Novel Absorbable Monomers and Polymers for Biomedical Applications

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INTRODUCTION

What monomers are to polymers, biomaterials are to medical devices. Bringing technologically differentiated and therapeutically diverse absorbable medical devices into the market requires innovative biomaterials that can transform existing medical devices. Absorbable polymers are designed to degrade under physiological conditions. These polymers are sometimes also referred to as biodegradable or bioerodible or bioabsorbable polymers. Of the variety of synthetic absorbable polymers, polyesters find numerous applications in medical, surgical and controlled delivery applications and are the key components of majority of absorbable medical devices ranging from sutures, staples, orthopedic screws and implantable surgical devices to tissue engineering scaffolds. These synthetic absorbable polyesters are mostly produced by ring opening homopolymerization or copolymerization of five key lactone based safe and biocompatible monomers. These are glycolide, L-lactide and its isomers, ε-caprolactone, p-dioxanone and trimethylene-carbonate (TMC).

Based on these five safe and biocompatible lactone monomers, we have developed novel absorbable technology platforms. These absorbable technology platforms not only include monomers and macromers but also absorbable polymers. The absorbable monomers and macromers include isocyanantes, functionalized phenolic compounds including natural products, biologically active compounds, drug molecules, amino acids and anti-microbial compounds, symmetrical and unsymmetrical ether acids, hydrolysable linkers and crosslinkers, and NO releasing absorbable monomers. Absorbable polymers based on these monomers include absorbable polyurethanes, polyesters, poly(NSAIDS), poly(amino acids), radiation stable polymers, poly(esteramides) and poly(amides). These absorbable monomers and polymers will find potential use in a variety of biomedical applications including drug delivery, tissue engineering, stent coatings, stents, and implantable medical devices.

Key aspects along with potential applications of each of our absorbable technology platforms will be discussed. Synthesis and characterization of selected monomers and polymers will be presented. *In Vitro* hydrolysis and the controllable hydrolysis profiles will be discussed during presentation. We believe that innovative technology behind these revolutionary monomers and polymers will enable us to make absorbable medical devices that can fulfill the unmet needs of the healthcare community.

RESULTS AND DISCUSSION

Absorbable Isocyanates. Highly reactive isocyanates that are similar to Methylenebis(phenylisocyanate) (MDI) but are biodegradable and have tunable hydrolytic degradation profiles were developed. What distinguishes these isocyanates from the commonly used isocyanate, MDI, is the presence of a degradable linkage bridging the aromatic rings instead of the non-degradable methylene group. Furthermore, the degradable linkage in these isocyanates is derived from safe and biocompatible glycolic acid, lactic acid, caprolactone, p-dioxanone and diols. Selected examples of these absorbable isocyanates are shown in Figure 1.

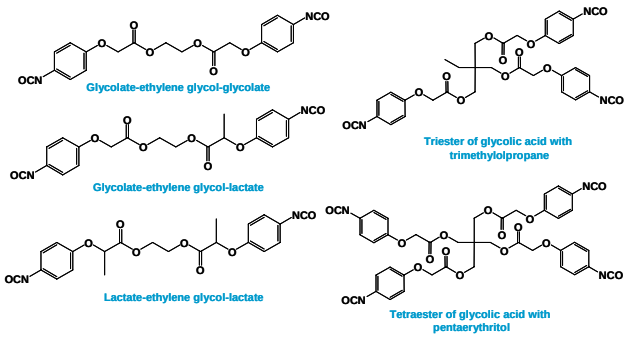

Figure 1. Novel absorbable aromatic isocyanates.

The polyurethanes derived from these novel isocyanates and chain extender diols will not only be absorbable but will also possess for the first time degradable hard segments. These polyurethanes will have toughness and mechanical properties of that of commercially available medical grade polyurethanes and absorbability of commercial biodegradable polymers. These absorbable polyurethanes will degrade into safe and biocompatible degradation products upon hydrolysis unlike polyurethanes derived from MDI. These absorbable polyurethanes may find applications in tissue adhesive and sealant, adhesion prevention and tissue engineering.

Drug Functionalized Absorbable Macromers and Polymers. Absorbable linear and multi-armed macromers wherein the end groups have been functionalized with therapeutically active anti-inflammatory drug molecules including Aspirin and Naproxen were developed. Selected examples of these absorbable macromers are shown in Figure 2 and Figure 3. The backbone of these oligomers is derived from safe and biocompatible glycolic acid, lactic acid, p-dioxanone and caprolactone monomers. 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.

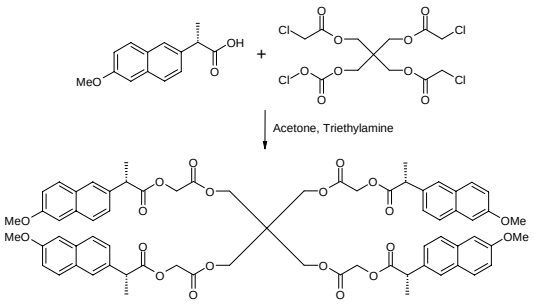

Figure 2. Naproxen (Aleve™) end functionalized macromers.

