

# Polymer in Medicine

CE 435

Introduction to Polymers  
Department of Chemical Engineering  
University at Buffalo-SUNY

Jeremy Robinson  
Pierre M. Saint Louis  
Anoop Padmaraju

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## Introduction

Biomaterials are substances other than food or drugs contained in therapeutic or diagnostic systems that are in contact with tissue or biological fluids. They are used in many pharmaceutical preparations, for example, as coatings for tablets or capsules or as components of transdermal patches. Biomaterials play a central role in extra Corporeal devices, from contact lenses to kidney dialyses, and are essential components of implants, from vascular grafts to cardiac pacemakers<sup>1</sup>.

Like their counterparts of long ago, medical practitioners today often seek to cure ailments or improve a patient's quality of life by replacing a defective body part with a substitute. But until quite recently, physicians were limited to using off-the-shelf supplies that weren't designed for the application. Motivated by a need for custom-made materials for specific medical applications, materials scientists, chemists, chemical engineers, and researchers in other disciplines have turned their attention to creating high-performance biomaterials. Among the new crop of substances are novel biodegradable polymers and modified natural substances designed for use in a wide range of implantable applications including

orthopedic and dental devices, drug-delivery systems, tissue engineering scaffolds, and other uses<sup>1</sup>.

Biodegradable polymers take center stage in a great variety of research efforts. Materials that can decompose and disappear from the body are desirable for short-term applications in orthopedics, tissue engineering, and other areas, where, for example, a physician may need a device to hold a bone in place long enough for the body to heal. They are many current biomaterials applications found in about 2,700 different kinds of medical devices, 2,500 separate diagnostic products, and 39,000 different pharmaceutical preparations<sup>2</sup>.

**Table 1**  
**Applications of Biomaterials<sup>2</sup>**

<b>Polymer</b>	<b>Applications</b>	<b>Polymer</b>	<b>Applications</b>
PDMS	Catheters, heart Valves	Polytetrafluoroethylene	Heart valves Vascular grafts Nerve repair
Polyurethane	ventricular assist Devices	Polyethylene	Catheters, hip prostheses
PGA, PLA, And PLGA	Drug delivery, devices	Polymethylmethacrylate (PMMA)	Fracture fixation
		Cellophane	Dialysis membranes

## **A brief history of polymers in medicine**

The inception of biomaterial was not seen until the 1860's with the introduction of aseptic surgical techniques<sup>3</sup>. Although not practical for many years to come, the early 1900's gave us early uses of bone plates made from metals like steel to help mend breaks and fractures. Metal alloys were continuously the only form of biomaterials used for many years to come. Their applications ranged from joint replacement to drug delivery systems.

Not until World War II, would the rapidly developing science of polymers be seen in medical applications. Polymethylmethacrylate (pMMA) was one of the first polymers used as a biomedical material serving as a material to replace the human cornea when damaged<sup>3</sup>. Since then scientists in the medical field have turned biomedical polymers into a billion dollar business. Polymers with their exceptional properties, their ability to be engineered and their abundance in the world have made a home in biomaterials and other medical applications.

Not only have polymers replaced many old applications in medicine such as the shift from metal catheters to those made of polyethylene, but also they have opened the door for new applications that no other material would permit.

Costly procedures have now been given new lower cost alternatives. At one time a severe heart condition called for an immediate transplant. In 1950's the first artificial heart was introduced. Brought in to practice in the late 1960's constant improvements, which include the uses of polyurethane's as ventricular assist devices, have not only made it safer to use in practice, but the cost reduction has increased availability and helped the some 18,000 people a year who can not receive a donor immediately, a chance to wait a little longer<sup>3</sup>.

What once cost \$480,000 and was only available to a few, now has a temporary alternative that costs less than half that. Polymers will continue to improve medicine and if the first fifty years of development is any indication, the next fifty years will serve to save many lives and help to make procedures and applications safer and more efficient.

