Controlled Release of Anti-inflammatory Drugs from Novel Biodegradable Oligomers

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Introduction: In this paper we present for the first time novel biodegradable linear and multi-armed oligomers wherein the end groups have been functionalized with therapeutically active anti-inflammatory drug molecules. 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 majority of commercial biodegradable medical devices. These end functionalized therapeutic oligomers upon hydrolytic degradation yields safe and biocompatible molecule including drug. Furthermore, they are designed to degrade in a controlled fashion wherein the rate of hydrolytic degradation can be controlled by (a) 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. The anti-inflammatory drug molecules used in the present study were Aspirin, Naproxen and Sulindac. These drugs are commonly used to alleviate pain, inflammation and stiffness associated with osteoarthritis, rheumatoid arthritis, tendonitis and menstrual cramps.

Motivations to control the rate of release of anti-inflammatory drug from few hours to months formed the basis of this work. In contrast to literature[1a-c] reported polyanhydrides and polyester-anhydrides polymers incorporating anti-inflammatory drug molecules such as Aspirin in the polymer backbone chain, the oligomers of the present study have a much faster degradation profile and are much easier to handle and process. Moreover, the hydrolysis results in the release of drug molecule as such.

Results and Discussion: ***End functionalized Oligomers:*** Figure 1 depicts a four armed Naproxen end functionalized biodegradable oligomers synthesized by reacting carboxylic acid group of Naproxen molecule with a four armed glycolic acid functionalized hydrolysable linker derived from pentaerythritol core. Similarly figure 2 shows a three-armed Aspirin end functionalized biodegradable oligomer synthesized by reacting carboxylic group of Aspirin molecule with a three armed glycolic acid functionalized hydrolysable linker derived from trimethylolpropane core. Similarly, we also have lactic acid, p-dioxanone and caprolactone functionalized hydrolysable linkers with varying length of repeat units in our inventory. All end-functionalized oligomers were characterized using NMR spectroscopy. The details of the oligomer synthesis and their characterization will be presented in the meeting.

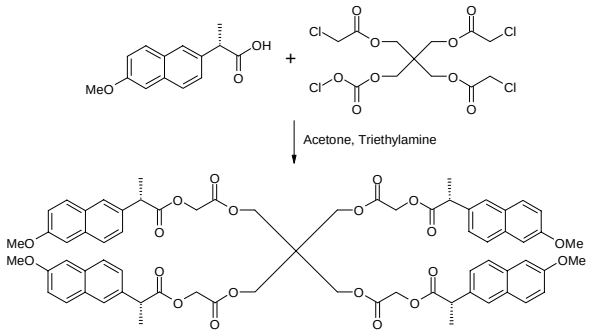

Figure 1. Naproxen end functionalized Biodegradable Oligomer

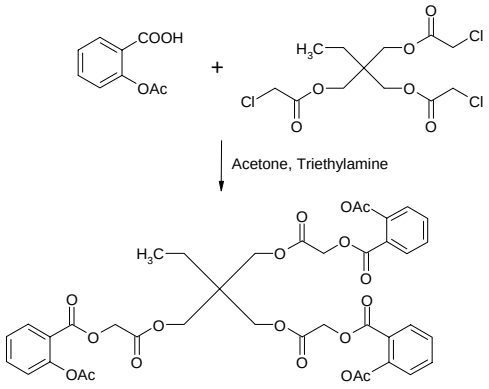

Figure 2. Aspirin end functionalized biodegradable Oligomer

Conclusions: For the first time, linear and multiarmed absorbable oligomers wherein the end groups have been functionalized with therapeutically active anti-inflammatory drug molecules are presented[1d]. These oligomers not only have a controlled hydrolytic degradation profiles but also degrade into safe and biocompatible molecules and drug molecule as such. These oligomers are excellent candidates for site-specific delivery of drugs in a controlled manner.

References:

(1) (a) Kathryn Uhrich. U.S. Patent Pub. 2005/0089506A1 (b) Kathryn Uhrich. U.S. Patent Pub. 2005/0031577A1 (c) Kathryn Uhrich. U.S. Patent Pub. 2005/0053577A1 (d) Bezwada Rao S. US Patent Application No. 60/969787.