Study of Polymer based Optimum Blend Compositions for Multifunctional Coatings of Drug Eluting Stents (DES) with Optimized Biodegradability and Biocompatibility

By

Areesha Kainat

(Registration No: 00000401672)

Department of Materials Engineering

School of Chemical and Materials Engineering

National University of Sciences and Technology (NUST)

Islamabad, Pakistan

(2024)

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Areesha Kaiant

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This thesis is submitted to the National University of Sciences and Technology, Islamabad, in partial fulfillment of the requirements for the degree of

Masters of Science in
Nanoscience and Engineering

Supervisor: Dr. Nasir Mehmood Ahmed

Co Supervisor: Dr. Nauman Naseer

School of Chemical and Materials Engineering

National University of Sciences and Technology (NUST)

Islamabad, Pakistan

October 2024

THESIS ACCEPTANCE CERTIFICATE

Certified that final copy of MS Thesis entitled **"Study of Polymer based Optimum Blend Compositions for Multifunctional Coatings of Drug Eluting Stents with Optimezed Biodegradability and Biocompatibility"** written by Ms Areesha Kainat (Registration No 00000401672), of School of Chemical & Materials Engineering (SCME) has been vetted by undersigned, found complete in all respects as per NUST Statues/Regulations, is free of plagiarism, errors, and mistakes and is accepted as partial fulfillment for award of MS degree. It is further certified that necessary amendments as pointed out by GEC members of the scholar have also been incorporated in the said thesis.

Signature: _____

Name of Supervisor: Dr Nasir M. Ahmed

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Signature (HOD): _____

Date: 28-11-24

Signature (Dean/Principal): _____

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MASTER'S THESIS WORK

Formulation of Guidance and Examination Committee (GEC)

Name: Areesha Kainat
Department: Department of Materials Engineering
NUST Reg No: 00000401672
Specialization: Master of Science in Nanoscience and Engineering
CGPA: 3.31
Credit Hour Completed: 24.0

Course Work Completed

S/No:	Code:	Title:	Core/Elective:	CH:	Grade:
1.	NSE-813	Essentials of Nanoscience and Engineering	Compulsory	3.0	B+
2.	MSE-854	Characterization Of Materials	Compulsory	3.0	B
3.	RM-898	Research Methodology	Additional	2.0	Q
4.	NSE-842	Nano Materials For Energy Applications	Elective	3.0	B+
5.	MSE-856	Nano Material and Processing	Compulsory	3.0	B
6.	NSE-812	Environmental Nanotechnology	Elective	3.0	A
7.	MSE-952	Materials For Biomedical Applications	Elective	3.0	B
8.	NSE-941	Nano Composite Materials	Elective	3.0	B
9.	CHE-815	Nano Catalysis	Elective	3.0	B+

Date: 23 - Jan - 2024

Student's Signature: [redacted]

Thesis Committee

1. Name: Nasir Mahmood Ahmad (Supervisor)
   Department: Department of Materials Engineering
   Signature:
2. Name: Muhammad Shoaib Butt (Internal)
   Department: Department of Materials Engineering
   Signature:
3. Name: Asad Ullah Khan (Internal)
   Department: Department of Chemical Engineering
   Signature:
4. Name: Nauman Naseer (External)
   Date: 23 - Jan - 2024

Signature of Head of Department:

APPROVAL

Date: 23 - Jan - 2024

Signature of Dean/Principal:

National University of Sciences &Technology (NUST)

FORM TH-4

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We hereby recommend that the dissertation prepared under our supervision by

Regn No & Name: 00000401672 Areesha Kainat

Title: Study of Polymer based Optimum Blend Compositions for Multifunctional Coatings of Drug Eluting Stents with Optimized Biodegradability and Biocompatibility.

Presented on: 07 Nov 2024 at: 1030 hrs in SCME

Be accepted in partial fulfillment of the requirements for the award of Masters of Science degree in Nanoscience & Engineering.

Guidance & Examination Committee Members

Name: Dr M. Shoaib Butt Signature:

Name: Dr Asad Ullah Khan Signature:

Name: Dr Nauman Naseer (Co-Supervisor) Signature:

Supervisor's Name: Dr Nasir M. Ahmed Signature:

Dated: 16th Nov. 2024.

