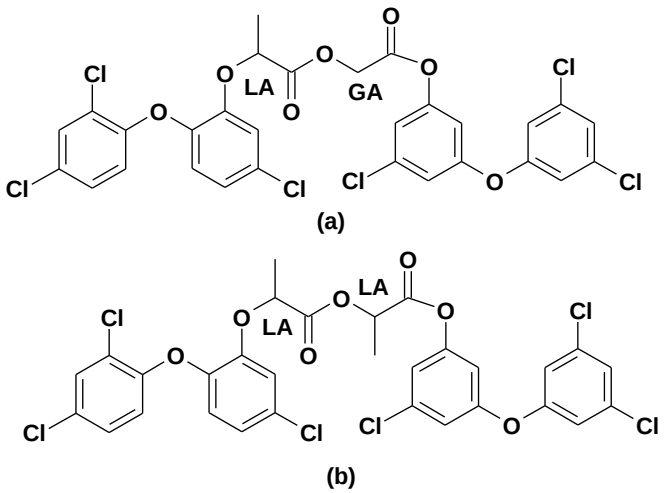

Figure 3. Triclosan End-Functionalized Dimers with Different Hydrolytic Degradation Rates Formed via Esterification of Triclosan with structures **2(c)** and **2(d).**

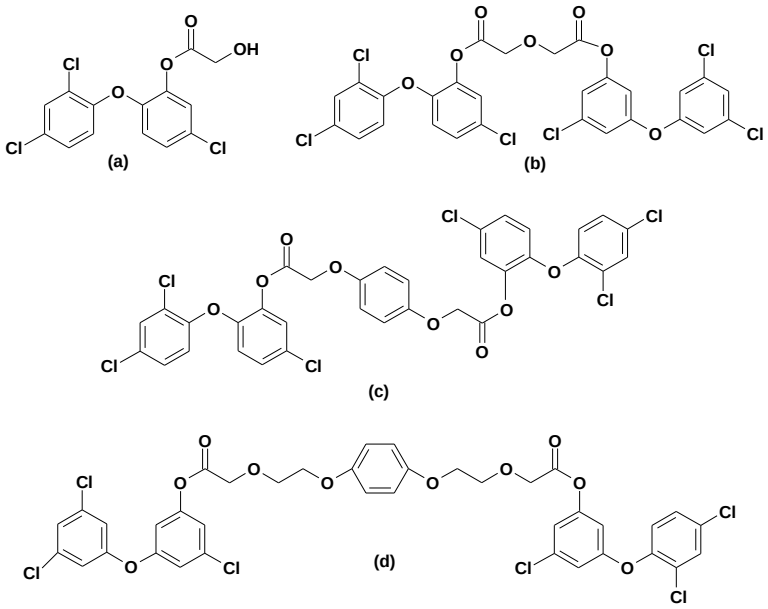

Figure 4. Hydrolysable Triclosan based Compounds and Dimers Formed via Esterification of Triclosan with Hydroxyacids and Diacids (a) Glycolic Acid Functionalized Triclosan (b) Diglycolic Acid Functionalized Triclosan (c) Hydroquinone Diglycolic Acid Functionalized Triclosan (d) Hydroquinone p-Dioxanone Functionalized Triclosan.

In a similar fashion, the Triclosan molecule was condensed with diacids via esterification to form hydrolysable compounds and dimers as shown in **Figures 4(b)-(d),** *and* Triclosan end-capped absorbable polyester, as shown in **Figure 5**.

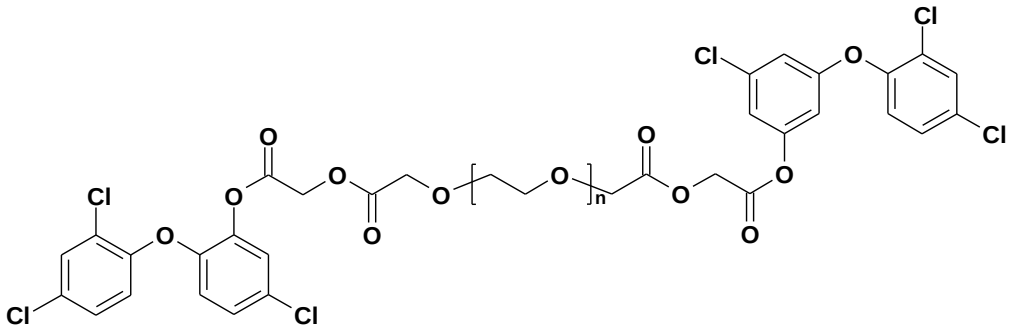

Figure 5. Triclosan End-Capped Absorbable Polyester formed via Esterification of Triclosan with Hydroxyacids and Polyethylene Glycol Diacid.

