Technical White Paper

Controlled Release of Drugs from Novel Absorbable Oligomers and Polymers

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1.0 Introduction

At Bezwada Biomedical, motivations to control the rate of release of drug molecules from a few hours to months formed the basis of the development of novel absorbable linear and multi-armed oligomers and polymers wherein the end groups have been functionalized with therapeutically active drug molecules. In contrast to literature reported polyanhydrides and polyester-anhydride polymers incorporating anti-inflammatory drug molecules such as Aspirin in the polymer backbone chain, the oligomers and polymers developed by our company have a much faster degradation profile and are much easier to handle and process. Moreover, the hydrolysis results in the release of the drug molecule as such, thus preserving the therapeutic activity of the drug molecule.

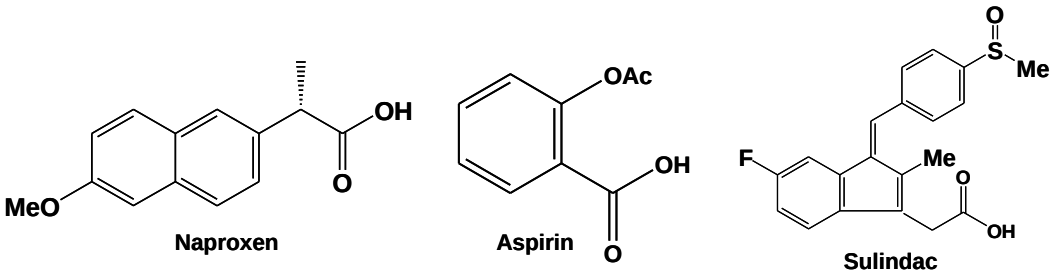

Figure 1. Chemical Structures of Some Common Anti-inflammatory Drug Molecules

This paper is intended to provide the readers with an overview of these novel absorbable oligomers and polymers developed by our company. In particular, this paper will focus on absorbable oligomers and polymers wherein the end-groups have been functionalized with anti-inflammatory drug molecules such as Aspirin, Naproxen and Sulindac, the structures of which are shown in **Figure 1**. These drugs are commonly used to alleviate pain, inflammation and stiffness associated with osteoarthritis, rheumatoid arthritis, tendonitis and menstrual cramps.

2.0 End-Functionalized Oligomers

Figures 2, **3** and **4** depict the structures of four armed Naproxen end-functionalized, Aspirin end-functionalized and Sulindac end-functionalized absorbable oligomers, respectively. They are synthesized by conjugating the carboxylic acid group of each of these drug molecules with either a four armed glycolic acid or lactic acid functionalized hydrolysable linker, derived from a pentaerythritol core. Similarly, **Figures 2(d)** and **4(a)** depict the structures of

Naproxen and Sulindac end-functionalized multiarmed oligomers, respectively, synthesized by conjugating the carboxylic acid group of each of these drug molecules with a four armed glycolic acid, as well as a lactic acid functionalized hydrolysable linker derived from a pentaerythritol core. Furthermore, we also have lactic acid, p-dioxanone and caprolactone functionalized hydrolysable linkers with varying length of repeat units in our inventory.