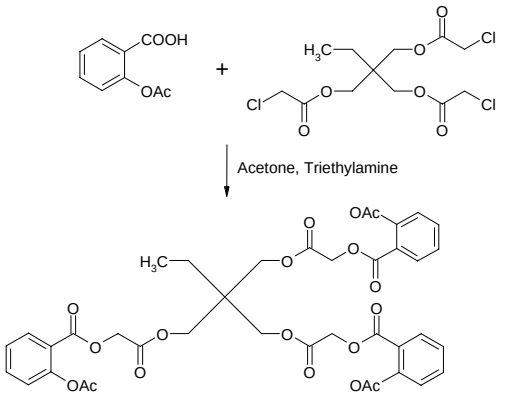

Figure 3. Aspirin end functionalized macromers

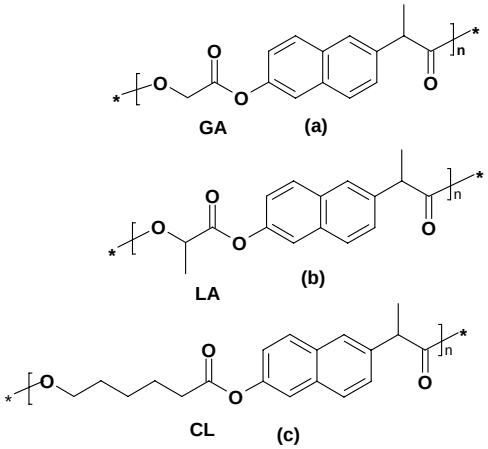

Figure 4. Absorbable polymers from functionalized Naproxen (Aleve™) monomers where GA is glycolic acid, LA is lactic acid and CL symbolizes caprolactone unit.

In addition, absorbable polymers were developed from functionalized drugs wherein; these drug molecules constitute the part of the polymer backbone chain. These polymers upon hydrolysis release the drug molecule as such without any change in the chemical structure. Figure 4 depicts the examples of absorbable polymers from functionalized Naproxen (Aleve™), a member of the profen family of non-steroidal anti-inflammatory drugs (NSAIDs) commonly used for the treatment of inflammation and stiffness associated with osteoarthritis, rheumatoid arthritis, tendonitis and menstrual cramps.

Absorbable Linkers and Crosslinkers. Hydrolysable linkers and crosslinkers were prepared by functionalization of p-aminobenzoic acid or p-aminophenol molecule with safe and biocompatible molecules such as glycolic acid, lactic acid, caprolactone and p-dioxanone. These hydrolysable linkers and crosslinkers have varying hydrolytic degradation profiles and are anticipated to degrade into safe and biocompatible molecules. These hydrolysable linkers and crosslinkers can be used to synthesize a variety of end-functionalized as well as reactive absorbable macromers and oligomers such as UV curable ester-urethane-acrylates or in-situ gelling oligomers. They can also be used to prepare linear or crosslinked but absorbable polymers including poly(ester-urethanes), poly(ester-amide-urethanes) and poly(ester-amides). Figure 5 below depicts the structures of novel hydrolysable aromatic diamine linkers with varying hydrolytic degradation rates.

Figure 6 depicts an example of acrylate end-functionalized hydrolytically degradable macromer.

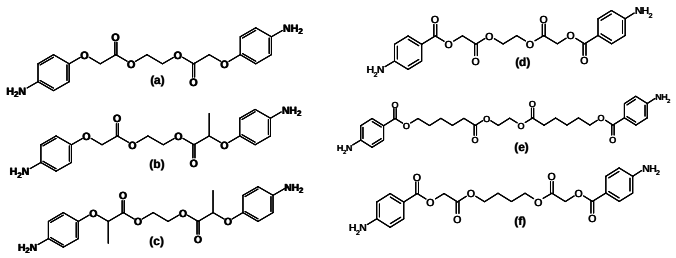

Figure 5. Absorbable aromatic diamine linkers with varying hydrolytic degradation rates.

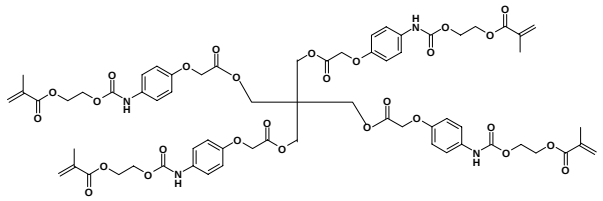

Figure 6. Absorbable acrylate end-functionalized crosslinker.

CONCLUSIONS

We have developed a variety of hydrolytically degradable absorbable monomers, macromers, linkers, crosslinkers and polymers from safe and biocompatible molecules such as glycolic acid, lactic acid, p-dioxanone and caprolactone. These monomers and polymers have tunable hydrolytic degradation profiles. These monomers and polymers are expected to find use in a variety of biomedical applications including controlled drug delivery, wound care applications, medical devices, medical device coatings and tissue engineering. An overview of various aspects of technology platforms from our company will be presented and discussed.

REFERENCES

1. Bezwada, Rao S., US Patent Application No. 2006/0173065 A1.
2. Bezwada, Rao S., World Patent Application No. WO2007053794A2.