Nitric Oxide and Drug Releasing Hydrolysable Macromers, Oligomers and Polymers

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Abstract: *This white paper is intended to provide readers with an overview of nitric oxide (NO) and drug releasing macromers and oligomers developed by our company. These NO and drug releasing macromers and oligomers are comprised of a drug molecule and a NO releasing moiety linked to each other via a hydrolytically degradable linker. This hydrolytically degradable linker is comprised of repeat units derived from safe and biocompatible molecules such as glycolic acid, lactic acid, p-dioxanone and caprolactone, key components of all commercially available absorbable medical devices. NO and drug releasing macromers and oligomers developed by our company have controllable hydrolysis profiles, increased solubility, improved bioavailability, improved efficacy and enhanced functionality. The controlled release profiles represent slow, moderate and/or rapid release of drug and nitric oxide. This release may be targeted to one or more specific organs or parts of the body. Furthermore, these macromers and oligomers developed by our company are anticipated to degrade into safe and biocompatible molecules. Moreover, hydrolytic degradation of some specific NO and drug releasing absorbable macromers and oligomers release the drug molecule as such with no change in chemical structure. This preserves the activity and efficacy of the drug molecule and provides extended therapeutic properties to the substrate when incorporated in a polymer matrix or applied as part of a coating on the substrate. These NO and drug releasing macromers and oligomers have a great potential for use in numerous therapeutic and biomedical applications, including, a) treatment of cardiovascular, gastrointestinal, inflammatory and respiratory diseases, b) therapies for central nervous system disorders and sexual dysfunctioning, c) NO releasing anti-proliferative agents to prevent restenosis, d) key components of coatings for medical devices to prevent platelet aggregation and adhesion, and e) key components of anti-microbial, wound healing and pharmaceutical formulations for controlled release applications.*

1.0 Nitric Oxide : Biological Importance

Nitric oxide (NO) is a vital biological molecule. It plays a significant role in diverse biological processes, such as host defense, cardiovascular regulation, signal transduction, neurotransmission and wound healing. NO also plays an important role in many diseases, including cardiovascular, gastrointestinal, inflammatory and respiratory diseases, and medical conditions such as central venous disorders and sexual dysfunctioning, by influencing many biochemical and physiological reactions.

NO is a well known inhibitor of platelet adhesion, activation and smooth cell proliferation. Continuous release of NO from the surface of endothelial cells effectively prevents the adhesion /activation of platelets on normal blood vessel walls. Agents that

release or generate NO locally have been proposed as systemic drugs to prevent and treat restenosis and thrombus formation in an individual that have come into contact with medical devices such as cardiovascular drug-eluting stents, diagnostic catheters, guide wires, guide catheters, intra-aortic balloon pump catheters, intravascular sensors, extra-corporeal blood loop circuits, intravenous grafts/shunts and adhesion prevention barriers.

In addition to helping body cells to communicate with each other by transmitting signals throughout the entire body, NO assists the immune system at fighting off bacteria and defending against tumors. Furthermore, it helps reduce inflammation and regulate blood pressure by dilating arteries. NO released from wound resident cells also plays an important role in unique cell signaling pathways and re-establishment of microcirculation as newly vascularized tissue is formed. Moreover, NO is anti-inflammatory and hence valuable for indwelling medical devices such as urethral or Total Parenteral Nutritional Catheters.

Medical research is rapidly discovering therapeutic applications for NO, including the fields of vascular surgery and interventional cardiology. For example, stents and drug eluting stents have been used clinically for treatment of occluded cardiac arteries for over fifteen years and their use has resulted in substantial clinical benefit for cardiac patients. However, a significant problem with bare-metal stents in clinical usage is restenosis of the artery, leading to recurrence of the primary cardiac symptoms. According to the literature, localized NO release appears to address some of the root causes of the restenosis. Furthermore, NO release also addresses problems associated with undesired smooth muscle cell growth, and provides a long-term biocompatible solution to the presence of a stent by stimulating rapid endothelialization of the stent itself. Stent endothelialization results in a natural cell coating for the stent that essentially makes the stent surface "invisible" to the blood and its components. Delayed endothelialization has been linked to late in stent thrombosis, a potentially fatal event. Thus, the use of nitric oxide eluting stent coatings has many advantages over antiproliferatives drugs, especially at the very early stages in the stent placement pathophysiology.

