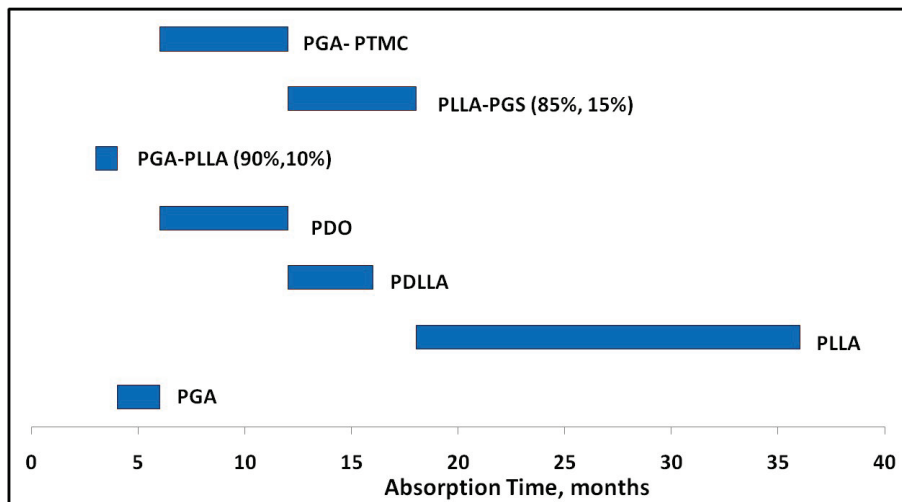


Essential Ingredients for Orthopedic Implants

The performance capabilities of orthopedic implants can be significantly increased by utilizing enhanced polymers that have been precision blended with additives using specialized processes and equipment. Long term implantable and bioresorbable polymers are enhanced with radiopaque fillers, bioactive bone growth additives and active pharmaceutical ingredients (API). These enhancements can increase therapeutic effect and reduce side effects, but special equipment and processes are required to realize their full potential.

Polymers used in orthopedic implants can be grouped into two families: long term implantable and bioresorbable. Long term implantable polymers commonly include polyethylene, urethane, and polyketone. They provide “permanent” structural support within the body in the form of sutures, fabric mesh, tubing, bone screws and anchors, or complete bone replacements. Implants utilizing these materials will remain intact and functional for the lifetime of the patient. Bioresorbable implantable polymers commonly include Polycaprolactone (PCL), polylactide (PLA), and polyglycolide (PGA). They provide “temporary” structural support as they are resorbed by the process of hydrolytic degradation. The process of bioresorption can be utilized to encourage natural bone and tissue regeneration or to deliver active pharmaceutical ingredients. Resorption times are customized by formulation according to the ideal therapeutic timeline for each application.

ABSORPTION TIME OF BIORESORBABLE MATERIALS



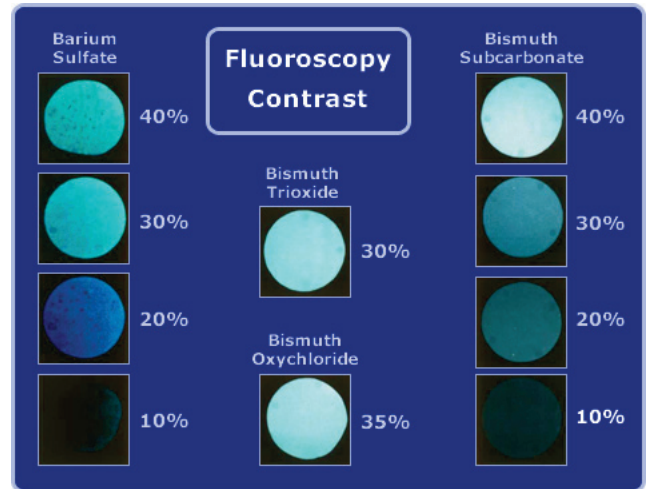
LEGEND

PGA-PTMC = Polyglycolic Acid – Poly-Tri-Methylene-Carbonate
 PLLA-PGS = Poly L-Lactide Acid / Poly Glycerol Sebacate
 PGA-PLLA = Poly Glycolic Acid / Poly L-Lactic Acid
 PDO = Polydioxanone

PDLLA = Poly – DL-Lactic Acid
 PLLA = Poly – L-Lactic Acid
 PGA = Poly Glycolic Acid

Polymers are naturally transparent to x-ray imaging, posing problems for their use in orthopedic implants. Increasingly common minimally invasive surgical (MIS) procedures rely on fluoroscopy for intraoperative positioning and postoperative monitoring of orthopedic implants rely heavily on x-ray imaging to ensure proper alignment and fusion. Polymers must be carefully blended with metallic salts and powders to achieve radiopacity in x-ray imaging both during and after surgery. Each of the commonly used radiopaque fillers exhibit unique properties and consideration must be given to how each will impact manufacturability as well as final device performance.