### A brief timeline of polymers in medicine

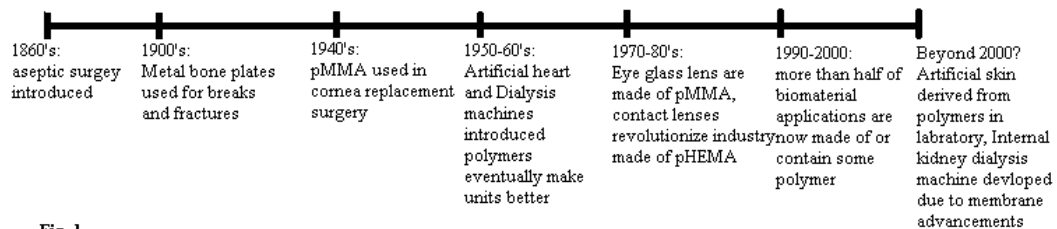


Fig. 1

## **Cellophane**

Often used in every day life to package our products or to keep our food fresh, cellophane is one of the most critical materials for the treatment of many kidney malfunctions. Cellophane is regenerated cellulose. It is in the form of a film; as opposed to rayon, which has the same properties yet is a fiber. Cellophane holds almost identical properties to the naturally occurring cellulose, it is "regenerated" for processing purposes. It has a typical chain length ranging from 2000 - 6000 angstroms (longer in fibers) and a molecular weight of varying widely from 300,000 to one million g/mol<sup>4</sup>.

Cellophane (regenerated Cellulose) was invented was invented by Jacques E. Brandenberger in 1908. In an attempt to develop a clear plastic cloth that was waterproof, he discovered that while his cloth that he produced was too stiff, a clear plastic film would be peeled off and soon known as cellophane<sup>5</sup>. While years later processes would seal the permeability of this regenerated cellulose and make it waterproof, the properties the original material held would soon help save and prolong many lives.

In 1959 Dr. Willem J. Kolff's first artificial kidney was installed in St. Paul's hospital in London. Ethical

debate would continue for 2 years, but in 1961 the first dialysis was performed. Within 5 years a separate unit was opened in the hospital to treat patients suffering from renal problems. This machine used the idea of countercurrent flow, osmosis and diffusion to remove waste products from the blood stream, which are normally removed by the kidneys<sup>6</sup>.

The first artificial kidney used vegetable parchment to serve as the separation membrane between the fluids, which would selectively remove the undesirables. Natural casings (i.e. intestines) were also used in the earlier stages of development of the artificial kidney. In the 1960's Brandenberger's original cellophane was put to use as the membrane that filters and separates the dialysis fluid from the blood. The precursor to the saran wrap that we use today had properties that are so desirable because of its ultra small permeability.

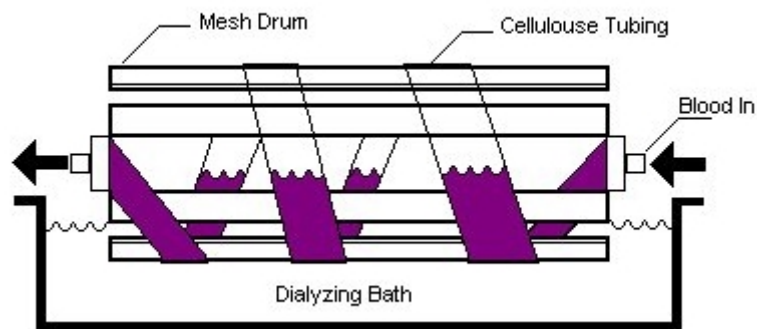


Fig. 2 A schematic of an artificial kidney (hemodialysis)



Cellophane membranes that separate the fluids in dialysis machines are expected to be hydrophilic ultra filters, with the driving force being the concentration gradient between the two fluids. Many other properties are required between the fluids to make dialysis. Most importantly the membrane permits many small particles in the blood with low molecular weights such as inorganic salts, urea, and creatine pass through the membrane while important components of the blood do not<sup>7</sup>.

The production of cellophane as stated earlier is simply the regeneration of cellulose. Obtained naturally from wood and cotton fiber. Cellulose is reacted with NaOH and carbon disulfide to produce cellulose xanthate. Cellulose xanthate is then treated with sulfuric acid. The result of the reaction is extruded to a sheet and after a small "aging" period, a thin clear film of cellophane can be peeled. The process by which cellophane is known is viscose<sup>4</sup>.