In light of its significant biological role and beneficial therapeutic properties, researchers have developed a number of compounds for in-vivo delivery of NO to tissues and organs at risk of injury. This includes organic nitrate pro-drugs such as nitroglycerin, isosorbide dinitrate, NO donor aspirin and naproxen, nitrosothiols, iron nitrosyl compounds, nitroprusside and N-diazeniumdiolates. Furthermore, NO releasing intravenous suspensions, sprays and transdermal patches have also been developed.

2.0 Nitric Oxide and Drug Releasing Hydrolysable Macromers and Oligomers

We at Bezwada Biomedical, LLC have developed nitric oxide and drug releasing hydrolysable macromers and oligomers represented by a general structure depicted in **Figure 1,** below. As shown, NO and drug releasing macromers and oligomers developed by us, are comprised of a drug molecule and a NO releasing moiety, linked to each other via a hydrolytically degradable linker. This hydrolytically degradable linker is comprised of repeat units derived from safe and biocompatible hydroxy acid molecules such as

glycolic acid, lactic acid, open chain p-dioxanone and open chain caprolactone. These hydroxy acids are 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.

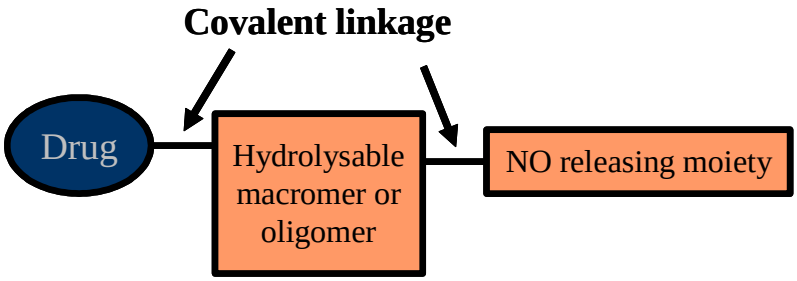

Figure 1. General structure of NO and drug releasing macromers and oligomers developed by Bezwada Biomedical, LLC

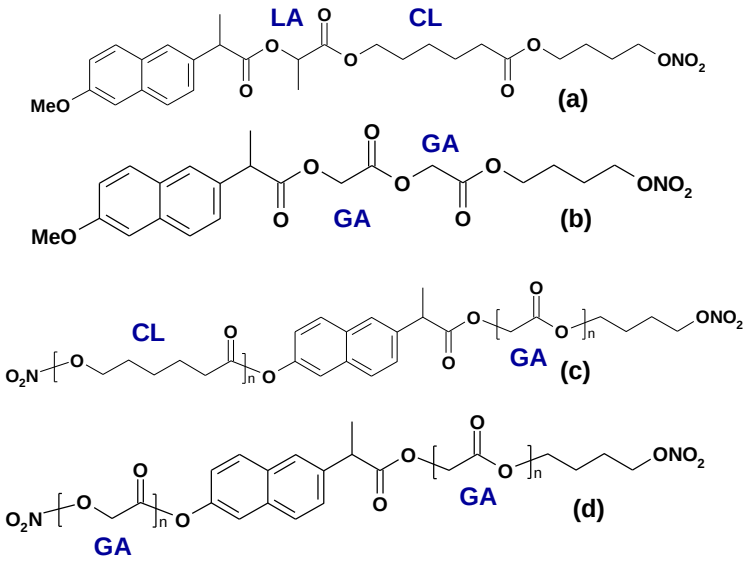

Figure 2 (a)-(d). NO and naproxen releasing macromers and oligomers with varying hydrolytic degradation rates, wherein GA, LA and CL represents glycolic acid, lactic acid and caprolactone repeat units

Figure 2 (a)–(d) shows the structures of NO and aspirin releasing macromers and oligomers developed by our company. Similarly, **Figure 3 (a)-(d),** below, shows the structures of NO and aspirin releasing macromers and oligomers. The rate of hydrolysis of these NO and drug releasing macromers and oligomers will depend upon a number of factors, including the number of repeat units in the linker as well as the choice of the safe

and biocompatible molecules from which the repeat units are derived. For example, NO and drug releasing macromers and oligomers comprised of a degradable linker containing repeat units derived from glycolic acid will hydrolyze faster than those comprised of repeat units derived from p-dioxanone. Similarly, NO and drug releasing macromers and oligomers comprised of a degradable linker containing repeat units derived from lactic acid and caprolactone should take much longer to hydrolyze than the ones wherein the degradable linker is comprised of repeat units derived from glycolic acid and dioxanone. Furthermore, it is expected that the rate of hydrolysis will vary with variation in the number of repeat units in the degradable linker. Thus, the desired time range may be obtained by altering the number of repeat units in the linker as well as by the choice of the safe and biocompatible molecules from which the repeat units are derived. For example, NO and naproxen releasing oligomers with structure **2(d)** will hydrolyze faster than oligomers with structure **2(c)**. Similarly, NO and aspirin releasing macromers of structure **2(b)** will hydrolyze faster than oligomers with structure 2(a).