- Barium Sulfate (4.5 g/cm³)
- Bismuth Subcarbonate (6.9 g/cm³)
- Bismuth Trioxide (8.9 g/cm³)
- Bismuth Oxychloride (10.0 g/cm³)
- Tungsten (19.3 g/cm³)



In many applications designers go to great lengths to ensure that medical devices are as inert and nonreactive as possible within the body. However in orthopedic applications it is common to desire just the opposite: an implant that bonds to or is even replaced by the body's natural tissues. Tricalcium phosphate (TCP) and Hydroxyapatite (HA) are blended with polymers to make them osteoconductive; a material onto which bone will grow and bond. Used in orthopedic, dental, and maxillofacial applications, TCP and HA are used for fixation implants such as bone screws as well as bone replacement implants used to fill voids left by trauma or disease.

Enhanced with Active Pharmaceutical Ingredients (API), bioresorbable polymers are used in orthopedic implants to deliver localized controlled releases faster and with fewer side effects than systemic drug delivery. Through the process of hot-melt extrusion (HME), ingredients such as non-steroidal anti-inflammatory drugs (NSAIDs), steroids, controlled substances, antibiotics and other small molecules are blended into the polymer to be released into the body during bioresorption. With release rates customized by the formulation, the ingredients treat a wide variety of indications. API formulations may be used in combination devices which serve other functions such as extruded catheter shafts or they may be delivered as a pure implantable dose for local pain relief and inflammation control in orthopedic procedures.

Enhancing polymers for use in orthopedic implants requires specialized capabilities and special consideration of the impact these processes have on device performance. First and foremost all batching and hot-melt extrusion processes must be conducted in a clean environment: ISO 100,000 class cGMP certified clean room at a minimum. To achieve the biocompatibility required for implants and precise release rates of bioresorbables, contamination must be kept to an absolute minimum.



Precision feeding of ingredients into the blending process is critical, particularly when scaling the product to produce commercial quantities. Polymers having dissimilar bulk densities are best fed separately using multiple single screw loss-in-weight feeders. Fine power additives must also be fed separately using twin screw or disk type loss-in-weight feeders. In both cases feed screw design is critical and must be optimized and validated before hot-melt extrusion process development can begin. Liquid ingredients are injected into the melt blend with peristaltic, gear, piston, or syringe pumps each with respective tradeoffs in precision and flow rate.

Twin screw extrusion offers the most flexibility to provide optimal distributive and dispersive mixing when melt blending liquid and powdered additives into a polymer matrix. The barrels and elements are all segmented allowing the process to be customized based on formulation. Feeding, liquid injection and devolatilization can be achieved in various barrel types. Mixing elements are selected to control residence time and provide distributive or dispersive mixing. Small scale twin screw extruders are required from an economic standpoint as ingredients for enhanced orthopedic implants are relatively expensive. Bioresorbable polymers range in cost from two to ten dollars per gram while active ingredients can cost several thousand dollars per gram. Twin screw extruders as small as 12mm are commercially available, however they have limited application due to low torque capabilities. Thermo Haake and Leistritz are well known twin screw extruder manufacturers that have twin screw machines as small as 16mm. This size provides adequate torque and residence time for effective mixing with batch sizes as small as 20 grams. Both manufacturers make larger extruders at 27 to 34mm which are capable of commercial production batches of between 2000 and 4000 grams.

Precision cooling of the polymer blend is essential for precise sizing and metering. Long term implantable polymers are cooled using water while bioresorbable polymers must be cooled with a dry air supply. In both cases the cooling medium must be clean and maintained at a specific temperature. Under-

cooling the polymer blend will result in smearing during cutting or pelletizing, while over-cooling will result in brittle fracture. In both cases dosage variation and scrap rates increase reducing production yields.

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