EXPERIMENTAL INVESTIGATIONS INTO 4D PRINTING OF SHAPE MEMORY POLYMER COMPOSITE FOR BIOMEDICAL APPLICATIONS

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by

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Submitted

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Dedicated

to

My Daughter

“AARYA”

Certificate

This is to certify that the thesis entitled **'Experimental investigations into 4D printing of shape memory polymer composite for biomedical applications'** submitted by **Ms. Garima Dixit** to the Indian Institute of Technology Delhi, for the award of the degree of ***Doctor of Philosophy*** is a record of the original bonafide research work carried out by him under my guidance and supervision. The results contained in it have not been submitted in part or full to any other institute or university for the award of any degree/diploma.

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(Garima Dixit)

Abstract

Four-dimensional (4D) printing provides a route for the incorporation of transformation information into 3D-printed structures which allows them to change shape, characteristics, or functionality with time. 4D printing includes 3-dimensional (3D) printing technology as well as smart materials such as shape-memory polymers (SMPs), and shape-memory polymer composites (SMPCs) along with some stimulants such as heat, temperature, etc. SMPs and SMPCs are increasingly being utilized in 4D printing and have gained popularity for their distinctive ability to change shape in response to external stimuli. These materials have a wide range of applications across several industries. Although SMPs have notable benefits when used in conjunction with 4D printing, their potential in 4D printing has only been partially investigated. Moreover, when it comes to biomedical applications 4D printing is an emerging technology that has a wide potential to be used in the development of smart implants and organs which can result in minimally invasive surgery. Hence, the objective of this study was to investigate and enhance the domain of 4D printing technology through the development and optimization of SMPCs for use in biomedical applications. The study also sought to create a structure for the future advancement of 4D-printed biomedical smart devices by comprehending the connection between the design, material characteristics, and effectiveness of SMPCs. To achieve that goal the SMPC system was developed by utilizing polylactic acid (PLA) and bioactive glass (BG) which can be further used for 4D printing for the development of some smart biomedical implants and devices. Due to its ability to undergo hydrolysis breakdown and bio-resorption, PLA is widely used in several biomedical applications. In this study, a range of 0 - 2 $wt\%$ of BG microparticles was incorporated into the PLA matrix. The composite mixture obtained was subsequently introduced into a solvent-cast 3D printing (SC3DP) setup to fabricate composites through a layer-by-layer manufacturing process. Based on the physiochemical analysis, it was shown that the BG particles were uniformly distributed

within the polymer matrix, leading to the formation of strong interfacial bonds between them. Mechanical properties were evaluated by examining the tensile and flexural behavior of the composites. According to the findings of the mechanical testing, the PLA/BG composites demonstrated qualities suitable for use in bioimplants. The cytocompatibility of all the composites was assessed by in vitro cellular assays. According to the findings, the materials that were developed were biocompatible, had a lower hemolysis rate, and possessed non-thrombogenic features, which indicated that they had the potential to be utilized in the field of biomedical implants.

Further investigation was conducted to analyze the impact of BG on the thermal and shape-memory properties of composites. It was hypothesized that the incorporation of reinforcement might potentially alter the SMPs in order to improve their thermal as well as shape memory qualities. Several kinds of bioceramics have already been employed to modify the thermal and shape memory characteristics of SMPs. Nevertheless, the utilization of BG as a filler to alter these qualities has not yet been investigated. Hence the developed composites were examined for the thermal and shape memory properties of PLA/BG composites. It was observed that the presence of BG altered the glass transition and melting temperature of the composites and increased the crystallinity. However, the presence of BG resulted in the reduced thermal stability of the composites. Better crystallinity and viscoelastic qualities of PLA/BG composites resulted in enhanced shape memory attributes, such as shape fixity and shape recovery. In the last, 4D printed structures demonstrated good shape fixity and recovery behavior under the influence of thermal stimulus. The results of this study provided hope for the future of smart biomedical devices and self-foldable structure development by combining the created SMPCs with 4D printing technology.

