REVIEW ARTICLE

An Insights into the Orthopaedic Implant Materials: a Comprehensive Study

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Abstract

Bones are involved in many physiological processes like the formation of blood and also act as calcium reserves. Out of 206 bones in the human body, many major bones get fractured easily due to low bone density, physical injury, or any other reasons. Normally bones get healed on their own by natural processes but sometimes fracture is so complex it does not allow normal healing or formation of bones. Sometimes such complex fractures, if left untreated can result in the loss of bone's normal functioning. So there arises a need for implants. An orthopedic implant is a medical device manufactured to replace a missing joint or bone or to support a damaged bone maintaining bone stability until fusion or fracture healing has occurred. The market is full of a plethora of such implants manufactured for bone fractures in different body parts and made of different materials like ceramics, metals, alloys, composites, etc. The present study is an exhaustive review of such implant materials and their advantages over one another. An exhaustive review of literature has been done in this study involving the content of scientific databases like PubMed, Google Scholar, Science Direct, Scopus, etc.

Keywords: Implants, Orthopaedics, Bone fracture, Biodegradable implants, Ceramic implants

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Introduction

The human skeleton consists of 206 bones. We are actually born with more bones (about 300) but many of them fuse together as a child grows up. These bones support our body and allow us to move. The longest bone in our body is the femur (thigh bone).[1] The smallest bone is the step bone inside the ear. Each hand has 26 bones in it. Our nose and ears are not made of bone; they are made of cartilage, a flexible substance that is not as hard as bone. Bones are connected to other bones at joints. There are many different types of joints, including: fixed joints (such as in the skull, which consists of many bones), hinged joints (such as in the fingers and toes), and ball-andsocket joints (such as the shoulders and hips). Bones contain a lot of calcium. Bones manufacture blood cells and store important minerals. Like liver, kidney and muscle; bone is a living tissue that responds to its environment. Two basic processes take place in bone as it responds to physiological demands. Bone modeling occurs primarily in children and young adults and results in bone growth; both in length and in crosssectional area.[2] The growth of bones through the addition of material to the endosteum or periosteum which is the result of the modeling process, can also continue throughout life. Bone remodeling involves the removal and in general replacement of bone. This process allows for the continual recycling of bone and in healthy tissue it prevents the accumulation of micro-cracks that could lead to fatigue failure of the structure. The same general processes are seen in fracture healing.[3]

Bone fracture

Bone fracture is a medical condition in which there is a break in the continuity of the bone. A bone fracture can be the result of high force impact or stress or trivial injury as a result of certain medical conditions that weaken the bones, such as osteoporosis, bone cancer or osteogenesis imperfecta where the fracture is properly termed a pathologic fracture.[4]

Surgical implants and other foreign materials have emerged as a common and often life-saving materials to improve the function of the human body.

Orthopaedic implant

An orthopaedic implant is a medical device manufactured to replace a missing joint or bone or to support a damaged bone.[5] The aim of Orthopaedic implant is to maintain stability until fusion or fracture healing has occurred. Major plus points for their penetration are the mechanical strength and proven biocompatibility. Success in orthopaedic implant surgery depends, in part on the quality of the material used to make

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the implant, its manufacturing routes, mechanical properties, biological stabilization and biocompatible surface coating.[6]

The implants market is an age driven market, with demand arising mostly from the elderly section of the population. In the market there is large potential in the worldwide market for these implants. Metal and alloys fit large range of biomedical applications, including devices for fracture fixation, partial and total joint replacement, external splints, braces and traction apparatus, as well as dental amalgams.[7] Presently major medical devices for different applications like, Orthopaedics, ENT, Cardiovascular, Dental etc. are made up of metals SS 316L, Co-Cr alloy, Ti6Al4V and Titanium. Orthopaedic implants can be for the hip, knee, spine, ear or for the extremity joints that include the fingers, feet and shoulder.

Orthopaedic implant made of 1) Metallic or 2) Polymer 3) Ceramic or ceramic composite different types of orthopedic implants can be seen in Figure 1.