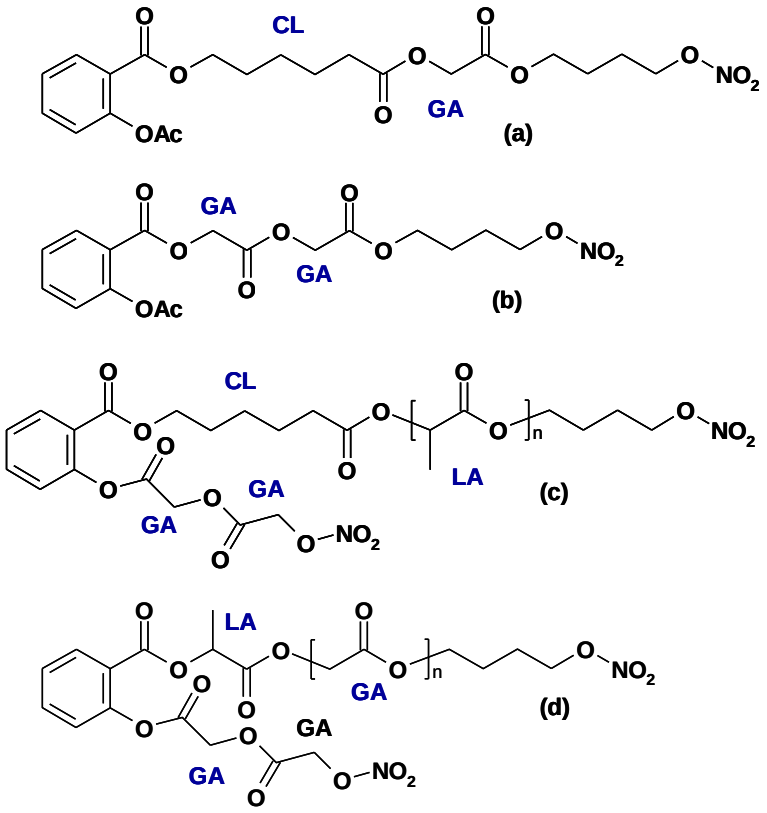

Figure 3. NO and aspirin releasing macromers and oligomers with varying hydrolytic degradation rates, wherein GA, LA and CL represents glycolic acid, lactic acid and caprolactone; repeat unit Ac represents an acetyl group.

In addition to macromers and oligomers comprising one drug molecule per macromer or oligomer, we have also developed macromers and oligomers wherein two or more drug

molecules functionalized with a NO releasing moiety are covalently linked to each other via a hydrolysable macromer or an oligomer. For example, **Figure 4,** below, depicts the structures of NO and naproxen releasing macromers containing two molecules of naproxen per macromer. Similarly, **Figure 5,** below, depicts the structures of NO and aspirin releasing macromers containing two or more aspirin molecules per macromer.

