By Aligoli Amir Nazmi Afshar©,October 2014

Chitosan Polysulfate as Anticoagulant and Dispersant for DVT

This research project involves synthesis of water soluble polymer, Chitosan polysulfate, made from crab or shrimp shells, as an effective anti-coagulant dispersant. The objective is to produce a highly dispersant low molecular polymer for the treatment and prevention of deep vein thrombosis (DVT). The emphasis is to break up the clot at any stage and prevent the formation of the cloth, with minimum side effects.

DVT is a blood clot that forms in a vein deep in the body. Blood clots occur when blood thickens and clumps together. Most deep vein blood clots occur in the lower leg or thigh. They also can occur in other parts of the body. A blood clot in a deep vein can break off and travel through the bloodstream. The loose clot or embolus can travel to an artery in the lungs and block blood flow, causing pulmonary embolism (PE) which is very serious condition. It can damage the lungs and other organs in the body and cause death.

At the present time there are several medicines/procedures to prevent or treat DVT.

Anticoagulants are the most common medicines for treating DVT. Warfarin and heparin are most common, Warfarin is given in pill form and heparin is given as an injection or through an IV tube. Heparin acts quickly and warfarin takes 2 to 3 days before it starts to work. These medicines decrease the blood's ability to clot. They also stop existing blood clots from getting bigger. However, blood thinners can't break up blood clots that have already formed. The most common side effect of blood thinners is bleeding. Bleeding can happen if the medicine thins the blood too much. This side effect can be life threatening.

Direct Thrombin Inhibitors (DTI) inhibit thrombin, a serine protease which affects the coagulation cascade in many ways. DTIs have undergone rapid development since the 90's. With technological advances in genetic engineering the production of recombinant hirudin was made possible which opened the door to this new group of drugs. DTIs are still under development, but the research focus has shifted towards factor Xa inhibitors, or even dual thrombin and fXa inhibitors that have a broader mechanism of action by both inhibiting factor IIa (thrombin) and Xa. These also suffer from disadvantages of anticoagulants in treating DVT.

Thrombolytic agents are used for the treatment of myocardial infarction (heart attack), thromboembolic strokes, deep vein thrombosis and pulmonary embolism to clear a blocked artery and avoid permanent damage to the perfused. They may also be used to clear blocked catheters that are used in long-term medical therapy.Doctors prescribe these medicines to quickly dissolve large blood clots that cause severe symptoms. Because thrombolytics can cause sudden bleeding, they're used only in life-threatening situations.

Other Types of Treatment include **Vena Cava Filter and Graduated Compression Stockings.** These are less effective than drugs and are used only if patient cannot take drugs.

In this research project, we would like to synthesize a drug that not only is a good anticoagulant, it is highly effective dispersant. It is also a natural and safe material. The goal is to design a drug that: (1) breaks up the clot at any site in the body; (2) effective immediately; (3) does not require hospitalization; (4) does not induce bleeding or other side effects and (5) does biodegrade rapidly.

Exopolysaccharides (EPSs), which are secreted by microorganisms, are natural, nontoxic, biocompatible and biodegradable polysaccharides. Chemical modifications of exopolysaccharides, such as phosphorylation, sulfation, oxidation, carboxylation, provide an opportunity to increase their biological activities or their solubilities. Sulfated polysaccharides have important bioactivities including antivirus, antioxidant, antitumor, and anticoagulant activities. One of the most promising EPS with good dispersant properties is chitosan. Over the past 40 years, chitosan, the (β-1,4)-linked D-glucosamine derivative of chitin, has been promoted as a promising renewable polymeric material. Chitosan has wide ranging applications in many areas, including the wastewater treatment, food, agriculture, cosmetic/personal care, biotechnological and pharmaceutical industries.

Chitin and chitosan are natural cationic polysaccharides found in fungus cell walls, crustacean shells, and insect cuticle. The three forms, α-, β-, and γ-forms, exist with different chitin microfibril orientations. Chitin and chitosan are biodegradable and biocompatible, and chemical modification of their amino and two hydroxyl groups can give rise to novel molecular biofunctionalities including antithrombogenesis, cell viability, antitumor activity, and blood compatibility. Applied research on chitin and chitosan is being actively carried out in various industrial fields, including the production of anticoagulants.

Three major parameters of interest are International Normalized Ratio (INR), Number Average Molecular Weight (Mn) and more importantly Polydispersity Index (PI or Mw/Mn). INR is a measure of anticoagulation status. The literature suggests that an INR range of 1.5 to 2.5 represents the most appropriate level of anticoagulation. Lower Mn results in lower PI, a better dispersant. PI is used as a measure of the broadness of a molecular weight distribution. The larger the PI, the broader the molecular weight, a less functional dispersant. A monodisperse polymer where the chain length are equal (such as a protein) has Mw/Mn=1. The best dispersant polymers have Mw/Mn of 1.02 to 1.1. polymaleic acid with Mn around 1000 has PI of 1.02. Step polymerization reactions typically yield of PI of around 2.0, whereas chain reactions yield PI values between 1.5 and 20. Other than these three, one also should consider degree of sulfation, molecular size and shape, dissociation of ionizable groups, and spatial considerations of N-sulfate groups.

In this research project, I propose a variety of sulfating reagents, solvents, depolymerization catalysts, temperatures and reaction times to be used and optimum reaction parameters for INR, Mn and PI to be determined.

More detailed information is available upon signing a confidentiality agreement.