Metallic Implant

Among commonly available materials like Austenitic stainless steels, CobaltChromium alloys and Titanium and its alloys, 316L SS are used as an implant material due to the availability and easy fabrication, superior inherent mechanical properties, reasonable corrosion resistance, biocompatibility, suitable density for load bearing purpose and low cost[8] (fig 1.01). The chemical composition of surgical grade of type 316L SS the specimen is (wt %): Cr (18.00), Ni (12.00), Mo (2.50), Mn (1.70), Cu (0.026), Si (0.15), C (0.02) and Fe (balance).[6] The nominal chemical composition of the pure Titanium is (wt %): H (0.015), C (0.15), N (0.03), O (0.18), Fe (0.20) and Ti (balance).[7] It is considered the universal material for permanent implants, such as endosseous dental implants. In other applications requiring higher mechanical strength, titanium based alloys or Co-Cr alloys are preferred.[8] Biocompatibility of the implant with body and bone tissue is essential to allow adequate new bone ingrowth into the synthetic prosthesis (Osseo integration or Osteogenesis) and makes a vital contribution towards the health of the patient.[9]

Bio-degradable polymers for implant material

Most of the commercially available biodegradable devices are polyesters composed of homopolymers or copolymers of Glycolide and Lactide [9]. The majority of results indicate that these polymers are sufficiently biocompatible. Currently biodegradable implants are used for stabilization of fractures, osteotomies, bone grafts and fusions particularly in cancellous bones, as well as for reattachment of ligaments, tendons, meniscal tears and other soft tissue structures.[10] Low molecular weight polyglycolic acid was synthesized by Bischoff and Walden in 1893.[11] The first synthetic absorbable suture was developed from polyglycolic acid (PGA) by American Cyanamid Co. in 1962. The 90:10 copolymer of glycolide and lactide polygalactin 910 - has been applied as the competitive suture 'Vicryl' since 1975.[17] Since then sutures

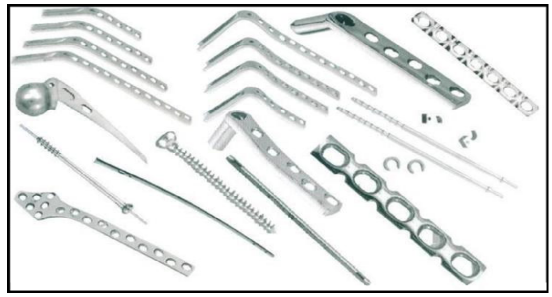

Figure 1: Different types of orthopaedic implants

of polyglycolide and polylactide have been used for many years and no carcinogenic, teratogenic, toxic or allergic side effects have been observed.[18] The only adverse reaction reported has been a mild non specific inflammation.[19,20] Use of PGA as reinforcing pins, screws and plates for bone surgery was first suggested by Schmitt and Polistina[12] in 1969. Since then there has been a lot of development in manufacturing biodegradable implants with properties appropriate for osteosynthesis Figure 2 showing Biodegradation mechanism of biodegradable polymers.

Crystalline polymers slowly degrade due to orderly arrangement of molecules and amorphous polymers are easily degrade due to random structure.[13] This biodegradable polymer excretes from the body via body's natural metabolic actions. In the process of degradation, the polymeric chains are cleaved by hydrolysis and enzymatic degradation process results in decrease of molecular weight to form monomeric acids and are eliminated from the body through the Krebs cycle (or TCA cycle), primarily as carbon dioxide and water in urine and release drug to local area. Polymeric coating on metallic implant prevents corrosion up to some extent.[14]

Poly L-Lactide (PLLA)

Lactide is the cyclic dimer of lactic acid that exists as two optical isomers, d and l. L-Lactide is the naturally occurring isomer. The homopolymer of LLactide is a semi-crystalline polymer. This types of material exhibits high tensile strength and low elongation and consequently has a high modulus that makes them more suitable for load-bearing applications such as in orthopaedic fixation and sutures. Poly (L-Lactide) is about 37% crystalline with a melting point of 175-178°C and a