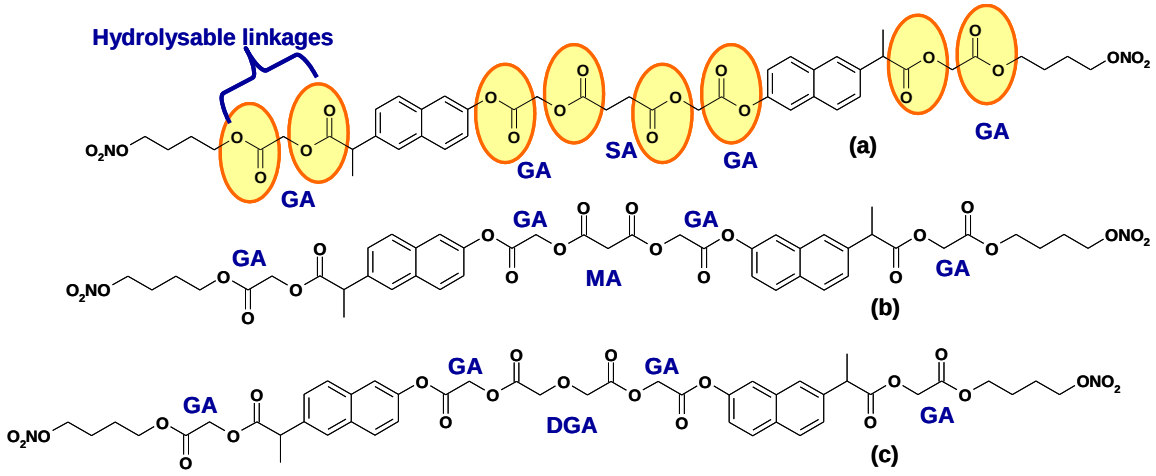

Figure 4. NO and naproxen releasing macromers containing two molecules of naproxen per macromer, wherein GA, SA, MA and DGA represents glycolic acid, succinic acid, malonic acid and diglycolic acid, respectively

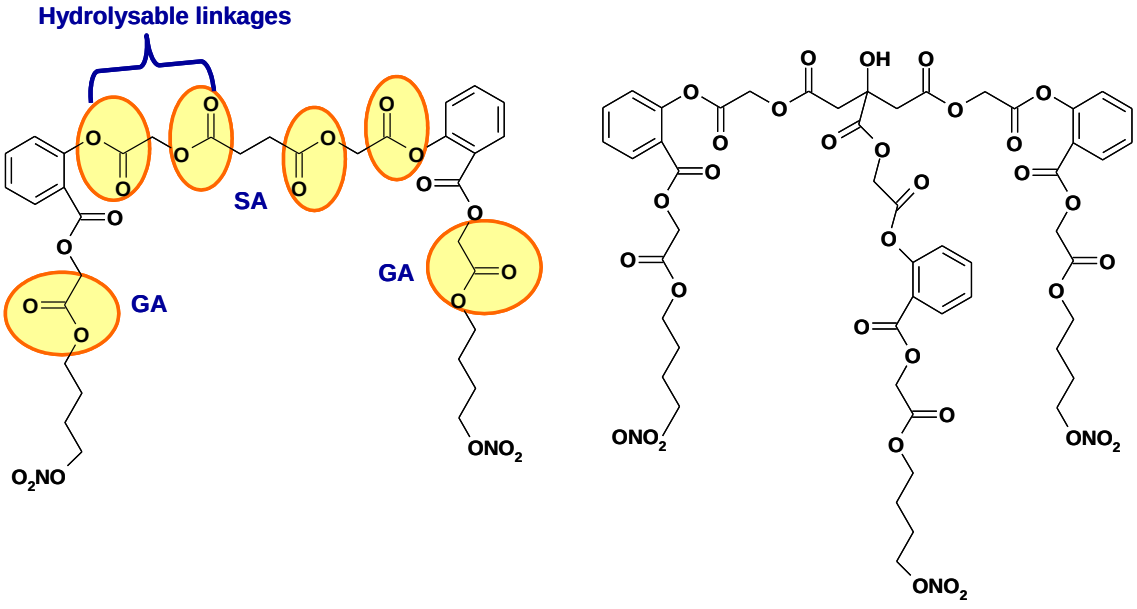

Figure 5. NO and aspirin releasing macromers containing two and three molecules of aspirin per macromer, wherein GA and SA represent glycolic acid and succinic acid, respectively

As shown in **Figures 2** to **5**, NO and drug releasing macromers and oligomers developed by our company have controllable hydrolysis profiles, increased solubility, improved bioavailability, improved efficacy and enhanced functionality. The controlled release profiles represent slow, moderate and/or rapid release of drug and nitric oxide. This release may be targeted to one or more specific organs or parts of the body. Furthermore, these macromers and oligomers developed by our company are anticipated to degrade into safe and biocompatible molecules. Moreover, hydrolytic degradation of some specific NO and drug releasing absorbable macromers and oligomers will release the drug molecule as such with no change in chemical structure. This will preserve the activity and efficacy of the drug molecule and is anticipated to provide extended therapeutic properties to the substrate when incorporated in a polymer matrix or applied as part of a coating on the substrate.

