A STUDY OF RADIOPACITY FOR MAKING BIORESORBABLE METAL/ POLYMER STENTS VISIBLE IN MRI/CT SCAN

Alok Srivastava

DEPARTMENT OF MECHANICAL ENGINEERING
INDIAN INSTITUTE OF TECHNOLOGY DELHI
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by

Alok Srivastava

Department of Mechanical Engineering

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Dedications

This thesis is dedicated to my respected parents, adorable sisters, and loving wife Mrs Stuti Srivastava, for taking good care of my little son Mr Kushagra Srivastava during my doctoral study. They believed and stood beside me all the time. My parents gave me free hands to take my discussion without doubting me. Similarly, my wife supported my decision, took good care of me and properly managed the house. They provided me with a positive environment to focus on my doctoral work. Finally, my little champ Kushagra, who was present with me during my journey and his contribution was equally important. We both enjoy the company, this reduces my work stress and makes me more responsible.

Certificate

This is to certify that the thesis entitled ***"A Study of Radiopacity for making Bioresorbable Metal/ Polymer Stents visible in MRI/CT Scan"*** *submitted by* ***Mr Alok Srivastava*** *to the Indian Institute of Technology Delhi for the award of the degree of* ***Doctor of Philosophy,*** *is a record of original research work carried out by him. He has worked under our guidance and supervision to fulfill the requirements for submitting the thesis to our knowledge and reaching the requisite standard.*

To the best of my knowledge, the results embodied in this thesis are original and have not been submitted, in part or full, to any other University or Institute for the award of any other Degree or Diploma.

Prof. Naresh Bhatnagar,
Department of Mechanical Engineering,
Indian Institute of Technology Delhi,
Hauz Khas, New Delhi-110016, India

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Abstract

All bioresorbable polymeric implants are radiolucent, making them undetectable under the X-rays. The high atomic number (at. no.) elements such as Pt, Au, Ta, Ba, or its alloy are attached to a body of bioresorbable polymeric implant to improve their X-ray visibility. However, during the *In Vivo* degradation, these bioinert heavy metals can either detach or leach out from the lesion site and can get accumulated into a vital organ, leading to severe health complications. A novel biodegradable and radiopaque Mg alloy was produced in this research to impart radiopacity to a known biopolymer. Here, Mg metal was alloyed with an optimized ratio of high atomic number elements of Zn and Y, to achieve enough radiographic visibility. The biodegradable radiopaque Mg-Zn-Y alloy contains three phases α-Mg, binary phase Mg_7Zn_3 and Icosahedral (I-phase) Mg_3Zn_6Y precipitated in the inter-dendritic region of α-Mg. The thermally stable intermetallic I-phase particles reinforce the Mg alloy to form in-situ composites.

Mg alloy was powdered and blended in different ratios with bioresorbable Poly-L-lactic acid (PLLA) by using a solvent casting method. The studies were carried out to evaluate the optimum quantity of Mg alloy required in PLLA to achieve not only desirable physicomechanical properties but also radiopacity. The X-ray linear attenuation coefficient (μ) and optical density (OD) were measured from the biocomposite radiographs. Thermal analysis revealed that Mg alloy microparticles acted as a nucleating site and further enhanced the crystallinity of the polymer.

The Mg alloy was further blended in a twin extruder with radiolucent PLLA and Polycaprolactone (PCL) polymer for a comparative study. The bi-axially expanded (BAE) tubes of PLLA/PCL and PLLA/PCL/Mg alloy were extruded for fabricating cardiovascular stents. The potential of 5% Mg alloy microparticles was found to be reinforcing as well as

acting as a radiopaque agent. *In Vitro* cell adhesion and blood compatibility studies were assessed by evaluating the proliferation of L929 fibroblasts and platelets, respectively on the developed blends to ensure complete cytocompatibility.

Furthermore, PLLA/PCL and PLLA/PCL/Mg alloy tubes were smoothly cut to stents. The crimping load, recoil, foreshortening, cyclic loading and unloading were estimated for comparative studies. The proposed biocomposite material thus can improve radiocontrast with enhanced mechanical properties as required for future BVS.

सार

सभी बायोरेसोरेबल पॉलीमरिक इम्प्लांट रेडिओलुकेंट होते हैं, जो उन्हें एक्स-रे के तहत पता लगाने योग्य नहीं बनाते हैं। उच्च परमाणु संख्या (संख्या में) तत्व जैसे कि Pt, Au, Ta, Ba, या इसके मिश्र धातु को उनके एक्स-रे दृश्यता में सुधार करने के लिए बायोरसोर्बेबल पॉलीमेरिक इम्प्लांट के शरीर से जोड़ा जाता है। हालांकि, इन विवो डिग्रेडेशन के दौरान, ये बायोइनर्ट हेवी मेटल या तो अलग हो सकते हैं या घाव वाली जगह से निकल सकते हैं और एक महत्वपूर्ण अंग में जमा हो सकते हैं, जिससे गंभीर स्वास्थ्य जटिलताएं हो सकती हैं। एक ज्ञात बायोपॉलिमर को रेडियोपेसिटी प्रदान करने के लिए इस शोध में एक उपन्यास बायोडिग्रेडेबल और रेडियोपैक एमजी मिश्र धातु का उत्पादन किया गया था। यहाँ, पर्याप्त रेडियोग्राफिक दृश्यता प्राप्त करने के लिए, Zn और Y के उच्च परमाणु संख्या तत्वों के अनुकूलित अनुपात के साथ Mg धातु को मिश्रित किया गया था। बायोडिग्रेडेबल रेडियोपैक Mg-Zn-Y मिश्र धातु में तीन चरण α-Mg, बाइनरी चरण Mg_7Zn_3 और Icosahedral (I-चरण) Mg_3Zn_6Y α-Mg के अंतर-वृक्ष क्षेत्र में अवक्षेपित होते हैं। ऊष्मीय रूप से स्थिर इंटरमेटेलिक I-चरण के कण इन-सीटू कंपोजिट बनाने के लिए Mg मिश्र धातु को सुदृढ़ करते हैं।