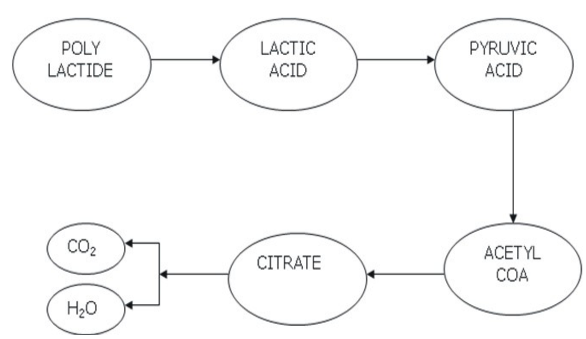

Figure 2: Biodegradation mechanism of biodegradable polymers

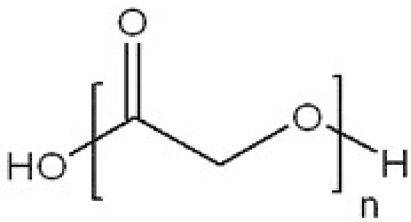

Figure 3: Structure of PGA

glass-transition temperature of 6065°C.[15] The degradation of PLLA is much slower than that of PDLLA, requiring more than 2 years to be completely absorbed.[16] Copolymers of L-Lactide and DL-Lactide have been prepared to disrupt the crystallinity of L-Lactide and accelerate the degradation process.

Polyglycolide (PGA)

PGA is the simplest linear aliphatic polyester and is prepared by ring opening polymerization of a cyclic lactone, glycolide structure of polyglycolide (PGA) is presented in Figure 3. It is highly crystalline, with a crystallinity of 45-55% and thus is not soluble in most organic solvents. It has a high melting point (220-225°C) and a glass transition temperature of 35-40°C.[17] PGA has excellent mechanical properties but its biomedical applications are limited due to its low solubility and its high rate of degradation yielding acidic products. Consequently, copolymers of glycolide with caprolactone, lactide or trimethylene carbonate have been prepared for medical devices.[18]

Polyvinyl Pyrrolidone

Polyvinyl Pyrrolidone (PVP) is a hygroscopic, amorphous polymer available in form of white, free flowing crystalline powder or in clear aqueous solution and available in several molecular weight grades structure of polyvinyl pyrrolidone is presented in Figure 4. It is soluble in water and insoluble in esters, ethers, ketones and hydrocarbons. It is highly adhesive. Polyvinyl Pyrrolidone has been shown to be biocompatible; UV cured films of PVP copolymers have been proposed as a potential bioadhesive wound dressing matrix. Due to its lubricity and viscous properties, PVP is applied to coat tissue contacting surfaces.[23]

Poly (D,L- Lactide)

Poly (D, L- Lactide) (-($C_6H_8O_4$) n-($C_2H_4O_2$)-($C_6H_8O_4$)$_n$-, CAS No: 2680-10-4) is a pale yellow colored semicrystalline polymer having glass transition temperature of 55-60°C and melting point of 174- 184°C which is soluble in acetone, dichloromethane and dimethyl formamide structure presented in Figure 5.[37] PDLLA is a racemic mixture of D-and L- enantiomers of lactic acid and severs as a biodegradable coating of medical implants.[24] In the human body, the Lisomer exists in carbohydrate metabolism and the D-isomer is found in acidic milk.

In order to regulate the drug delivery rate, biodegradable polymers are widely used due to their excellent

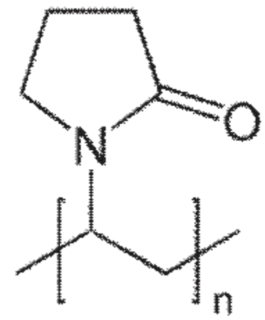

Figure 4: Structure of PVP

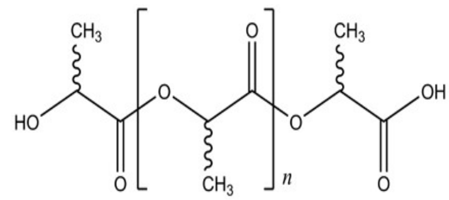

Figure 5: Structure of poly (D, L- Lactide)

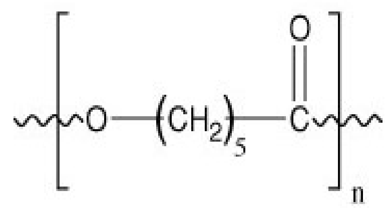

Figure 6: Structure of Polycaprolactone

biocompatibility and low toxicity. Poly (D, L-Lactide) is a biocompatible, bioabsorbable, osteoconductive and biodegradable polymer that is used previously to formulate many types of implantable and injectable drug delivery systems for humans and other animals. Poly (D, L- Lactide) can degrade due to its amorphous structure.