3.0 Polymers Bearing NO and Drug Releasing Pendant Groups

In addition to NO and drug releasing macromers and oligomers, we have also developed polymers bearing NO and drug releasing pendant groups. In order to prepare these polymers, we first developed monomers such as diols having the NO releasing and/or biologically active agent releasing moieties. **Figure 6 (a)** and **(b)** depict the structures of NO and naproxen and NO and aspirin releasing hydrolytically degradable diols, respectively. These diol monomers having the NO releasing and/or biologically active agent releasing moieties can be reacted with isocyanates to prepare polyurethanes, as depicted in **Figure 7,** below. In a similar fashion, polyesters bearing NO and drug releasing pendant groups were prepared via reaction of diol monomers with diacids, as shown in **Figure 8,** below. Polymers bearing NO and drug releasing pendant groups with varying molecular weights were developed. Furthermore, the frequency of occurrence of pendant groups along the polymer backbone was also controlled. These NO and drug releasing polymers will find use in a number of biomedical and pharmaceutical applications such as NO and drug-eluting stents, medical device coatings, transdermal patches for wound healing, and controlled delivery.

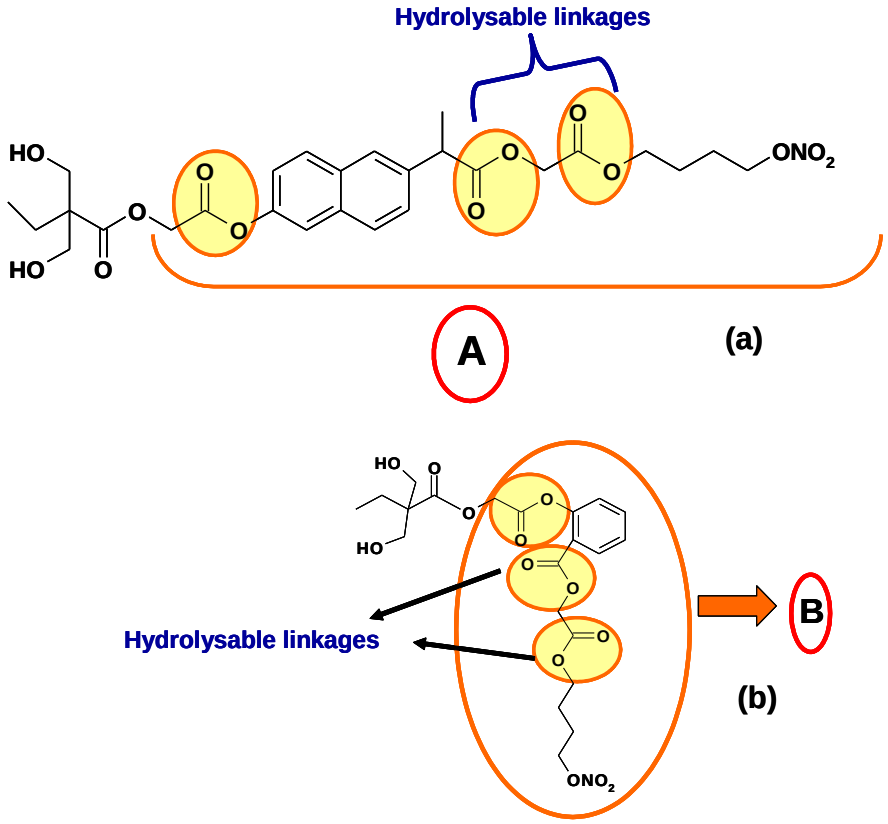

Figure 6(a). NO and naproxen releasing hydrolytically degradable diol monomer; **(b)** NO and aspirin releasing hydrolytically degradable diol monomer

