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Review Article

Antibiotic Eluting Orthopedic Implants

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ABSTRACT

Infection of orthopedic devices in the post-operative era is a crucial complication that brings significant health problems and financial implications. Prevention strategy could be based on the local release of antibiotics from the orthopedic device itself to avoid bacterial adhesion and advancement. Drug eluting implants aid in wound healing in addition to providing support. They are also called as active implants. This is accomplished by the controlled release of active pharmaceutical ingredients (API) into the surrounding tissue. A synthetic biomaterial to be utilized effectively in the body, it ought to have certain properties; biocompatibility, osteoconductivity, capacity to be fabricated into useful shapes effectively, no immunogenic probability and controlled bioresorbability. The development of calcium phosphate particularly with tricalcium phosphate has drawn extensive consideration. At present these ceramic materials are currently recognized as biomaterials that essentially stimulate the mineralogical structure of bone. Clinical achievement of bioceramics has prompted an advance in the quality of life for millions of people. This review gives an outline of continuous endeavors in biomaterial research for orthopedic applications, with emphasis on tricalcium phosphate (TCP) as emerging biomaterial that is used in the construction of drug eluting orthopedic implants.

Key Words: Orthopedic implants, Tricalcium phosphate, Bioceramics, Bone grafts, Antibiotics

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INTRODUCTION

Orthopedic implants are commonly used in the treatment of bone fractures and deformities. Orthopedic implant use is increasing and it improves the clinical performance of modern treatment techniques.[1] The structure of an orthopedic device incorporates physiochemical elements of the bulk biomaterial. Novel formulations of present biomaterials are being considered to enhance their characteristics, durability, and reaction with the surrounding biological environment.

There is also a growing focus on modifying the material characterics of bioabsorbable and composite materials with fillers for nonpermanent devices. Nonpermanent devices also cover the utilization of cells, signaling factors, or scaffold material to restore tissue function. Coatings are provided on implants to improve compatibility with tissues. There are several forms of coatings, such as beaded, plasma spray, and sintered, etc. The objective of enhancing their osseointegration characteristics and fusing antimicrobial properties is a ceaseless undertaking. In circumstances where bone substitutes are required, upgraded and novel joint materials are being investigated.

NEED OF DRUG ELUTING ORTHOPEDIC IMPLANT:

A mixture of bone cement and antibiotics can then be regarded as a precursor in a drug delivery system for orthopedic applications. Treatment of bone diseases (osteomyelitis) was justified due to the poor availability of the infection site by common systemically administered antibiotics. Drug penetration into the joint space and bone after systemic administration is restricted under poor blood supply to the infected zone. To improve treatment bioceramic materials have been used as transporters for antibiotics. Thus a combination of bone cement and antibiotics can be considered as a drug delivery system for orthopedic application.[2]

BONE REPLACEMENT MATERIALS

Bone is the hard connective tissue that constitutes the rigid skeleton of among most vertebrate mammals and other animals. The main role of bone is to physically support the body, ensure the safety of inner organs, and help in cell development, calcium deposition, and mineral storage. Bone substitution materials give mechanical support and chemical components that the body can use to heal more rapidly. In case of damage or infection of a bone, it more practical to utilize a substitute material that will remain forever in the body.

1. Natural Replacement Materials: At a point when the bone is lost due to injury or illness, bone grafts are introduced to perform bone fixation. Ninety percent of bone graft techniques utilize normal bone from autografts (the patient's bone) or allografts (transplant from one person to another).[3] Natural bone is the ideal replacement choice, as it has the whole bone structure, comprising of both inorganic and organic segments. There are several disadvantages to bone graft methodology. The reason is that the autografts include a second incision to collect the substitution tissue.

This requires extra healing at the donations site and can include long-term postoperative pain. Additionally, the allografts bring with them the danger of viral disease, immune system rejection and resorption due to immunological responses. Also, donor material is not promptly accessible. It is for these reasons that the development of suitable synthetic materials is required.

2. Synthetic Replacement Materials: Synthetic materials are a prominent option in contrast to natural substitution materials. No current synthetic material can adequately copy both the biological and mechanical properties of normal bone. Synthetic materials right now utilized and it incorporates polymers, metals. It covers an extensive variety of bioaffinities, from the alleged bioinert to bioresorbable. Toward one side of the field, the body responds to bioinert materials, for example, alumina, by producing a fibrous capsule around the implant. As the body offers no methods for chemical bonding, bioinert materials must attach to bone with cement or through bone growth into surface irregularities of the material. On the other hand, a bioresorbable material, for example, tricalcium phosphates (TCP), degrades after some time and is gradually supplanted by natural tissue. While bioresorbable materials would appear to be perfect from various perspectives, the degradation process can unfavorably influence the mechanical integrity of the material and the stability of the biomaterial/natural tissue interface, thus compromising the implant bone system during the resorption and replacement process. The Bioactive materials evoke a biological reaction at the material interface and bond with the surrounding tissue, yet avoid degradation. For load-bearing implants this class of synthetic substitution materials generally used.