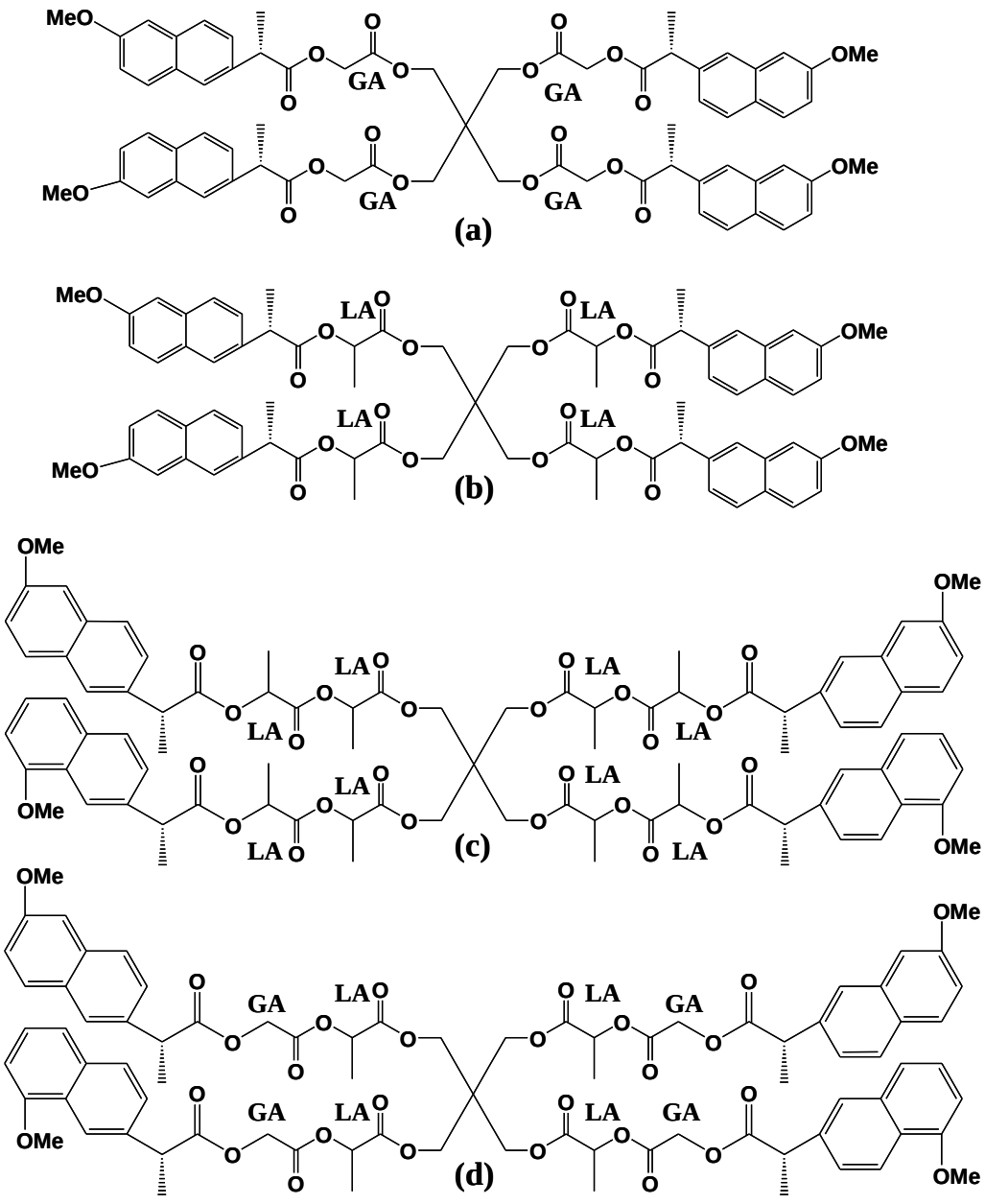

Figure 2. Naproxen End-functionalized Multiarmed Absorbable Oligomers with Varying Hydrolytic Degradation Rates, where GA is a Glycolic Acid and LA is a Lactic Acid Moiety