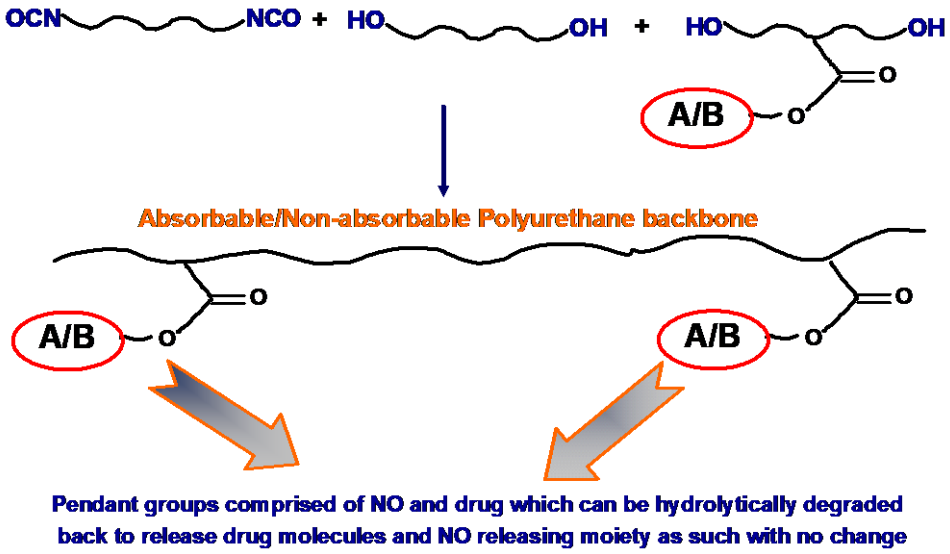

Figure 7. Polyurethanes bearing NO and drug releasing pendant groups

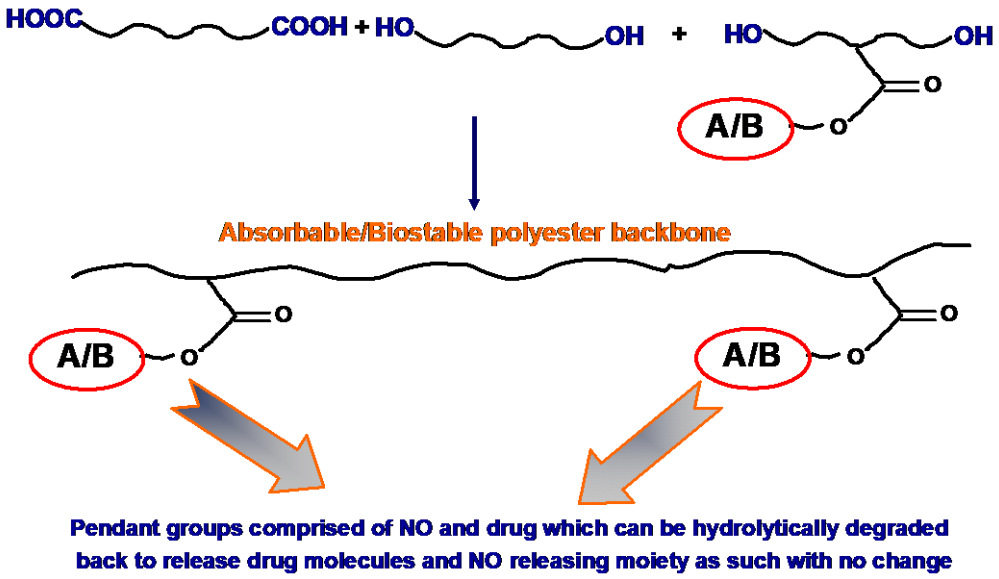

Figure 8. Polyesters bearing NO and drug releasing pendant groups

4.0 Summary

- At Bezwada Biomedical, we have developed NO and drug releasing macromers and oligomers. These NO and drug releasing macromers and oligomers are comprised of a drug molecule and a NO releasing moiety covalently linked to each other via a hydrolytically degradable linker. This hydrolytically degradable linker is comprised of repeat units derived from safe and biocompatible molecules such as glycolic acid, lactic acid, p-dioxanone and caprolactone, which are key components of all commercially available absorbable medical devices.

- These macromers and oligomers have tunable hydrolytic degradation profiles and hence the rate of release of NO and drug molecules can be controlled. Furthermore, these macromers and oligomers are anticipated to degrade into safe and biocompatible molecules upon hydrolysis.

- Hydrolytically degradable macromers and oligomers comprising two or more drug molecules, functionalized with a NO releasing moiety, were developed also. This serves to release the drug molecule as such without any change in chemical structure, activity and efficacy.

- The active portion of these macromers and polymers will have improved bioavailability, increased solubility and better control on degradation rates.

- Absorbable polymers, including polyurethanes, polyesters and polyesteramides bearing pendant NO and drug releasing groups, were developed also. These absorbable polymers will find use in a number of biomedical and pharmaceutical

applications, such as NO and drug-eluting stents, medical device coatings, transdermal patches for wound healing, and controlled delivery.

- These NO and drug releasing macromers and oligomers will find use in preparing a variety of therapeutic formulations for treatment of cardiovascular diseases, osteoarthritis, respiratory diseases, diabetic retinopathy, hypertension, pain and inflammation.

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

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