Further study was conducted which aimed to minimize shrinkage and maximize strength as well as structural transition responsiveness for SMPCs with the help of the central composite

design (CCD) approach commonly referred to as response surface methodology (RSM). It is very necessary to develop statistical models that can relate the effect of different process parameters with the different responses of the developed composites. SMPCs were made by blending PLA in a suitable solvent, reinforcing with 45S5 BG, and printing parts using SC3DP. Three different factors infill density, printing speed, and BG concentration with three different levels were considered for the study. The results revealed that increasing printing speed caused the component to shrink more, whilst increasing the infill density and BG concentration reduced the amount of shrinkage. An increase in infill density and BG concentration led to greater ultimate tensile strength but an increase in printing speed led to lower values of strength. At last, it was found that shape recovery of the printed components declined with increasing infill density and printing speed, but it improved with increasing BG concentrations. The model was validated by conducting confirmation tests using the best possible combination of parameters for the process, as determined utilizing the genetic algorithm multi-objective optimization method. different structures were 4D printed by utilizing the optimum parameters and their shape-changing behaviour was also recorded.

To address the issue of stent-related thrombosis and in-stent restenosis, self-expandable biodegradable vascular stents were created using 4D printing and developed PLA/BG composite. The printed stents were capable of being crimped into a temporary form with a reduced diameter, which could make it easier to implant. The dimensional study demonstrated the deviation in dimensions from the CAD model and manufacturing precision. The mechanical properties of the stents were investigated by axial compression and three-point bending tests. The findings demonstrated that stents possessed sufficient mechanical characteristics to effectively carry out the essential functions within the human coronary system. With a significant fixity and recovery ratio of 85%, and 90%, the printed stent demonstrated shape memory capabilities and was able to retain its temporary shape while being stored at ambient

temperature. Finite element analysis was used to calculate the longitudinal contraction or radical expansion under operating conditions and compared with the ballon expanded vascular stent. In vitro biological testing showed that the stents were biocompatible, hemocompatible, and thrombosis-resistant. The integration of self-expansion and personalized 4D printing in the creation of vascular stents offers a promising alternative for the treatment of cardiovascular diseases. This approach has the potential to address the limitations of balloon angioplasty.

So, the current work contributed to filling the gap between various aspects of 4D printing by developing and optimizing the SMPCs for biomedical applications. The current work also concluded with an extensive understating of how to tailor the properties of SMPC for different end applications. The present study enhanced the application area of 4D printing by creating smart biomedical devices that can be triggered by external stimuli inside the human body touching a new horizon beyond the static nature of biomedical implants and devices.

सार

चार-आयामी (4D) प्रिंटिंग 3D प्रिंटिंग संरचनाओं में परिवर्तन जानकारी को शामिल करने का मार्ग प्रदान करती है जो उन्हें समय के साथ आकार, विशेषताओं या कार्यक्षमता को बदलने की अनुमति देती है। 4D प्रिंटिंग में 3D प्रिंटिंग तकनीक के साथ-साथ स्मार्ट सामग्री जैसे शेप-मेमोरी पॉलिमर, शेप-मेमोरी पॉलिमर कंपोजिट के साथ-साथ कुछ उत्तेजक जैसे गर्मी, तापमान आदि शामिल हैं। शेप मेमोरी पॉलिमर (SMPs) और उनके कंपोजिट (SMPCs) लोकप्रिय सामग्रियों के रूप में उभरे हैं जिनका उपयोग 4D प्रिंटिंग में किया जा सकता है और बाहरी उत्तेजनाओं के जवाब में आकार बदलने वाले व्यवहार के अपने अनूठे गुणों के कारण विभिन्न उद्योगों में कई अनुप्रयोग प्रदान करते हैं। 4D प्रिंटिंग तकनीक के साथ संयुक्त होने पर शेप-मेमोरी पॉलिमर (SMPC) के महत्वपूर्ण लाभों के बावजूद, 4D प्रिंटिंग में उनकी क्षमता का केवल एक सीमित सीमा तक ही पता लगाया गया है। इसके अलावा, जब बायोमेडिकल अनुप्रयोगों की बात आती है तो 4D प्रिंटिंग एक उभरती हुई तकनीक है जिसका उपयोग स्मार्ट प्रत्यारोपण और अंगों के विकास में किया जा सकता है, जिसके परिणामस्वरूप न्यूनतम न्यूनतम इन्वेसिव शल्य – चिकित्सा हो सकती है। इसलिए, इस काम ने पॉलीलैक्टिक एसिड (PLA) और बायोएक्टिव ग्लास (BG) का उपयोग करके एक SMPC प्रणाली विकसित की, जिसका उपयोग आगे कुछ स्मार्ट बायोमेडिकल इम्प्लांट्स और उपकरणों के विकास के लिए 4D प्रिंटिंग के साथ किया जा सकता है। हाइड्रोलिसिस ब्रेकडाउन और अपने उत्पादों के जैव-अवशोषण की पेशकश के लाभ के