Polycaprolactone (PCL)

ε-caprolactone is a relatively cheap cyclic monomer. A semi-crystalline linear polymer is obtained from ring-opening polymerization of εcaprolactone in presence of tin octate catalyst. PCL is soluble in a wide range of solvents. Its glass transition temperature is low, around -60 °C and its melting point is 60–65°C. PCL is a semi-rigid material at room temperature has a modulus in the range of low-density polyethylene(LDPE) and high-density polyethylene(HDPE), a low tensile strength of 23 MPa and a high elongation to break (more than 700%) structure presented in Figure 6. Due to its low Tg, PCL is often used as a compatibilizer or as a soft block in polyurethane formulations.[25]

Ceramics

Ceramics, particularly alumina was first introduced by a french orthopaedic surgeon as structural orthopaedic biomaterials in the late 1960, where failures of the biomaterials in use got exploited then material such as steel, cobalt alloys and

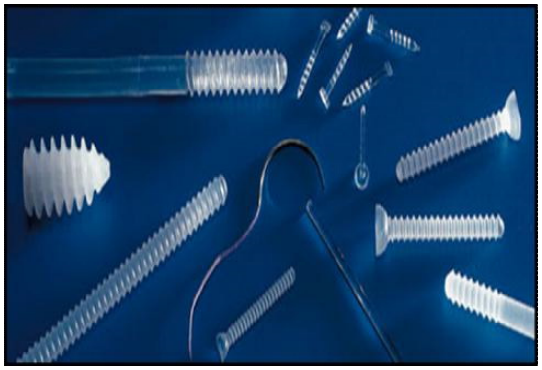

Figure 7: Biodegradable Implants

poly methyl methacrylate began to be detected.[26] However, limitations in processing technology and lack of quality control led to materials with higher than desired levels of impurities and imperfections, including high porosity levels. These defects caused a further reduction in the strength of ceramics in tensile or shear loading, resulting in premature failure in a number of clinical cases.[27]

Hence, attention was directed to ceramic materials in an attempt to find good bone integration features. Ceramics are now commonly used in the medical fields as dental, and bone implants . The ceramic materials used are not the same as porcelain type ceramic materials. Rather bio-ceramics are closely related to either the body's own materials or are extremely durable metal oxides. Artificial teeth and bones are relatively commonplace. Joint replacements are commonly coated with bioceramic materials to reduce wear and inflammatory response. Examples of medical uses of bio-ceramics are in pacemakers, kidney dialysis machines and respirators. Bio-ceramics fulfil a unique function as biomedical materials. The development of biomaterials and manufacturing techniques has broadened the diversity of applications within the human body.

Various Bio-ceramics like-alumina, zirconia, pyrolytic carbon, bioglass, silica, calcium phosphate group etc. have been matter of interest for scientists for their higher biocompatibility over metals. The ceramic-based biomaterials have been accepted after biological evaluation through several in vivo and in vitro tests. Bio-ceramics are either bioinert, biodegradable or bioactive. Bio-inert materials form a fibrous capsule around the implant. Bioactive materials on the other hand do an interfacial bond with the implant, whereas bioresorbable (biodegradable) materials are replaced with the new tissue as the implant dissolved. Due to their brittle nature and low load bearing capacity, they are not widely popular to be used as prosthesis and alternatives for metallic implants.