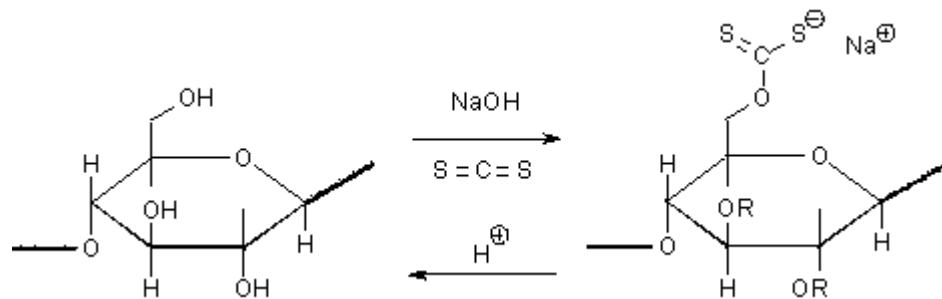


Fig. 3 The regeneration of Cellulose (cellophane).

While early in history there were many concerns about potential health risks involved with cleaning a person's blood by a machine, debate quickly subsided with proof of effectiveness. Today dialysis machines save thousands of lives daily. The only true alternative to dialysis is kidney transplant. Even in the very unlikely case of a successful transplant (over 50% rejection rate) dialysis is continued for many month or years, to ensure stability.

The future of cellulose membranes in the treatment of renal failure has no limits. Perhaps one-day membrane efficiency will be so effective, predictable, and controllable enabling an actual internal artificial kidney. The main inconvenience with dialysis is the actual administration of the lengthy procedure. With improvements in the engineering of the membrane in dialysis, the result has been healthier patients and longer lives for the unfortunate victims.

#### **PGA, PLA, and PLGA**

The polymer polyglycolic acid, PGA, initially started out as an absorbable suture named Dexon. Dupont, under the direction of Norton Higgins, first synthesized PGA by a three-step process from glycolic acid by manipulating temperature and pressure. The ability of PGA to form biodegradable sutures, however, wasn't found until 1963 by

Edward Schmitt and Rocco Polistina of the American Cyanamid Corporation. Since the birth of PGA, derivatives of this polymer have been found to have useful medical properties as well.

Modifying the chemical and structural properties of PGA, PLA, and PLGA allows the polymers to be used for a wide variety of applications within the human body. These polymers are then used for drug-delivery systems, to construct synthetic scaffolding, etc. The amorphous form of PLA is used for drug delivery applications. The latest treatment in treating brain tumors involves attaching dime-sized wafers directly into the skull<sup>8</sup>. The wafers are made out of PLA or PLGA and slowly distribute cancer-killing reagents directly into the location where it's needed. The more crystalline form of PLA has been found to useful as well. The mechanical toughness and strength of the semi crystalline form of PLA and PGA is exploited for use in orthopedic devices. Employing the polymers for the construction of 3-D scaffolding does this. The scaffolding is then implemented to grow new tissues to replace damaged organs in the body.

All the polymers have very low polydispersity index ratios, for example, the P.D.I. ratio for PLA is around 1.6-1.9. The low ratio is useful to maintain mechanical and

structural consistency for later applications. The most common method of commercial production of PLA and PGA is by utilizing ring-opening polymerization combined with an insertion mechanism using a metal oxide<sup>4</sup>. Depending on structure, the polymers can be fitted for different applications. A more amorphous form of the polymer can be used for drug delivery devices while the crystalline form is good for building scaffolding and other biodegradable structures. PLGA, for example, is completely amorphous so therefore it is used only in drug delivery devices. For scaffolding, a more crystalline form of polymer is useful. Two essentials in building scaffolding are having a high surface to volume ratio, and it has to be highly porous. This is advantageous since it allows to cells to easy proliferate and pathways for nutrients and metabolites. The cells are first grown in a culture, and then are seeded onto the scaffolding to grow the damaged organ<sup>9</sup>. The scaffolding gradually erodes away as cells began to grow and replace lost tissue around the region. Using a lower molecular weight polymer can speed up degradation. PGA, PLA, and PGLA are new novel ways to treat a variety of medical concerns. There are some drawbacks, however, to their effectiveness. The use of certain drugs, for example, is prohibited by the relatively temperatures used in