Moreover, the glycolic acid functionalized Triclosan molecule as shown in **Figure 4(a)** was further functionalized with fatty acids such as Stearic acid via esterification to produce hydrolysable Triclosan containing compounds as shown in **Figure 6** for potential cosmetic applications.

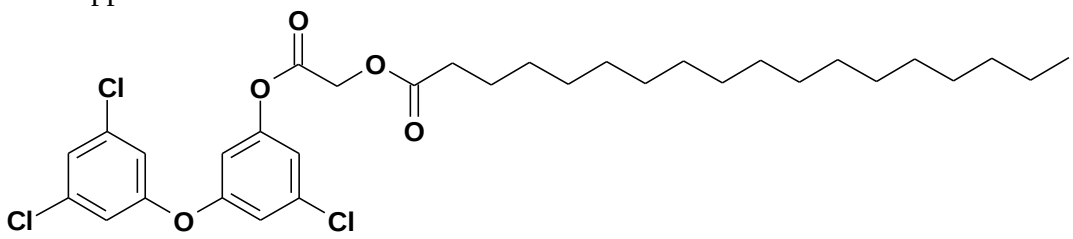

Figure 6. Stearic Acid Functionalized Triclosan Glycolate Molecule for Potential Cosmetic Applications and Medical Device Coatings

As shown in **Figures 4, 5 and 6,** functionalization of Triclosan produces hydrolysable compounds, macromers and/or polymers. This process enhances the native value of Triclosan by providing the resultant monomer, dimer or polymer or their combinations with a specific, controlled degradation profile or range, enabling the controlled release of triclosan over an extended, controllable time range. The different controlled release profiles represent slow, moderate and/or rapid release of Triclosan. This release may be targeted to one or more specific organs or parts of the body. This functionalization greatly extends the usefulness of Triclosan and provides greater control of the bioavailability of the Triclosan while retaining the inherent biological properties of the Triclosan.

3.0 Potential Applications

The functionalized Triclosan-based compounds; macromers as well as Triclosan end-functionalized absorbable polymers, retain the innate properties of the active Triclosan and hence have potential applications in the same or similar areas as the non-functionalized Triclosan compounds. Hence, these novel compounds and macromers can be used as anti-microbial agents, or can be blended with various absorbable polymers for extended and controlled antimicrobial activity in medical device coatings, cosmetics, surgical sutures and implantable medical devices.

4.0 Summary

- At Bezwada Biomedical, we have developed novel hydrolysable Triclosan based compounds, macromers as well as Triclosan end functionalized polymers. They have been prepared by functionalization of the Triclosan molecule with safe and biocompatible molecules such as glycolic acid, lactic acid, caprolactone and p-dioxanone.

- These hydrolysable Triclosan based macromers and Tricolsan end functionalized polymers have different as well as controlled degradation profiles. For example, glycolic acid functionalized Triclosan will degrade faster than lactic acid and caprolactone functionalized Triclosan.

- The active portion of functionalized Triclosan based macromers and polymers will have improved bioavailability, increased solubility and better control on degradation rates. This provides a site specific controlled delivery of the active Triclosan molecule.

- These hydrolysable Triclosan based compounds; macromers and Triclosan end-functionalized polymers will find applications as anti-microbial agents, medical device coatings, cosmetics and controlled release applications, surgical sutures and implantable medical devices.

Contact Us

For further information on how we can help you engineer your success, please contact us at rao@bezwadabiomedical.com or visit us at www.bezwadabiomedical.com

References:

1. Bezwada, Rao S., US Patent Application No. 12/212,233.
2. Bezwada, Rao S., Functionalized Biodegradable Triclosan Macromers for Controlled Release Applications, 2008 Society for Biomaterials Meeting on Translational Research, September 11-13, Atlanta, GA.

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