Increasing the Biocompatibility and Reducing the Infections Caused by Biomedical Devices

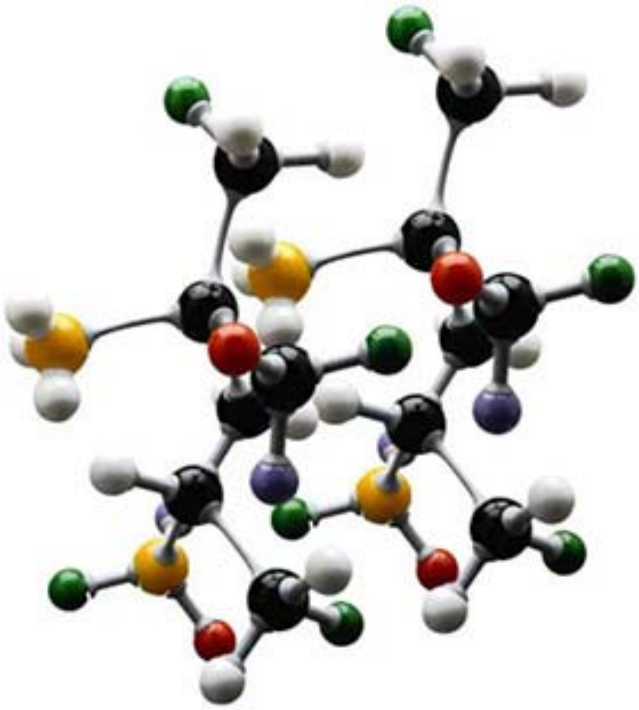

Figure 1.

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Abstract

Polyurethane and heparin, the polymers currently used in the coverage of biomedical devices, were analyzed in order to increase hemocompatability and reduce infections inside the body. Studies have shown that the source of the infection was predicted to be the uncovered lead of the device, and not the polymers being used. As a result, a new modification of the polymers was considered. In this modification, a hybrid of polyurethane and polyethylene glycol, a biocompatible and biodegradable polymer, were used. The alcohol group of polyurethane was replaced with polyethylene glycol. In this reaction, water was hydrolyzed and the modified polymer was expected to be polar, elastic, durable, hydrophilic, tear resistant, and oxygen resistant. The predictions could then be tested via computer simulations and performing several experiments, such as testing the blood interaction with the modified polymer. If the tailored polymer passed the majority of the tests, and the results were close to the predictions, the polymer could then be used as coverage for biomedical devices.

Introduction & Methods

This research is designed to evaluate the polymers that are being used in biomedical devices, in order to increase biocompatibility, and reduce the infections that occur after implantation. As the first option, the current polymers were examined to find the source of the infection. The lead and the casing of the biomedical devices, usually made of titanium or a titanium alloy, are coated by a polymer such as polyurethane. [1]