Alumina

Since 1975 alumina ceramic has proven its bio-inertness. An alumina ceramic has characteristics of high hardness and high abrasion resistance. The reasons for the excellent wear and friction behavior of Al_2O_3 are associated with the surface energy and surface smoothness of this ceramic. There is only one thermodynamically stable phase, i.e. Al_2O_3 having a hexagonal structure with Aluminum ions at the octahedral interstitial sites. Abrasion resistance, strength and chemical inertness of alumina have made it to be recognized as a ceramic for dental and bone implants. The biocompatibility of alumina ceramic has been tested by many researchers. The results showed no signs of implant rejection or prolapse of the implanted piece. Loosening is the most frequently observed long-term complication following joint replacement. The reason is thought to be foreign-body reaction of the tissue against wear particles of various biomaterials. Relationship between the size and type of biomaterials and tissue reaction has not been clarified completely. When alumina ceramic (Al_2O_3, 3.9 μm) was surgically inserted in the knee joints of Japanese white rabbits, the consequent histological reaction was examined. Alumina ceramic induced weak tissue reaction. These properties are exploited for implant purposes, where it is used as an articulating surface in hip and knee joints. Its ability to be polished to a high surface finish make it an ideal candidate for this wear application, where it operates against materials such as ultra high molecular weight polyethylene. Porous alumina has also been used as a bone spacer, where sections of bone have had to be removed due to disease.

In this application, it acts as a scaffold for bone ingrowth. Single crystal alumina or sapphire has also been used in dental applications, although its use in this application is declining with the advent of more advanced materials such as resin-based composites.

Bioglass

Bioglass was introduced to the scientific world in the late 1960s by Dr. Hench. These glassceramics, which contained varied proportions of SiO, Na_2O, CaO, P_2O_3, CaF_2, and B_2O_3 were designed to interact with the normal physiology of bone to allow strong bone bonding. The bonding mechanism was found to depend on the composition of the glass, and this has sparked the development of other variations of glass-ceramics. Glass-ceramics have low tensile strength and fracture toughness, limiting their use in bulk form to applications subject to purely compressive loading. Attempts have been made to use these materials as part of composite structures to increase their application. The most common method is to coat a ceramic or metallic implant with the glass to create an osteo-inductive surface. The coating may be applied in a pure layer of glass or as an enamel coating with embedded glass particles. For the enamel systems, it is important to ensure that the components of the enamel do not interfere with the bone-formation process. The glass coating is still a brittle material and must be handled with care; any substantial impact may lead to failure of the entire coating system. Glass composites have also been investigated using stainless steel fibers (50 to 200 μm thick) to reinforce

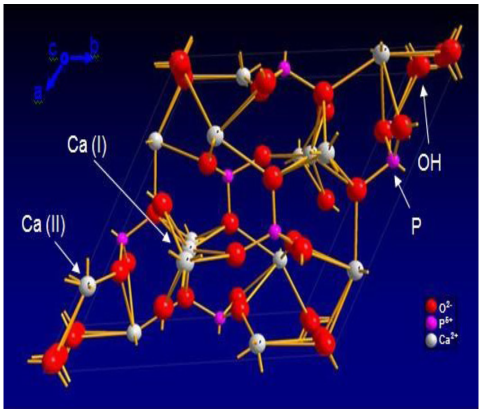

Figure 8: Structure of hydroxyapatite

the glass-ceramic goal of these composites follows that of other fiber-reinforced materials to increase their resistance to fracture by blunting crack growth and introducing a residual compressive stress within the material. This procedure was found to make the material significantly more ductile and stronger, thus reducing its tendency to fail catastrophically. In addition, the elastic modulus was reduced from that of the pure glass, bringing it closer to the ideal properties for bony replacement biodegradable screws are shown in Figure 7.[29]

Hydroxyapatite

Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$ – CAS Number: 7758-87-4) is synthetic white odorless inorganic powder, free form biological contamination they do not elicit foreign body reaction when implanted structure of hydroxyapatite is shown in Figure 8. It is insoluble in water. Naturally occurring apatite may have brown, yellow or green colorations compared to the discolorations of dental flouorosis. Hydroxyapatite (HAp) is widely used as a bioactive ceramics since it forms a chemical bonding to bone.[30]