constructing these polymers. Another drawback is in the controlled release of drugs. Bulk erosion has a somewhat inconsistent release of drugs. Depending on the amount of drug loaded onto the polymer, the hydrophilic or hydrophobic properties, the initial rate of release can vary. These persistent problems are likely to be solved in the future. Due to recent legislation, which bars suppliers of ingredients of medical components from being sued, researchers and companies are freer to pursue medical applications and problems.

#### **Polydimethyl siloxane**

The polymer polydimethyl siloxane (PDMS) is used in pacemakers, the delivery of vaccines, and the construction cerebrospinal fluid shunts. PDMS is an amorphous structure with low cross-linked elasticity. As a vulcanized rubber it cannot be melted or dissolved. The glass transition temperature of PDMS is very low (150K), and the polymer is very permeable to gases. The low glass transition temperature allows for fast molecular relaxation, which is beneficial for molding applications.

An English chemist, Dr. Frederic Stanley Kipping, discovered siloxanes in 1927. Kipping however, incorrectly analyzed the structure of his newly found macromolecule and as a result he called his discovery

silicone. This name still persists today. It wasn't until 1943, however, that mass production silicones occurred. General Electric started industrial production under the direction of Eugen Rochow.

PDMS are used in numerous beneficial applications. For example, PDMS became an essential ingredient for use in glass eyes in World War 2. Prior to the inception of localized drug delivery within the human body, antigens had to be taken orally and it was difficult, if not impossible to simulate local immune response in the body. This principle of localized drug delivery using PDMS comes into play in radical prostatectomy and radiation therapy for treatment of prostate carcinoma. There are several complications due to the surgery " the most significant complication is post operative incontinence, which affects 30% of patients"<sup>10</sup>. Since PDMS stays localized in the injection site a lesser dosage of drugs is needed due to the increased concentration in the affected area. For the delivery of the vaccine, biodegradable pellets made of PDMS are used. The pellets are very small in diameter and generally contain soluble antigens to be released within the body. The pellets consist of vulcanized rubber and have a mean diameter of 188 um which allows for the particles to stay in the localized region. Drug release is controlled "

by the relative magnitude of the velocity of macromolecular relaxation to the velocity of drug diffusion through the rubbery region."<sup>11</sup>. Also PMS isn't very susceptible to bacterial infection. This property also makes it ideal for use in pacemakers and the construction of cerebrospinal fluid shunts where the chance for cancer becomes nil.

One method for the production of dimethyl siloxane starts with the monomer, dichlorodimethylsilane. Hydroxyl groups, through hydrolysis, replace the two chlorines in the monomer. To achieve a higher molecular weight, however, a different approach is used. This new method is done by a "base catalyzed ring-opening polymerization of the siloxanes."<sup>4</sup>. Most major producers of PDMS aren't involved in the medical industry. PDMS is mainly found in worldly applications such as lubricants, foaming agents, etc.

The main public concern for the use of PDMS stems from post-operative complications. Troubles in surgery usually start after the implanted device becomes contaminated with microorganisms or the wound becomes infected. Even under the most stringent antiseptics conditions, contamination is still a factor that has to be taken into account. Bacterial infection at the site of the catheter could occur for several reasons including surface adhesion and growth, production of extracellular components (slime), etc.

PDMS, however, is still at the forefront of medical research, whose novel properties warrants further research.

### **Polyethylene and Polymethylmethacrylate (PMMA)**

Many common thermoplastics, such as polyethylene and polyester, are used as biomaterials. Thermoplastics usually exhibit moderate to high tensile strength (5 to 1,000 megapascals) with moderate elongation (2 to 100 percent), and they undergo plastic deformation at high strains. Depending on the structure and molecular organization of the polymer chains, thermoplastics may be semi-crystalline or highly crystalline.