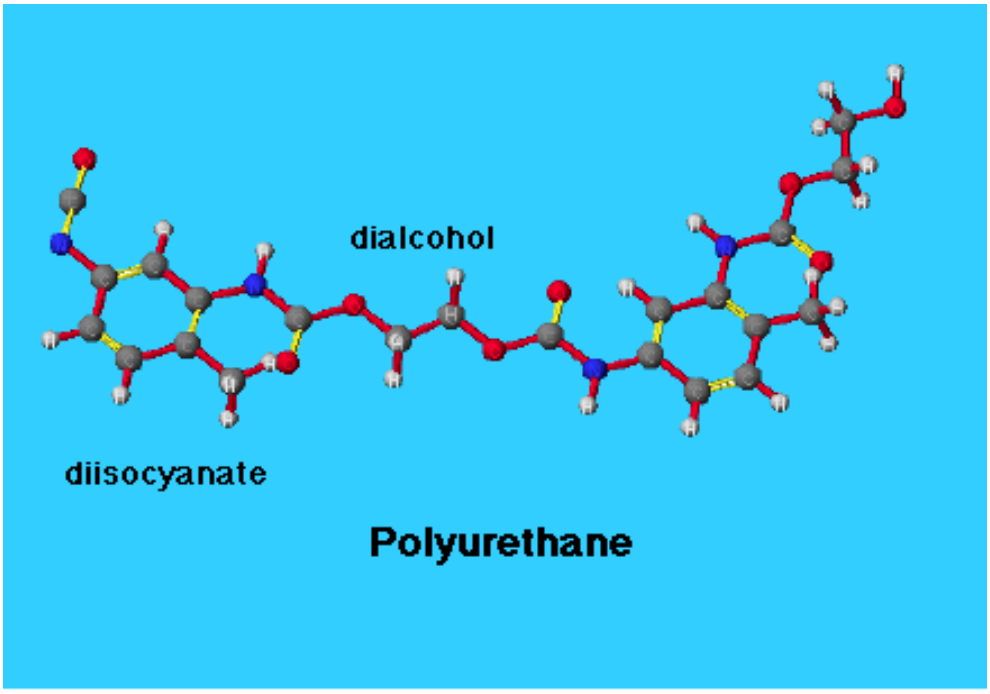


Figure 2. Polyurethane

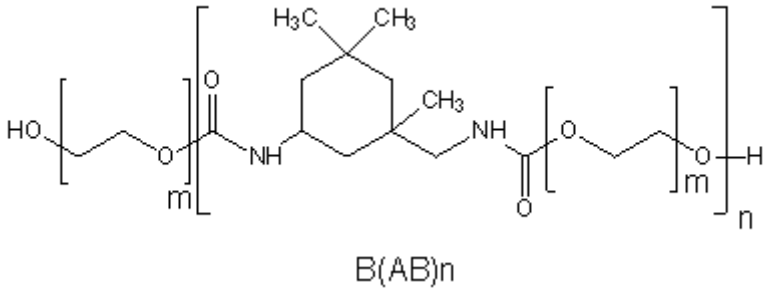


Figure 3. Polyurethane

Polyurethane (PU) contains a series of organic molecules connected by urethane links. [2] This polymer has its own unique properties. For example, it has the elasticity of rubber but the stiffness and strength of metal. PU polymers are produced via step-growth polymerization, a process in which two monomers are combined in the presence of a catalyst. In this process, one of the monomers contains at least two isocyanate functional groups and the other one contains at least two hydroxyl (alcohol) groups. [3] Some significant advantages to polyurethane include oil

and solvent resistance, outstanding resistance to oxygen, flexibility, electrical properties, thermal resistance, a high load bearing capacity, excellent wear properties, and elastic memory. PU is also more tear resistant than rubber, and has a greater impact resistance than plastic. [4] Even though the majority of the biomedical devices are covered by polyurethane, the metal tip of the lead is uncovered and continuously decomposes and reacts inside the body. The contact between blood and the metal tip or any other exterior surfaces of a biomedical device can cause infection and, in most severe cases, result in an unspecific post-perfusion syndrome. [5] In addition, long-term implants constantly react with platelet, which eventually cause blood coagulation. In order to reduce these side effects, multiple coating-techniques have been created to produce devices with improved hemocompatibility. As a result, heparin is added into polyurethane films by solvent casting, a process in which a polymer is dissolved in an organic solvent.