Mechanism of action of hydroxyapatite is described by Gorbunoff as follows

- After implantation, calcium phosphate solid-solution equilibrium are established by calcium and phosphate ions which are released from implant and surrounding bone.
- This means slight dissolution of HAp or bioglass is very important for the so-called bioactivity of these bioactive materials.
- This process results in calcium and phosphate ions super-saturation in the surrounding body fluid, and then carbonate apatite crystallites epitaxially reprecipitate on the surface of the Hap.[31]
- These modified surfaces are known to accommodate protein adsorption and cell adhesion more rapidly; in particular, cells (osteoblasts) associate with bone bonding.
- In six months, mineralization within the implant sites is comparable to the surrounding bone.
- TEM image analysis of dense HAp bone interfaces show almost perfect epitaxially alignment of some growing bone crystallites with the apatite crystals in HAp implant.
- Due to this chemical bonding interface, the bonding strength of HAp and bone is much higher than bare metallic implants.
- Thereby the relative micro-movement between the implant and bone is dramatically reduced by this direct bonding, and no fibrous tissue capsule can be found between the implant and bone.[32]
- This is important for the patient's recovery in the early period after implantation.

Clinical Significance and Future Directions

In the world of orthopaedic implants, a lot has changed. Patient outcomes have improved as a result of newer designs, better materials, and innovative surgery. Despite these developments, some issues remain. The use of more modern, safe, and efficient devices requires the use of peer-reviewed data and impartial implant research. In several orthopaedic treatments, implants are employed. One cannot overestimate the significance of knowing how to choose the appropriate implant based on the task at hand. Orthopedic implant design is still changing as we work to overcome the problems of cost, dependability, longevity, and infection control.

CONCLUSION

In conclusion, the traits of the most widely used materials and techniques for implants have been discussed, and the path of future research is suggested, with a focus on innovative materials to produce individualised and incredibly long-lasting bioinert implants. Due to their excellent durability, wide availability, and standardised technology and know-how for their fabrication, metals make up the vast majority of implants today. Moreover, there are several opportunities to synthesise novel polymer materials, and production is quite inexpensive. Thus, it stands to reason that polymers could eventually replace metals and their alloys in orthopaedic applications.

REFERENCE

1. B aksakal, OS yildirim, Okur. Coating Analysis of Implant Materials Used in Orthopaedic Surgery. J INT MED RES 31: 418 – 421. 2003
2. N. Eliaz, T. M. Sridhar, U. Kamachi Mudali, Baldev Raj. Electrochemical and Electrophoretic deposition of hydroxyapatite for orthopaedic applications. Surf. Eng. 21(3): 1-5. 2005
3. www.asminternational.org
4. U kamachi mudali, T.M. Sridhar, Baldev Raj. Corrosion of bio implants. Sadhana 28(3,4): 601–637. 2003
5. Kannan S.,Balmurugan A, Rajeswari S. Development of calcium phosphate coating on type 316L SS and their in vitro response. J. Trends .Biomat. Artif.Organs 16(1): 8-11. 2002
6. S.K. Yen, C.M. Lin. Cathodic reactions of electrolytic hydroxyapatite coating on pure titanium. Mater. Chem. Phys. 77(1, 2) : 70-76. 2003