Joint replacements, particularly at the hip, and bone fixation devices have become very successful applications of materials in medicine. The use of pins, plates, and screws for bone fixation to aid recovery of bone fractures has become routine, with the number of annual procedures approaching five million in the USA alone<sup>12</sup>.

Hip-joint replacements are principally used for structural support. Consequently, materials that possess high strength, such as metals, tough plastics, and reinforced polymer-matrix composites dominate them. In addition, biomaterials used for orthopedic applications must have high modulus, long-term dimensional stability, high fatigue resistance, and biocompatibility(i.e., there



should be no adverse tissue response to the implanted device). Early developments in this field used readily available materials such as stainless steels, but evidence of corrosion after implantation led to their replacement by more stable materials, particularly titanium alloys, cobalt-chromium-molybdenum alloys, and carbon fiber-reinforced polymer composites. A typical modern artificial hip consists of a nitrided and highly polished cobalt-chromium ball connected to a titanium alloy stem that is inserted into the femur and cemented into place by in situ polymerization of polymethylmethacrylate.

Consequently, much research on the development of hip-joint materials has been devoted to optimizing the properties of the articulating components in order to eliminate surface wear. Other modifications include porous coatings made by sintering the metal surface or coatings of wire mesh or hydroxyapatite; these promote bone growth and integration between the implant and the host, eliminating the need for acrylic bone cement<sup>13</sup>.

### **Polytetrafluoroethylene**

PTFE is a thermosetting polymer with very limited application in medicine, but its characteristic properties, which combine high strength and chemical resistance, are useful for some orthopedic and dental devices. It also has

high modulus and tensile properties with negligible elongation. The polymer chains in this material are highly cross-linked and therefore have severely macromolecular mobility; this limits extension of the polymer chains under an applied load.

Biomaterials are used in many blood-contacting devices. These include artificial heart valves, synthetic vascular grafts, ventricular assist devices, drug releases, and a wide range of invasive treatment and diagnostic systems. An important issue in the design and selection of materials is the hemodynamic conditions in the vicinity of the device. For instance, mechanical heart valve implants are intended for long-term use. Consequently, the hinge points of each valve leaflet and the materials must have excellent wear and fatigue resistance in order to open and close 80 times per minute for many years after implantation. In addition, the open valve must minimize disturbances to blood flow as blood passes from the left ventricle of the heart, through the valve and into the ascending aorta of the arterial vascular system. To this end, the bileaflet valve disks of one type of implant are coated with pyrolytic carbon, which provides a relatively smooth, chemically inert surface.

Synthetic vascular graft materials are used to patch injured or diseased areas of arteries, for replacement of whole segments of larger arteries such as the aorta, and for use as sewing cuffs. Such materials need to be flexible to allow for the difficulties of implantation and to avoid irritating adjacent tissues; also, the internal diameter of the graft should remain constant under a wide range of flexing and bending conditions, and the modulus or compliance of the vessel should be similar to that of the natural vessel. A biomaterial used for blood vessel replacement will be in contact not only with blood but also with adjacent soft tissue. Experience with different materials has shown that tissue growth into the interstices of the biomaterials aids healing and integration of the material with host tissue after implantation. In order for the tissue, which consists mostly of collagen, to grow in the graft, the vascular graft must have an open structure with pores at least 10 micrometers in diameter. Fibroblasts synthesize the structural protein tropocollagen, which is needed in the development of new fibrous tissue as part of the healing response to a surgical wound.

Artificial heart valves and vascular grafts, while not ideal, have been used successfully and have saved many thousands of lives. However, the risk of thrombosis has

limited the success of existing cardiovascular devices and has restricted potential application of the biomaterials to other devices. Considerable advances have been made in the ability to manipulate molecular architecture at the surface of materials by using chemisorbed or physisorbed monolayer films. Such progress in surface modification, combined with the development of nanoscale probes that permit examination at the molecular and submolecular level, provide a strong basis for optimism in the development of specialty biomaterials with improved blood compatibility<sup>14</sup>.