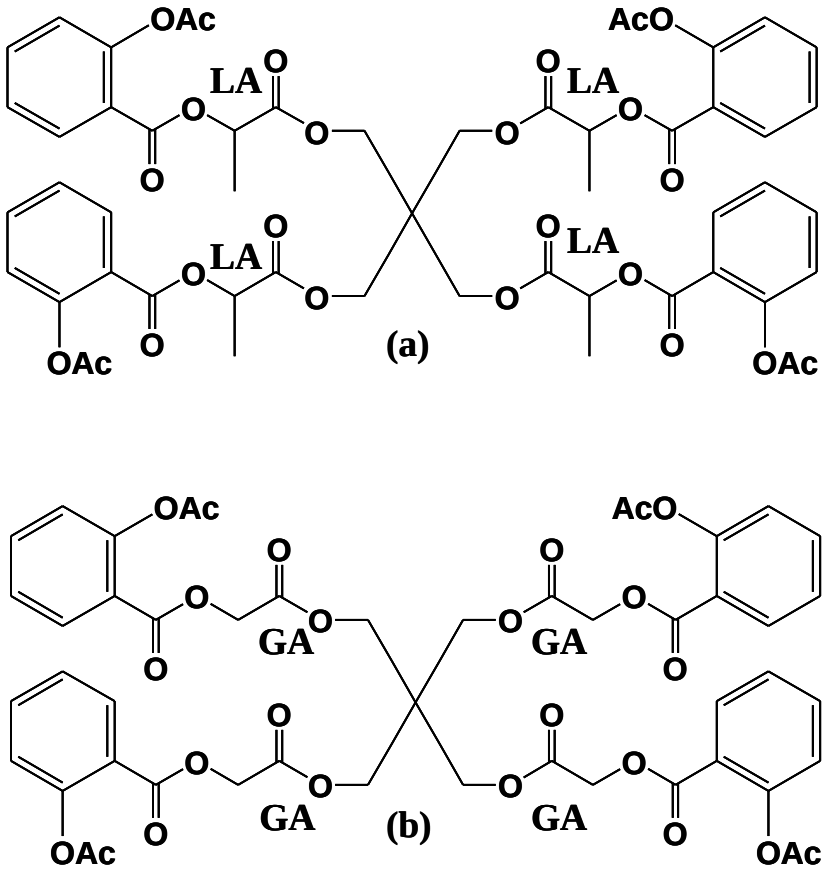

Figure 3. Aspirin End-functionalized Multiarmed Absorbable Oligomers with Varying Hydrolytic Degradation Rates, where GA is a Glycolic Acid and LA is a Lactic Acid Moiety

As can be seen from **Figures 2** to **4**, the backbone of these oligomers is derived from safe and biocompatible glycolic acid, lactic acid, p-dioxanone and caprolactone monomers. These monomers are the key material components of a majority of commercial absorbable medical devices, ranging from sutures, staples, orthopedic screws and implantable surgical devices to tissue engineering scaffolds. These end functionalized therapeutic oligomers, upon hydrolytic degradation, yield safe and biocompatible molecules including drugs. Furthermore, they are designed to degrade in a controlled fashion wherein the rate of hydrolytic degradation can be controlled (a) by varying the chain length of the repeat units derived from absorbable, safe and biocompatible glycolic acid, lactic acid, p-dioxanone and caprolactone monomers in the oligomer backbone, and (b) by changing the absorbable monomer component in the repeat units of oligomer backbone. For example, oligomers of the present study with backbone repeat units derived from glycolic acid will degrade much faster than those derived from lactic acid. Moreover, by varying the number of arms of the oligomers, the payload of the drug molecule to be delivered can also be controlled.