साथ, PLA कई जैव चिकित्सा अनुप्रयोगों के लिए सबसे अधिक उपयोग किए जाने वाले पॉलिमरों में से एक है। इसके लिए सबसे पहले, PLA/BG के कंपोजिट का उत्पादन विलायक-कास्ट त्रि-आयामी मुद्रण (SC3DP) प्रक्रिया को नियोजित करके किया गया था। इसे पूरा करने के लिए, 0-2 wt% BG कणों (आकार $\leq 2\mu m$) को PLA में सुदृढ़ किया गया था। परिणामस्वरूप मिश्रित मिश्रण को तब कंपोजिट के परत-दर-परत निर्माण के लिए एक SC3DP में डाला गया था। विकसित यौगिकों को पहले भौतिक रासायनिक गुणों, यांत्रिक और जैविक गुणों के लिए चिह्नित किया गया था। फिजियोकेमिकल जांच के अनुसार, BG कण पूरे पॉलिमर मैट्रिक्स में समान रूप से बिखरे हुए थे, जिसके परिणामस्वरूप उनके बीच अंतरफलक बंधन हुआ। फिजियोकेमिकल जांच से पता चला कि PLA और BG रासायनिक रूप से परस्पर क्रिया नहीं करे थे। यौगिकों के तन्यता और लचीले व्यवहार की जांच करके यांत्रिक गुणों का मूल्यांकन किया गया। यांत्रिक परीक्षण के निष्कर्षों के अनुसार, PLA/BG कंपोजिट ने जैव प्रत्यारोपण में उपयोग के लिए उपयुक्त गुणों का प्रदर्शन किया।. इन विट्रो सेलुलर परीक्षणों द्वारा साइटोकोम्पेटिबिलिटी के लिए सभी कंपोजिट का मूल्यांकन किया गया था। निष्कर्षों के अनुसार, विकसित की गई सामग्री जैव-संगत थी, हेमोलिसिस दर कम थी, और इसमें गैर-थ्रोम्बोजेनिक विशेषताएं थीं, जिसने संकेत दिया कि उनमें जैव चिकित्सा प्रत्यारोपण के क्षेत्र में उपयोग किए जाने की क्षमता थी।

कम्पोजिट की तापीय और आकार-स्मृति क्षमताओं पर BG के प्रभाव की आगे जांच की गई। यह परिकल्पना की गई थी कि सुदृढीकरण का समावेश संभावित रूप से SMPs को उनके थर्मल और आकार स्मृति गुणों में सुधार करने के लिए बदल सकता है। विभिन्न प्रकार के बायोसेरामिक्स का उपयोग पहले से ही SMPs के थर्मल और आकार स्मृति व्यवहार को बदलने के लिए किया जा चुका है। हालांकि, इन गुणों को संशोधित करने के लिए पूरक के रूप में BG का उपयोग करने का अभी तक पता नहीं चला है। इसलिए PLA/BG यौगिकों के तापीय और आकार स्मृति गुणों के लिए विकसित यौगिकों की जांच की गई। यह देखा गया कि BG की उपस्थिति ने कंपोजिट के कांच का अवस्थांतर और पिघलने के तापमान को बदल दिया और क्रिस्टलीयता में वृद्धि की। हालांकि, BG की उपस्थिति के परिणामस्वरूप कंपोजिट की तापीय स्थिरता कम हो गई। PLA/BG यौगिकों की क्रिस्टलीयता और विस्कोइलास्टिक विशेषताओं की डिग्री में वृद्धि से आकार स्थिरता और आकार पुनर्प्राप्ति जैसे आकार स्मृति गुणों में सुधार हुआ। अंतिम 4D मुद्रित संरचनाओं में थर्मल उत्तेजना के प्रभाव में एक अच्छे आकार स्थिरता और पुनर्प्राप्ति व्यवहार का प्रदर्शन किया गया। इन निष्कर्षों ने भविष्य में स्व-मोड़ने योग्य संरचनाओं और स्मार्ट जैव चिकित्सा उपकरणों के लिए जटिल आकार विकसित करने के लिए 4D प्रिंटिंग तकनीक के साथ विकसित SMPC का उपयोग करने की क्षमता का सुझाव दिया।