### **Polyurethane**

Seen today in everyday uses such as shoe soles, tires and foams, polyurethane holds an extremely important role in cardiac medicine today. Polyurethane is a thermoset that is also a non-condensation step growth polymer<sup>4</sup>.

Polyurethane has a very low molecular weight compared to many other polymers with a molecular weight average of only 47,000 g/mol. The benefits of this material lie in the basics of its visible physical properties. Polyurethane is often described to bridge the gap between rubber and plastic. It holds one of the best load-bearing capacities of almost any materials around<sup>15</sup>.

Invented back in 1937 by Otto Baker, polyurethane was the result of a search for a material that has high

strength and good environmental resistance. For both reasons polyurethane today is one of the most important materials in use for ventricular assist devices. Differing from artificial hearts, VAD's are for short-term assistance to cardiac circulation attached to one or both of the heart ventricles. Most commonly seen in the operating room during open-heart surgery, postoperatively, and in the cases of extreme cardiac trauma. They consist of tubing attached to the heart valves leading to a pump that can be centrifugal, electrical, or pneumatic.

While Dr. D. Liotta of Baylor University developed the principles of this device in the 1950's, two doctors, Pierce and Donachy in 1971, significantly refined the technology. Rewriting the book on fluid mechanics (relating to blood flow) and taking advantage of polymers as a material. Polyurethane (segmented) stabilized the VAD, making not only the contact barrier of the blood and machine the safest possible, but also using the compressive properties that it exhibits made it function more like the actual heart itself. The once majority metal device was revealed in 1976 and approved for use by the FDA in 1980<sup>16</sup>.

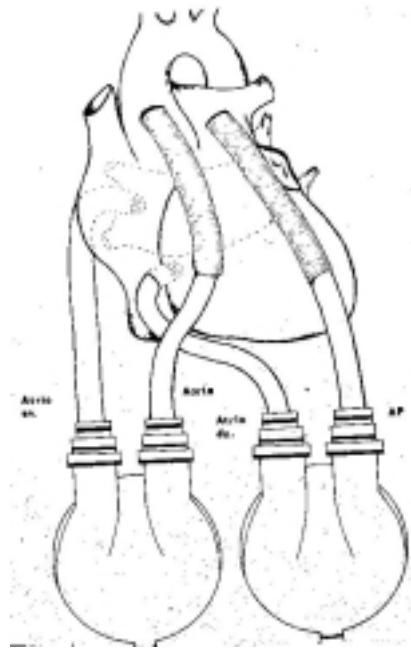


Fig. 4 Schematic of a Ventricular Assist Device

There are two ways to produce polyurethane. However, the most abundant source (95% of world production) is obtained through step growth polymerization of diisocyanates with dihydroxyl compounds. The result is a polymer that has a load bearing capacity comparable to cast steel. Polyurethane is molded most often through injection molding. Additionally as of recent years, reaction injection molding (RIM) has become one of the more popular ways to produce in industry. For the most polyurethane used for VAD's are produced under careful supervision and not often RIM produced. The largest debate over the use of these materials was potential for mechanical failure. Past occurrences of failure have been attributed to poor processing and not the material itself<sup>17</sup>.

VAD's have made great strides in the past 20 years. Where once limited to external unit only, today there are internally placed VAD's and as the technology improves, it may one day replace transplant surgery to cure cardiac conditions. While there are many types of VAD's, the only material that is a true alternative in some sense to the polyurethane is stainless steel. Advancements in the use of ventricular assist devices can be seen in the decrease in number of deaths of patients awaiting transplant, even with a great increase of people on the waiting list. Perhaps not a solution, the temporary alternative that exists in VAD's can only be attributed the integration of polymers into their design.

### **Conclusion**

Indeed, biomaterials have already made a huge impact on medical practices. But, the opportunities that lie ahead of us are enormous. "Tissue engineering and related subjects have the potential to change paradigms" for treating diseases that today cannot be treated effectively like certain forms of liver failure, paralysis, and certain disorders. " Clearly we are faced with big challenges ". But, the message I try to get across to everyone mostly to young students is that the field holds a tremendous promise<sup>1</sup>.

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