BIOCERAMICS

Ceramic biomaterials were first explored and utilized in the domain of orthopedic medical procedure as an option in contrast to metallic biomaterials. Ceramic materials are biocompatible, have corrosion resistance and exhibit tremendous bioactivity.

Bioceramics are utilized in medical procedures and dentistry. Bioinert ceramics production does not react with living tissues while bioactive ceramics respond with tissues in a pretty much controlled way. Dense alumina is a case of inert material while calcium phosphates encapsulate bioactive materials. TCP is extremely receptive, which implies it tends to be 'decomposed' by tissues over a short period of time. This conduct enables TCP to be utilized for resorbable implants and coatings on inert materials to enhance the inter face between the prosthesis and surrounding tissues. *β*-TCP ceramic production can be handled to create different microstructures. Consequently, TCP ceramic offer the potential to tailor bioactivity.[4] The events taking place at the interface between bioceramics and the surrounding biological environment is as shown below:[5]

1. The dissolution of bioceramics on the solid surface
2. Bioceramic precipitation from solution
3. The ion exchange and structural rearrangement occurs at the bioceramic/tissue interface
4. The Interdiffusion from the surface boundary layer into the bioceramics
5. Effects of the solution on cellular activity
6. The deposition of either the mineral phase (a) or the organic phase (b) without integration into the bioceramic surface
7. The deposition with integration into the bioceramics
8. Chemotaxis takes place to the bioceramic surface
9. Attachment of cells and proliferation
10. Cell differentiation tends to occur on the surface
11. The formation of extracellular matrix on surface.

All phenomena, collectively, lead to the gradual incorporation of a bioceramic implant into developing bone tissue as shown in figure 1.

Types of bioceramics:

1. Bioinert ceramics: Alumina and zirconia for dental implants and orthopedic applications.[6]
2. Bioactive ceramics: Bioactive glasses, hydroxyapatite (HAp) and glass ceramics for the coating of titanium alloy implants to improve their osteointegration.[7]
3. Resorbable ceramics: Tricalciumphosphate for scaffold applications.[8]

TRICALCIUM PHOSPHATE

Tricalcium phosphate (TCP) is known to have a compound structure like bone tissue mineral. TCP has two diverse crystalline structures: α- TCP and β-TCP. TCP has a good resorbability and bioactivity with a higher rate of biodegradation than hydroxyapatite under *in vivo* conditions. Due to its osteoconductivity and resorption properties, it is utilized for renovating bone graft. TCP is additionally utilized for the application in orthopedic, dental and maxillofacial applications. Complete TCP resorption is observed in rat tibia and canine models for bone reconstruction. Bone grafts made of TCP shows a moderate resorbability by osteoclasts over a range of 10 months to 2 years. Currently, *α*- TCP and *β*- TCP are clinically used in orthopedics. *α*-TCP is the primary element in the bone cement, *β*- TCP is the component in the mono or biphasic Bioceramics. The *α* and *β*- TCP have chemical composition same but they differ in their structure, density and solubility, which have an impact on their biological properties and clinical applications.[]

***1. α*-Tricalcium phosphate** (*α*-TCP**)**

α-tricalcium phosphate is used as a raw material in bone repair as a composite and biodegradable bioceramic. By heating the *β*-TCP which is low-temperature polymorph or by using amorphous precursors which have constituents above the transformation temperature which are undergone thermal crystallization to produced *α*-TCP. The metastable state of *α*-TCP is mainly retained at room temperature. The ionic substitutions strongly influence stability. *α*- TCP is very soluble and calcium deficient hydroxyapatite is formed rapidly due to hydrolyzes, which makes *α*-TCP a useful raw material for preparing composites and biodegradable bioceramics and also as osteotransductive bone cement for bone repairing.[10]

Structure: *α*-TCP has a crystalline structure that belongs to the mineral glaserite. The monoclinic crystal system is observed when *α*-TCP crystallizes. Unit cells of *α*-TCP are constituted with Ca and PO_4 and columns are packed by polymorphs along the direction. There are two forms of columnsin *α*-TCP, out of which one is said as C- C that contains Ca cations and the other is named as Ca which contains PO_4 anions and Ca cations.

Solubility: The *α*-TCP shows high solubility at pH<5 and pH(7.2–7.4). The *α*-TCP shows a decrease in the concentration of Ca and P produced by dissolving calcium orthophosphates.

Synthesis: The α-TCP synthesis is done by using thermal transformation or by solid state reaction. Combustion synthesis and self-propagating using high temperature synthesis can also be used. For getting pure phase α-TCP doping with silicate is done. In doping the PO_4 is substituted with SiO_4.