आगे का अध्ययन किया गया जिसका उद्देश्य प्रतिक्रिया सतह पद्धति (RSM) की मदद से SMPCs के लिए संकोचन को कम करना, शक्ति को अधिकतम करना और संरचनात्मक संक्रमण प्रतिक्रियाशीलता को कम करना था। सांख्यिकीय मॉडल विकसित करना बहुत आवश्यक है जो

विभिन्न प्रक्रिया मापदंडों के प्रभाव को विकसित कंपोजिट की विभिन्न प्रतिक्रियाओं से संबंधित कर सके। SMPCs को एक उपयुक्त विलायक में PLA को मिलाकर, 45S5 BG पार्टिकल्स के साथ सुदृढ़ीकरण और SC3DP का उपयोग करके मुद्रण भागों द्वारा बनाया गया था। अध्ययन के लिए तीन अलग-अलग स्तरों के साथ तीन अलग-अलग कारकों-भराव घनत्व, मुद्रण की गति और BG सांद्रता पर विचार किया गया। परिणामों से पता चला कि बढ़ती मुद्रण गति के कारण घटक अधिक सिकुड़ गया, जबकि भराव घनत्व और BG सांद्रता में वृद्धि ने सिकुड़न की मात्रा को कम कर दिया। इनफिल घनत्व और BG सांद्रता में वृद्धि ने अधिक अंतिम तन्यता शक्ति को जन्म दिया, लेकिन मुद्रण गति में वृद्धि ने शक्ति के कम मूल्यों को जन्म दिया। अंत में, यह पाया गया कि मुद्रित घटकों की आकार वसूली में बढ़ती भराव घनत्व और मुद्रण गति के साथ गिरावट आई, लेकिन बढ़ती BG सांद्रता के साथ इसमें सुधार हुआ। आनुवंशिक एल्गोरिदम बहु-उद्देश्य अनुकूलन विधि का उपयोग करके निर्धारित प्रक्रिया के लिए मापदंडों के सर्वोत्तम संभव संयोजन का उपयोग करके पुष्टि परीक्षण आयोजित करके मॉडल को मान्य किया गया था। विभिन्न संरचनाओं को इष्टतम मापदंडों का उपयोग करके 4D मुद्रित किया गया था और उनके आकार बदलने वाले व्यवहार को भी दर्ज किया गया था।

स्टेंट से संबंधित थ्रोम्बोसिस और इन-स्टेंट रेस्टिनोसिस के मुद्दे को संबोधित करने के लिए, 4D प्रिंटिंग और विकसित PLA/BG कम्पोजिट का उपयोग करके स्व-विस्तार योग्य बायोडिग्रेडेबल वैस्कुलर स्टेंट बनाए गए थे। मुद्रित स्टेंट कम व्यास के साथ एक अस्थायी रूप में सिकुड़ने में सक्षम थे, जिससे प्रत्यारोपण करना आसान हो सकता था। आयामी अध्ययन ने CAD मॉडल और विनिर्माण परिशुद्धता

से आयामों में विचलन का प्रदर्शन किया। स्टेंट के यांत्रिक गुणों की जांच अक्षीय संपीड़न और तीन-बिंदु झुकने वाले परीक्षणों द्वारा की गई थी। निष्कर्षों से पता चला कि स्टेंट में मानव कोरोनरी प्रणाली के भीतर आवश्यक कार्यों को प्रभावी ढंग से करने के लिए पर्याप्त यांत्रिक विशेषताएं थीं। 85% और 90% की महत्वपूर्ण स्थिरता और वसूली अनुपात के साथ, मुद्रित स्टेंट ने आकार स्मृति क्षमताओं का प्रदर्शन किया और परिवेश के तापमान पर संग्रहीत होने के दौरान अपने अस्थायी आकार को बनाए रखने में सक्षम था। परिमित तत्व विश्लेषण का उपयोग प्रचालन स्थितियों के तहत अनुदैर्ध्य संकुचन या कट्टरपंथी विस्तार की गणना करने के लिए किया गया था और गुब्बारे द्वारा विस्तारित संवहनी स्टेंट के साथ तुलना की गई थी। इन विट्रो जैविक परीक्षण से पता चला कि स्टेंट बायोकॉम्पैटिबल, हीमोकॉम्पैटिबल और थ्रोम्बोसिस प्रतिरोधी थे। संवहनी स्टेंट के निर्माण में स्व-विस्तार और व्यक्तिगत 4D प्रिंटिंग का एकीकरण हृदय रोगों के उपचार के लिए एक आशाजनक विकल्प प्रदान करता है। इस दृष्टिकोण में गुब्बारे की एंजियोप्लास्टी की सीमाओं को दूर करने की क्षमता है।