Head of Department

Date 14-11-24

14-11-24

Date

COUNTERSIGNED

15/11/24

Dean/Principal

School of Chemical &Materials Engineering (SCME)

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DEDICATION

To my venerated parents

Malik Muhammad Akhtar Nawaz and Ghulam Sakina

This thesis is a testament to the values you have imparted to me — resilience, perseverance, and the pursuit of knowledge. Every page is infused with gratitude for the countless ways you have enriched my life and paved the way for my academic pursuits.

Mrs. Nadia Nauman

Thank you for consistently supporting my beliefs and providing encouragement by saying "I have confidence in your abilities, and I believe you will succeed.

ACKNOWLEDGEMENTS

In the name of Allah, the Most Gracious, the Most Merciful, I humbly begin by expressing my deepest gratitude to Allah Almighty, whose boundless wisdom and infinite guidance have been the cornerstone of my journey. It is through His blessings that I have found the strength and perseverance to undertake and complete this academic endeavor.

I extend my heartfelt thanks to my esteemed supervisor, Professor Dr. Nasir Ahmed, whose profound expertise, and unwavering support have been instrumental in shaping the direction and success of this research. His insightful guidance and constructive critiques have significantly contributed to the refinement of my work.

Equally deserving of my gratitude is my co-supervisor, Dr. Nauman Naseer. His invaluable input and encouragement have provided a solid foundation upon which this thesis has been built. Dr. Naseer’s dedication and commitment to excellence have been a continuous source of inspiration.

I am also deeply appreciative of the members of my Graduate Examination Committee, Dr. Shoaib Butt and Dr. Asad Ullah Khan. Their critical evaluations and thoughtful feedback have greatly enhanced the quality of my research. Their scholarly perspectives have broadened my understanding and enriched the academic rigor of this thesis.

A special note of thanks is reserved for Miss Nida Abid, my first-hand mentor. Her mentorship has been a guiding light throughout this journey. Her wisdom, patience, and encouragement have been invaluable, and her unwavering belief in my abilities has greatly contributed to my personal and academic growth.

To my siblings, whose constant support and understanding have been a source of immense comfort and motivation, I offer my sincerest appreciation. Their encouragement and sacrifices have been vital in enabling me to reach this milestone.

I acknowledge the support that the School of Material's Engineering, SCME NUST, has given me. It gives me great pleasure to express my gratitude to all engineers and laboratory professionals for their support and technical advice during my research project.

Lastly, I am profoundly grateful to all those who have contributed in various ways to my academic and personal development. Each act of kindness and support has played a crucial role in my success, and I am deeply thankful for the collective effort and generosity of everyone involved.

May Allah Almighty reward each of you abundantly and grant you continued success and prosperity.

-Areesha Kainat

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LIST OF ABBREVIATIONS, SYMBOLS, AND ACRONYMS

CAD	Coronary artery disease
PCL	Poly Caprolactone
CS	Chitosan
PB	Polymer Blends
DES	Drug eluting stents
BDS	Biodegradable stents
CHD	Coronary heart diseases

ABSTRACT

In the recent advancements in the field of coronary artery diseases, drug-eluting stents have gained a lot of recognition and significance due to their ability to play the vital roles in regulating problems like restenosis, vessel blockage, occlusion, etc. In this study, blends of Polycaprolactone (PCL) and Chitosan were prepared as the drug carriers in which the coronary stents were coated with bi-layer drug-loaded coatings. Entirely variant compositions of blends were prepared using an intense blend mixer. The compositions were hot pressed in composite press and cold pressed to prepare the sheets of different thickness. Different tests were performed to analyze the changes in weight loss, surface morphology and biodegradability using scanning electron microscopy (SEM), weight loss, and biodegradability tests. Thermal gravimetric chemical analysis and Fourier Transform Infrared Microscopy were also done for thermal and functional group analysis. In-vitro drug content analysis was performed to investigate the effects of PCL, Chitosan, and the drug using UV-Vis chemical analysis technique. The outcomes unequivocally demonstrated that while the promotion of Chitosan almost completely failed to promote the drug release, the addition of PCL did. The composition of blend portions can be changed to modify the mechanical characteristics of these different films. When assessing the efficacy of bioresorbable drug-eluting stents, the variables driving the drug's release become a very important concern. Consequently, the chemical blends that are being employed may be useful drug carrier materials for coatings for drug-loaded tubing that can release drug in a very controlled and customizable way.