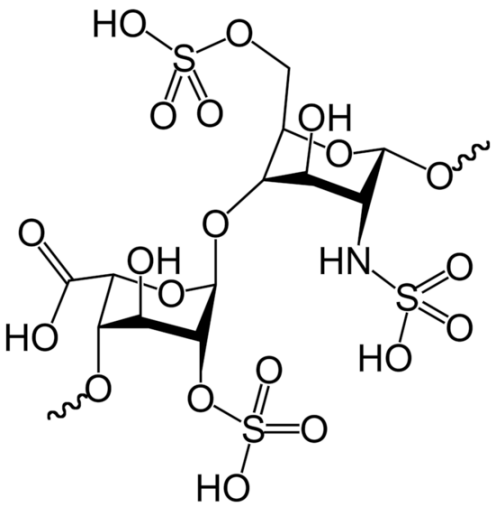


Figure 4. Heparin

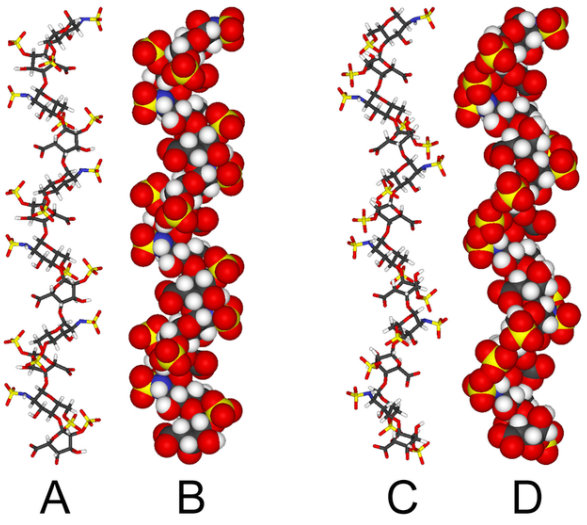
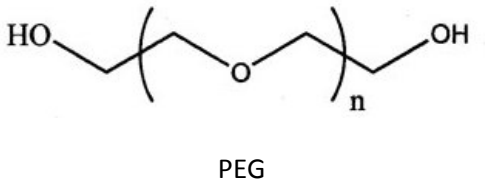


Figure 5. Heparin 3D view

The modified surface of heparin offers the best resistance to platelet devotion and thus it is the least thrombogenic. Heparin, by using a cofactor (antithombin), attaches to the active site

of thrombin and deactivates it, which results in immobilization of the thrombin. Heparin-coated equipment also reduces the risk of oxygenator failure. [6] Therefore, polyurethane and heparin are two polymers which are being used as coverage for biomedical devices, but neither of them is the source of the infection. Hence, a new modification needs to be done on the current polymers in order to increase biocompatibility and reduce the infection. To do so, a hybrid of polyurethane and a new biodegradable polymer are considered. Polyethylene glycol's modification makes chemicals and surfaces more biocompatible. This property is very useful for biomedical devices. As a result, polyethylene glycol (PEG), a biodegradable and biocompatible polymer, is introduced to polyurethane. During PEG biodegradation, the chains are shortened leading to the formation of ethylene glycol (MEG) and diethylene glycol (DEG).

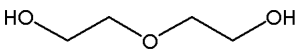


PEG

Figure 6. Polyethylene glycol

MEG

Figure 7. Ethylene glycol



DEG

Figure 8. Diethylene glycol

Ethylene glycol is somewhat toxic, and along with its toxic byproducts, can first affect the central nervous system, then the heart, and finally the kidneys. [7] Nevertheless, diethylene glycol is much less toxic and would not cause any serious damage. [8] If PU and PEG are combined, the byproducts and their properties might, however, change. Since the new byproducts might be either nontoxic or even more toxic, the polymer and its byproducts need to be tested before the polymer can be used. PEG is a polar molecule which interacts actively with water and structures water around its polar groups. This water forms dense hydrophilic layer around PEG molecules at the surface-solution interface. Hydrophilic surfaces are found to resist