सॉल्वेंट कास्टिंग विधि का उपयोग करके Mg मिश्र धातु को अलग-अलग अनुपात में बायोरेसोरेबल पॉली-एल-लैक्टिक एसिड (PLLA) के साथ मिश्रित किया गया था। न केवल वांछनीय भौतिक-यांत्रिक गुण बल्कि रेडियोपेसिटी भी प्राप्त करने के लिए पीएलएलए में आवश्यक

एमजी मिश्र धातु की इष्टतम मात्रा का मूल्यांकन करने के लिए अध्ययन किए गए थे। एक्स-रे रैखिक क्षीणन गुणांक (μ) और ऑप्टिकल घनत्व (OD) को बायोकोम्पोसिट रेडियोग्राफ़ से मापा गया। थर्मल विश्लेषण से पता चला है कि Mg मिश्र धातु के माइक्रोपार्टिकल्स ने एक न्यूक्लियेटिंग साइट के रूप में काम किया और बहुलक के क्रिस्टलीयता को और बढ़ाया।

एक तुलनात्मक अध्ययन के लिए Mg मिश्रधातु को रेडिओलुकेंट PLLA और पॉलीकैप्रोलैक्टोन (PCL) पॉलीमर के साथ एक जुड़वां एक्सट्रूडर में मिश्रित किया गया था। कार्डियोवास्कुलर स्टेंट बनाने के लिए PLLA/PCL और PLLA/PCL/Mg Alloy की द्वि-अक्षीय रूप से विस्तारित (बीएई) ट्यूबों को एक्सट्रूड किया गया था। 5% Mg अलॉय माइक्रोपार्टिकल्स की क्षमता प्रबल होने के साथ-साथ रेडियोपैक एजेंट के रूप में कार्य करने वाली पाई गई। विट्रो सेल आसंजन और रक्त संगतता अध्ययनों में विकसित मिश्रणों पर क्रमशः L929 फाइब्रोब्लास्ट्स और प्लेटलेट्स के प्रसार का मूल्यांकन करके पूर्ण साइटोकम्पैटिबिलिटी सुनिश्चित करने के लिए मूल्यांकन किया गया था।

इसके अलावा, PLLA/PCL और PLLA/PCL/Mg अलॉय ट्यूब को स्टेंट में आसानी से काटा गया। तुलनात्मक अध्ययन के लिए क्रिम्पिंग लोड, रिकॉइल, फोरशॉर्टिंग, चक्रीय लोडिंग और अनलोडिंग का अनुमान लगाया गया था। प्रस्तावित बायोकोम्पोसिट सामग्री इस प्रकार भविष्य के बीवीएस के लिए आवश्यक उन्नत यांत्रिक गुणों के साथ रेडियोकॉन्ट्रास्ट में सुधार कर सकती है।

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BAE: Bi-axially Expanded

BRM: Biodegradable Radiopaque Material

BRS: Bioresorbable radiopaque Stent

BVS: Bioabsorbable Vascular Stent

CAD: Coronary Artery Disease

CVD: Cardiovascular diseases

DCM: Dichloromethane

DES: Drug-eluting stent

D_r: Degradation rate

DSC: Differential scanning calorimetry

DTA: Differential Thermal Analysis

d_c^a & d_e^a: Diameter of a stent after crimping and expansion, respectively

d_e: Expanded Stent diameter

EDS: Energy dispersive spectrometer

ELISA: Enzyme-linked immunoassay kit

ε_c^p: Plastic strain of composite, ε_P^p: Plastic strain of polymer

e^-: Electron, eV: Electron volt

FTIR: Fourier Transform Infrared Spectroscopy

HU: Hounsfield Number

H: Hemolysis

H Frg: Human Fibrinogen

HT & HTAT: Thrombin & Human Thrombin Anti-Thrombin, respectively

I_o: Incident X-ray beam intensity, I_s: Transmitted X-ray beam intensity

K_α & K_β: vacancy in the K shell filled by an electron from the L & M shell, respectively

MRI: Magnetic resonance imaging

MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide

OD: Optical Density

PBS: Phosphate buffer saline

PCI: Percutaneous coronary intervention

PCL: Polycaprolactone

PLLA: Poly-L-lactide

PPP & PRP: Platelet-Poor Plasma & Platelet-Rich Plasma

R_a & R_p: Average and Peak surface roughness

RM: Radiopaque Material

SEM: Scanning electron microscope

TGA: Thermal gravimetric analysis

T_g & T_m: Glass Transition temperature & Melting Point, respectively

U_C^d & U_P^d: Stain energy dissipated in composite & Polymer, respectively

XRD: X-ray Diffraction

UV: Ultraviolet Rays

$Z_{eff.}$: Effective Atomic Number

λ & λ': Wavelength of Incident & Transmitted X-ray

ɵ: Contact Angle

α: Primary Phase

ω: Weight Fraction

μ: Linear Attenuation coefficient

μCT: Micro Computed Tomography

$\boldsymbol{\chi}_c$: Degree of Crystallinity