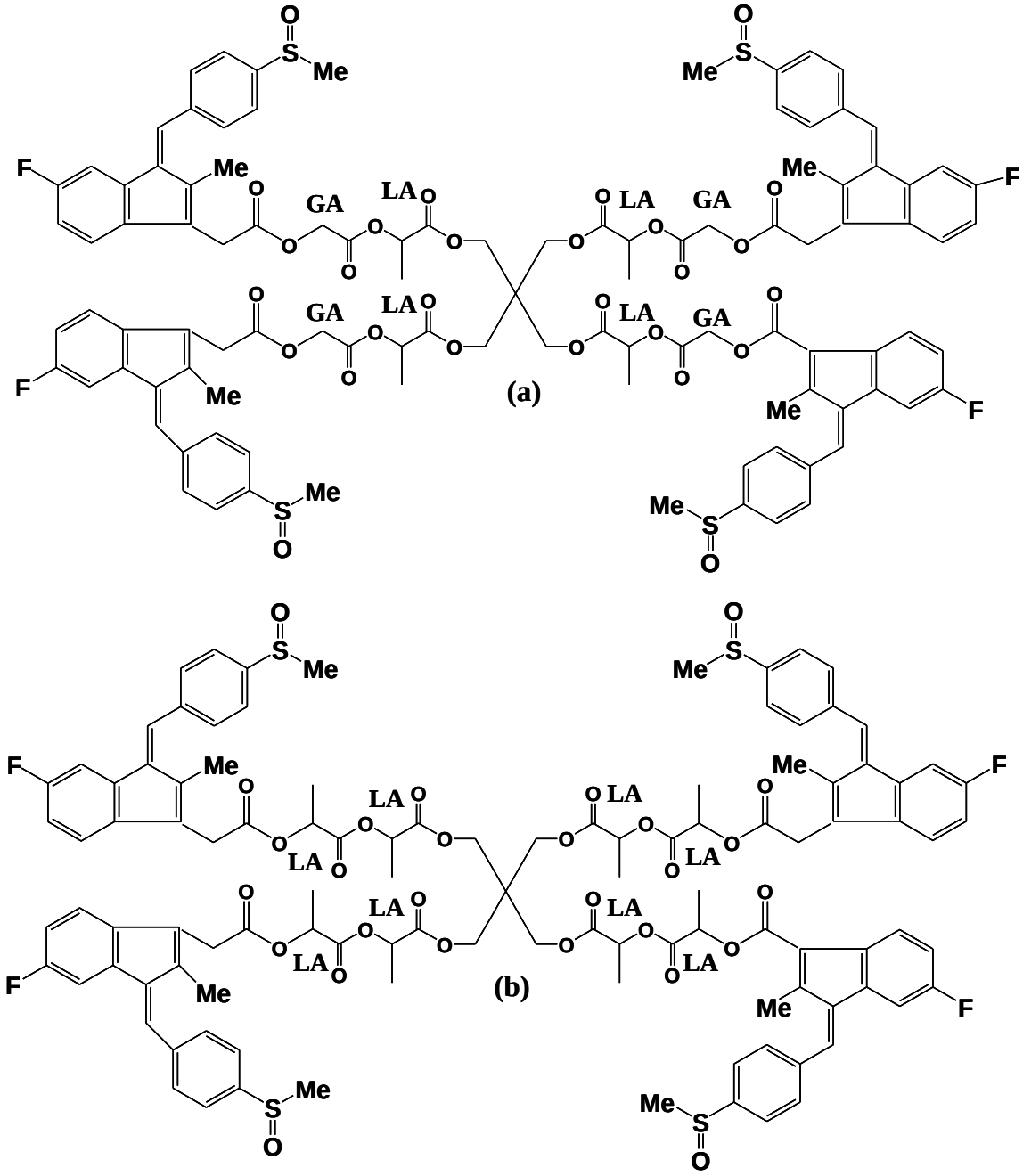

Figure 4. Sulindac End-functionalized Multiarmed Absorbable Oligomers with Varying Hydrolytic Degradation Rates, where GA is a Glycolic Acid and LA is a Lactic Acid Moiety

End-functionalized Polymers: In addition to the end-functionalized oligomers, we have also developed absorbable polymers wherein the end groups have been functionalized with anti-inflammatory drug molecules. For example, **Figures 5(a)**, **(b)** and **(c)** depict the structures of Naproxen end-functionalized, Aspirin end-functionalized and Sulindac end-functionalized with linear absorbable polymers, respectively. In addition, we have also developed multiarmed absorbable polymers end-functionalized with these drug molecules. As shown in **Figures 2-5**, end-functionalization of the hydrolysable oligomer or polymer chain with these

drug molecules enhances the native value of these drugs by providing the resultant oligomer or polymer or their combinations with a specific, controlled degradation profile, thereby enabling the controlled release of these drugs over an extended, controllable time range. The different controlled release profiles represent slow, moderate and/or rapid release of these drugs. This release may be targeted to one or more specific organs or parts of the body. This functionalization greatly extends the usefulness of drug molecules and provides greater control of the bioavailability of the drug while retaining the inherent biological properties of the drug molecule.