7. Cristina Costa de Almeida, Lidia Agata Sena, et al. In vivo characterization of titanium implants coated with synthetic hydroxyapatite by electrophoresis. Braz Dent J 16(1): 75-81. 2005
8. John C. Middleton, Arthur J. Tipton. Synthetic biodegradable polymers as orthopedic devices. Biomaterials 21: 2335-46. 2020
9. MS Dhillon, et al. Bioabsorbable implants in orthopaedics. Indian J Orthop 40: 205-9. 2006
10. Frazza EJ, Schmitt EE. A New absorbable suture. J Biomed Mater Re Symposium. 1: 43-58. 1971
11. Schmidmaier G, Lucke M, Wildemann B, Haas NP, Raschke M. Prophylaxis and treatment of implant-related infections by antibioticcoated implants: a review. Injury. 37 (2): 105-12. 2006
12. Russell GV Jr, King C, May CG. Once daily high-dose gentamicin to prevent infection in open fractures of the tibial shaft: a preliminary investigation. South Med J. 94(12): 1185-91. 2001
13. Bertazzoni Minelli E, Benini A, Magnan B, Bartolozzi P. Release of gentamicin and vancomycin from temporary human hip spacers in Chapter 6 164 two-stage revision of infected arthroplasty. J Antimicrob Chemother. 53(2): 329-334. 2004
14. Giuliano RA, Verpooten GA, De Broe ME. Renal cortical kinetics of gentamicin after implantation of gentamicin-polymethylmethacrylate beads in rats. Antimicrob Agents Chemother. 30(3): 385-9. 1986
15. Raiha JE, et al Fixation of trochanteric osteotomies in laboratory beagles with absorbable screws of polylactic acid. VCOT. 3:123-9. 1990
16. Conn J Jr, Oyasu R, Welsh M, Beal JM. Vicryl (polyglactin 910). synthetic absorbable sutures. Am J Surg. 128(1): 9-23. 1974
17. Schmitz JP, Hollinger JO. Priliminary study of the osteogenic potential of a biodegradable alloplastic osteoinductive implant. Clin Orthop. 237: 245-55. 1988
18. Gammelgaard N, Jensen J. Wound complications after closure of abdominal incisions with Dexon R or Vicryl R. A randomized double blind study. J. Acta Chir Scand.149: 505-8. 1983
19. Chegini N, Metz SA, Masterson BJ. Tissue reactivity and degradation patterns of absorbable vascular ligating clips implanted in peritoneum and rectus fascia. J Biomed Mater Res. 24: 929-37. 1990
20. Schmitt, EE, Polistina, RA. Polyglycolic acid prosthetic devices. U. S. Patent 3 463 158. 1969
21. K. Gurunathan, A. Vadivel Murugan, et al. Electrochemically synthesized conducting polymeric materials for applications towards technology in electronics, optoelectronics and energy storage devices. Mater. Chem. Phys. 61: 173-191. 1999
22. James K. Mitchell and William E. Carter. Modeling Antimicrobial Activity of CloroxTM Using an Agar-Diffusion Test: A New Twist on an Old Experiment. Bioscene. 26: 9-13. 2000
23. Jongjan Mahadlek, Thawatchai Phachamud, Chantana Wessapun. Antimicrobial Studies of Sonneratia caseolaris Using Different Agar Diffusion Method. RJPBCS 3: 404 -10. 2012
24. Alagesaboopathi C, Sivakumar R. Antimicrobial Properties of Various Extracts of Andrographis neesiana Wight - An Endemic Medicinal Species from India. Int.J. pharmTech. Res. 3(1): 27-31. 2011
25. S. A. Ibrahim, S. R. Dharmavaram, C. W. Seo, G. Shahbazi. Antimicrobial Activity of Bifidobacterium longum (NCFB 2259) as Influenced by Spices. Int. J. Food Saf. 2: 6-8. 2002
26. M. Chasin, and R. Langer, Marcel Dekker D. H. Lewis. Biodegradable polymers as drug delivery systems, Controlled release of bioactive agents from Lactide/ Glycolide polymers, in Biodegradable polymers as drug delivery systems. (Ed): New York:1-43. 1990
27. R. L. Kronenthal, R. L. Kronenthal, Z. Oser, E. Martin. Biodegradable polymers in medicine and surgery, in Polymers in medicine and surgery, (Ed), Plentum Press: New York: 119. 1975
28. M. Reed and D. K. Gilding. Polymer, 22:494-8. 1981
29. Hsueh-Chang Wu, Fu-Wen Shen, Xuan Hong, et al. Monitoring the degradation process of biopolymers by ultrasonic longitudinal wave pulse-echo technique. Biomaterials 24: 3871–76. 2003
30. Miller, R.A.; Brady, J.M.; Cutright, D.E. Degradation rates of oral resorbable implants (polylactates and polyglycolates): Rate modification with changes in PLA/ PGA copolymer ratios. J. Biomed. Mat. Res. 11: 711-9. 1977
31. K. Dickers, G. Milroy, H. Huatan and R. Cameron. The use of biodegradable polymers in drug delivery systems to provide preprogrammed release. The Drug Delivery Companies Report Autumn/ Winter : 26–28. 2002
32. Daniela N Mannel, Georges E Grau. Role of platelet adhesion in homeostasis and Immunopathology. J Clin Pathol: Mol Pathol 50: 175-185. 1997
33. Nair, L.S.; Laurencin, C.T. Biodegradable polymers as biomaterials. Progr. Polym. Sci.32: 762-798. 2007