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Abbreviations

3D	3-Dimensional
4D	4-Dimensional
AFM	Atomic Force Microscopy
ALP	Alkaline Phosphatase
AM	Additive Manufacturing
ANOVA	Analysis of Variance
ASTM	American Society for Testing and Materials
BDS	Biodegradable Stents
BG	Bioactive Glass
BSA	Bovine Serum Albumin
BSMP	Biodegradable Shape Memory Polymers
CCD	Central Composite Design
CN	Carbon Nanotubes
CS	Chitosan
DC	Direct Current
DCM	Dichloromethane
DD	Dimensional Deviation
DIW	Direct Ink Writing
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl Sulfoxide
DSC	Differential Scanning Calorimetry
DMA	Dynamic Mechanical Analyzer
EDX	Energy-Dispersive X-Ray Spectroscopy

FBS	Fetal Bovine Serum
FDM	Fused Deposition Modelling
FFF	Fused Filament Fabrication
FITC	Fluorescein Isothiocyanate
FTIR	Fourier Transform Infrared Spectroscopy.
GNPs	Graphene Nano Palettes
HAp	Hydroxyapatite
HDI	Hexamethylene Di Isocyanate
HPED	N, N, N', N'-tetrakis(2-hydroxypropyl) Ethylene Diamine
ISO	International Organization for Standardization
ISR	In-Stent Restenosis
MNP	Magnetic Fe_3O_4 Nanoparticles
MTT	3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide
PBG	Polylactic Acid and Bioactive glass Blend
PBS	Phosphate Buffer Saline
PCL	Poly E-Caprolactone
PCL-TES	Polycaprolactone-Triethoxysilane
PCL-b-ODX	Poly E-Caprolactone- (oligo(p-dioxanone) diol)
PDLLA	Poly-D, L-Lactide
PE	Polyethylene
PEG	Polyethylene glycol
PE/PP	Polyethylene/Polypropylene
PLA	Polylactic Acid
PLA/BG	Polylactic Acid/Bioactive Glass Blend
PLLA	Poly-L-Lactic Acid

PHAs	Polyhydroxyalkanoates
PRP	Platelet-Rich Plasma
PVDF/PMMA	Polyvinylidene fluoride/ Polymethyl Methacrylate
RR	Recovery Ratio
RSM	Response Surface Methodology
SC3DP	Solvent Cast 3D Printing
SD	Standard Deviation
SEM	Scanning Electron Microscopy
SH	Shrinkage
SLA	Stereolithography
SLM	Selective Laser Melting
SMAs	Shape Memory Alloys
SMEs	Shape Memory Effects
SMPs	Shape Memory Polymers
SMPCs	Shape memory Polymer Composites
TBCP	Tri Block Co Polymer
TGA	Thermogravimetric Analysis
TPU	Thermoplastic Polyurethane
TRITC	Tetramethylrhodamine
UTM	Universal Testing Machine
UTS	Ultimate Tensile Strength
UV	Ultraviolet
XRD	X-Ray Diffraction

Nomenclature

T_g	Glass transition temperature
T_m	Melting temperature
T_{trans}	Transition temperature
T_c	Crystallization temperature
σ_F	Flexural strength
M_F	Flexural modulus
ΔH_m	Heat of fusion
ΔH_m^*	Heat of fusion for 100% crystalline PLA
X_c	Crystallinity
w	Mass fraction of PLA in PLA/BG composites
$\in_d$	Maximum strain
$\in_f$	Fixed strain
$\in_r$	Recovered strain
R_f	Shape fixity ratio
R_r	Shape recovery ratio
$T_{1\%}$	1% degradation onset temperature
T_O	Degradation onset temperature
T_D	Degradation temperature
E'	Storage modulus
$\tan\delta$	Damping parameter
$\hat{R}$	Response term

ϵ	Random error
β	Regression coefficients
L_r	Radial compressive load
L_f	Flexural bending load
W	Weight of stents