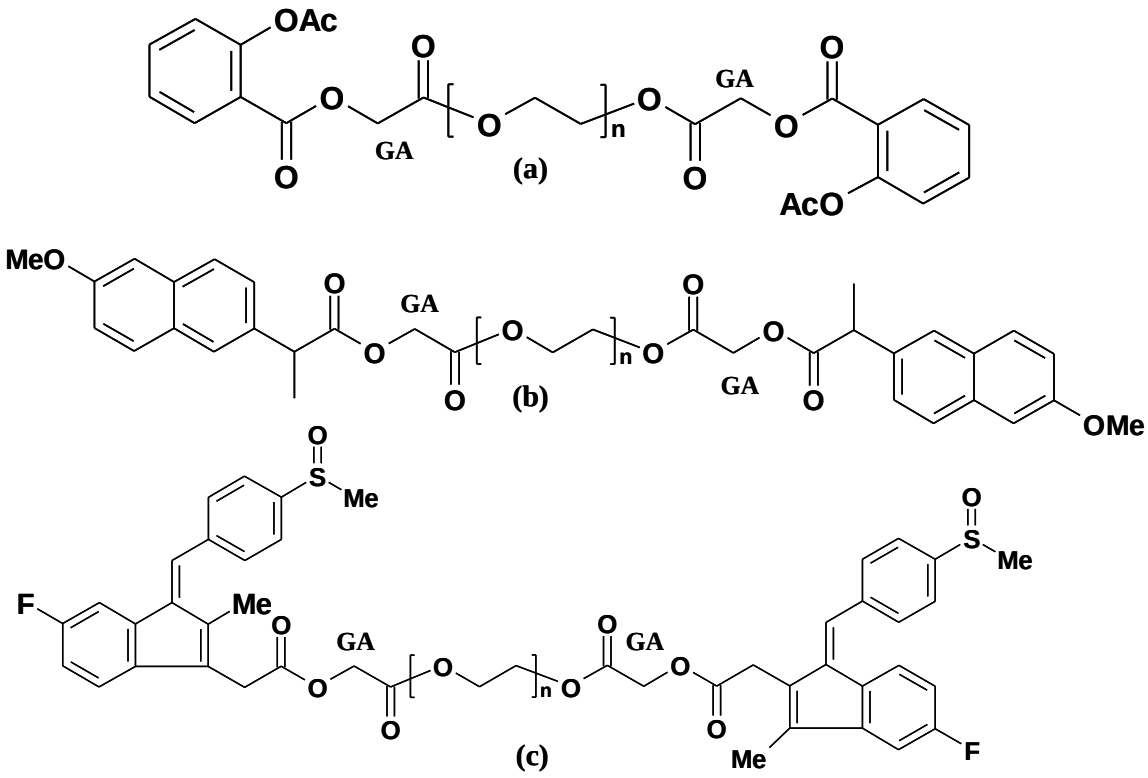

Figure 5. (a) Aspirin End-functionalized, **(b)** Naproxen End-functionalized and **(c)** Sulindac End-functionalized Linear Absorbable Polymers

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3.0 Potential Applications

Absorbable oligomers and polymers end-functionalized with drug molecules with a controlled degradation profile, as presented in this paper, have potential applications in the same or similar areas as the non-functionalized drug molecule. This is attributed to the release of the drug molecule as such over a period of time upon hydrolysis of the end-functionalized oligomer and polymer. Hence, these absorbable oligomers and polymers can be used as such for controlled drug delivery, or can be blended with various absorbable polymers for extended and controlled therapeutic activity.

4.0 Summary

- At Bezwada Biomedical, we have developed linear and multiarmed absorbable oligomers and polymers wherein the end groups have been functionalized with therapeutically active anti-inflammatory drug molecules. They have been prepared by conjugation of these drugs with a linear or multiarmed hydrolysable linker wherein the arms are derived from safe and biocompatible glycolic acid, lactic acid, p-dioxanone, or caprolactone monomers and their combinations.

- These hydrolysable oligomers and polymers, end-functionalized with drug molecules, not only have a controlled hydrolytic degradation profile but also degrade into safe and biocompatible molecules and the original drug molecule as such. These oligomers and polymers are excellent candidates for site-specific delivery of drugs in a controlled manner.

- The active drug portion of end-functionalized hydrolysable oligomers and polymers will have improved bioavailability, increased solubility and better control of degradation rates. This provides a site specific controlled delivery of active drug molecules.

- These hydrolysable oligomers and polymers, end-functionalized with drug polymers, will find use in numerous applications, including controlled delivery of drugs as well as biologically active compounds, medical device coatings, and cosmetics.

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. 60/969787.
2. Bezwada Rao S. Transactions of the Society for Biomaterials, 2008, Abstract Number 68
3. Bezwada Rao S. Transactions of the Society for Biomaterials, 2007, Abstract Number 515

4. Bezwada Rao S. Transactions of the Society for Biomaterials, 2007, Abstract Number 516