The silicate doping of α-TCP helps to enhance osteogenesis. The silicone that is released from the materials helps for bone regeneration.

2. β- Tricalcium phosphate (β-TCP)

β-TCP based bioactive biomaterials, have excellent biocompatibility and allow bone integration by allowing the reaction between cells and body fluids. They do not induce any tissue toxic or foreign body reaction. They do not have osteo-inductive properties because the bone is not formed when β-TCP materials are implanted in body but β-TCP materials are osteo-conductive.

Structure: β-TCP is in the form of polycrystalline and powder materials. β-TCP is an anhydrous tricalcium phosphate. Structural analysis can be done using conventional X-ray powder diffraction data to obtain the unit cell parameters. High resolution powder neutron diffractometry can be used to investigate crystal structure.

Synthesis: The synthesis of β form can be done by heating amorphous calcium phosphate (ACP) between 800 and 1000^0C. β-TCP can also be synthesized by heating a mixture of solid as $CaHPO_4$ and $CaCO_3$ at 1000^0C for one hour. Pure β-TCP cannot obtain directly from the solution. β-TCP, $Ca_3 (PO_4)_2$, is prepared either by sintering appropriate calcium deficient apatite obtained from solutions or by solid state reaction. Mg- and Zn-substituted β-TCP has been recommended as potential bone graft materials or implant coatings.[11]

GLOBAL ORTHOPEDIC IMPLANTS MARKET

The orthopedic implants market assumed to have $45,901 million in 2017 and is predicted to reach $66,636 million by 2025.[12] The use of orthopedic implants is rising significantly in the population suffering from osteoporosis, osteoarthritis and some other factors like increase in the rate of injuries. The global market of orthopedic implants is divided into five regions: Asia Pacific, Africa, Latin America, North America, and the Middle East. North America is the region with leading growth in the market of orthopedic devices followed by Europe. There is an increase in the number of individuals subjected to treatment related to orthopedic procedures in the United States. The second largest share for the Global orthopedic market belongs to Europe. As per the prediction of the analyst the market for the orthopedic implant will reach a CAGR of over 4% by 2023.[13]

CONCLUSION

There is great concern to establish new biomaterials for orthopedic implants, using either new material, amend the formulations of existing materials, or finding new function for existing materials. Biomaterials produce should be safe and effective but also from a commercial point of view it should be produce on a large scale in a cost effective manner.

Advances in material science, manufacturing and cell biology have directed the improvement of novel biological coatings for orthopedic implants that desire to restate the natural surroundings of growing bone. Coatings containing of calcium phosphates exploit the essential cellular mechanisms that is osteogenesis to encourage osteointegration of the implant. The construction of osteogenic coating must also help for anti-infective specifications of orthopedics devices. The capability to transcribe the *in vitro* evaluations, pilot clinical studies and animal studies to large scale use will help to regulate the growth of many of these biomaterials from an effectiveness and safety standpoint, but also from a commercial standpoint the biomaterials should be able to produce in an efficient cost and on a large scale.

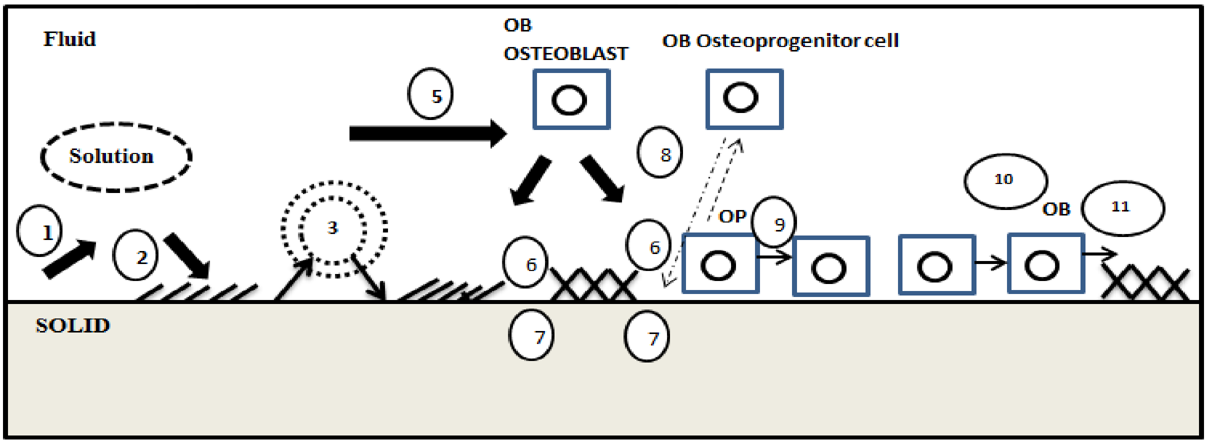

Figure 1: A schematic diagram representing the events taking place at the interface between bioceramics and the surrounding biological environment

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