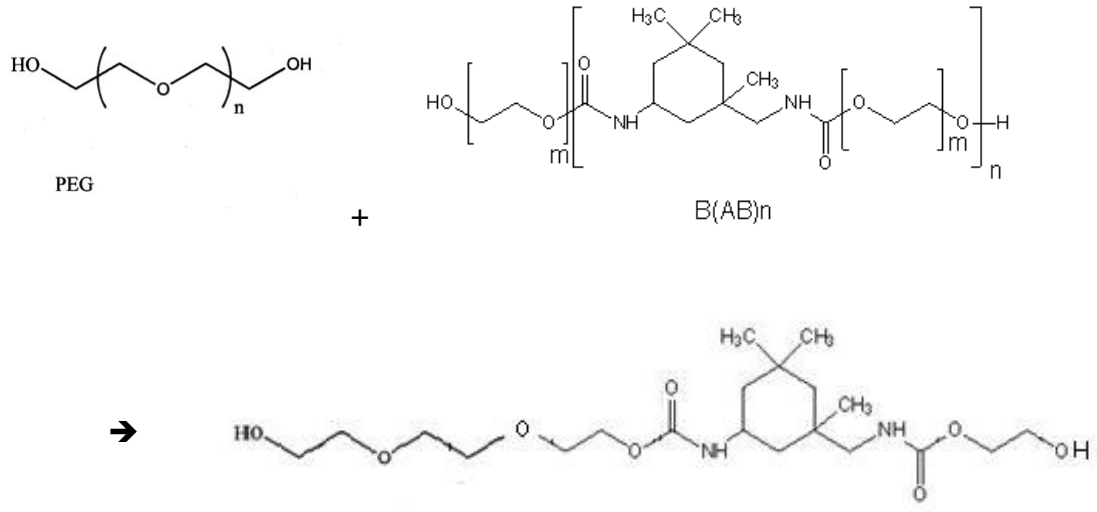
attachment of proteins and cells. In addition, PEG has no ionic charge and therefore no protein can interact with it due to electrostatic attraction. As a result, PEG is able to repeal adhesion of proteins and inhibit/repel attachment of recognition molecules, such as antibodies. Therefore, modification of drugs with PEG hides these chemicals from the immune system, and decreases their immunogenicity. PEG is also non-fouling, which means the surface prevents deposition/attachment of bacteria.

PEG is a polyether which has similar properties to an ether functional group. Ether molecules cannot form hydrogen bonds with each other, resulting in a relatively low boiling point compared to that of the analogous alcohols. However, the differences in the boiling points of the ethers and their isometric alcohols become smaller as the carbon chains become longer. This is caused as the hydrophobic nature of the carbon chain becomes more predominant over the presence of hydrogen bonding. Ethers can also act as Lewis bases. They are more polar than alkenes but not as polar as alcohols, esters, or amides of comparable structure. However, the presence of two lone pairs of electrons on the oxygen atoms makes hydrogen bonding with water molecules possible, causing the solubility of alcohols and ethers to be quite different.

Results

After examining the properties of polyurethane, the alcohol group PU is replaced with a chlorine atom. Since chlorine functions as a leaving group, the polyethylene glycol is then introduced to the polyurethane polymer. Polyethylene glycol can attack the chlorine atom and replace it. Therefore, the alcohol group of polyurethane is replaced with polyethylene glycol, to produce a hybrid of polyurethane and polyethylene glycol. The predictions about the modified polymer should then be tested to observe if the reaction can actually proceed and whether or not the indications are correct. In order to test the possibility of the reaction, computer simulations

can be done on the modified polymer. If the polymer passes the simulation, the products and byproducts need to be tested in order to ensure that the new created polymer does not increase the side effects or cause other problems. Since the polymer will be used inside the body, the interaction between the polymer and blood need to be examined. The polymer also needs to be inspected for its oxygen resistance, tear resistance, elastic properties, toughness and durability, electrical properties, polarity, and the ability to prevent the attachment of proteins and bacteria. One approach is to make a model of the required functions of the real polymer. In this model, the polymer can be placed as a cover for a biomedical device. The device can be tested via a laboratory animal, such as a mouse or a rabbit. If the modified polymer passes the majority of the tests with the results close to the predictions, the polymer can be employed as coverage for biomedical devices.



Conclusion

By analyzing polyurethane and heparin, the source of the biomedical devices infection is determined to be something other than the polymers being used. A possible source for these

infections is the uncovered lead of the device, which is constantly reacting with blood. Therefore, a hybrid of polyurethane and polyethylene glycol, a biocompatible and biodegradable polymer, is considered to reduce infections. In this modification, the alcohol group of polyurethane is substituted with polyethylene glycol. This reaction is expected to release a new polymer, which is predicted to be oxygen and tear resistant, strong, and elastic. This polymer is also expected to protect the device from bacterial growth and protein attachments. The polymer will then be tested to check for the possible problems that may occur with the modification. If the polymer passes all the examinations, it can eventually be applied in biomedical devices, leading to an increase in biocompatability and a reduce in the follow up infections.

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