Keywords: cardiovascular diseases (CVD), coronary heart diseases (CHD), polymer blends, biodegradable and biocompatible, drug eluting stents

CHAPTER 1: INTRODUCTION:

1.1 Background of Coronary diseases

Coronary artery disease (CAD) is a prevalent form of cardiovascular illness. It impacts the primary blood vessels responsible for supplying blood to the heart, known as the coronary arteries. CAD is characterized by diminished blood circulation to the myocardium. Coronary artery disease is typically caused by the accumulation of lipids, cholesterol, and other chemicals in and on the walls of the arteries, a condition known as atherosclerosis. Plaque accumulation causes arterial narrowing.

Coronary artery disease typically manifests gradually over an extended period of time. The symptoms arise due to insufficient blood circulation to the heart. Common symptoms of this condition may encompass chest pain and difficulty breathing. A total obstruction of blood circulation can lead to a myocardial infarction.

Therapeutic interventions for coronary artery disease may encompass pharmacological agents and surgical procedures. Adhering to a wholesome diet, engaging in consistent physical activity, and abstaining from smoking might effectively mitigate the risk of developing coronary artery disease and its associated ailments. Coronary artery disease is often referred to as coronary heart disease.

Coronary heart disease (CHD) is the primary cause of mortality in most developed nations and numerous developing nations. The clinical ramifications of coronary heart disease (CHD) result in significant impairment and serve as a primary contributor to the increasing expenses in healthcare. CHD incidence is declining in western Europe, the United States, and Australia, but it is sharply rising in central and eastern Europe, as well as to a certain extent in Asia and Africa. Globally, there is an immediate and pressing need for more efficient preventative measures against coronary heart disease (CHD) that cannot be delayed. In the past decade, significant knowledge has been acquired on preventative measures, encompassing both population-wide and individual-focused approaches. The International Task Force for Prevention of Coronary Heart Disease (CHD) has created a revised document that considers the outcomes of recent, significant studies focused on reducing lipid levels for both primary and secondary prevention of CHD. The assessment of the overall risk of coronary heart disease (CHD) is conducted using clinical and quantitative methods. These methods consider both traditional and recently identified risk factors, allowing for the determination of an acceptable level of intervention against these risk factors. This focused approach optimizes therapy.

Evaluating the risk of coronary heart disease (CHD) in a thorough and detailed manner is of utmost significance. The idea of "global risk" underscores the importance of considering all relevant independent risk variables when assessing a patient's cardiovascular risk profile. This approach aims to address each risk factor, especially hyperlipidemia and hypertension, within the broader context of overall risk. Hence, assessing global risk is crucial for defining the patient's prognosis, selecting the appropriate treatment, and establishing the target levels for reducing risk factors (such as serum cholesterol levels to be achieved at a specific risk level).

1.2 Stents:

Stents, which were initially introduced in 1977 by Grüntzig through the use of balloon angioplasty (BA), are a highly effective and favored alternative to surgery. Sigwart et al. reported the initial human implantation of a self-expanding stent in 1987 [2], while Palmaz et al. reported the first human implantation of a balloon-expandable stent in the same year [3]. Palmaz et al. further advanced this development [4]. Stents are typically cylindrical implants that offer structural support to narrow arteries or other non-vascular conduits until the possibility of full blockage is eliminated.

1.3 Types of Stents:

Stents can be classified into two categories: self-expanding and balloon-expandable [5]. Historically, stents were mostly composed of metals, until recently. Therefore, bare-metal stents are considered the initial iteration of stents. These metal frameworks consist of stainless steel and cobalt-chrome (CoCr) alloys for balloon-expandable stents and nickel-titanium alloys for self-expanding stents. Although it was seen as a moment of progress, the revolution was also seen as a moment of deterioration in the field [6]. The field of surgery has its own drawbacks, namely an elevated susceptibility to thrombosis and restenosis.

1.4 In-stent Restenosis (ISR):

In-stent restenosis (ISR) is very probable to result from intravascular damage that occur during stenting procedures. Ischemic restenosis (ISR) is the primary factor responsible for the gradual obstruction of arteries, leading to the eventual failure of stents due to the loss of arterial patency [7]. The loss of arterial patency is caused by cascade occurrences. Specifically, defective vascular endothelium immediately leads to the occurrence of in-stent restenosis (ISR). This occurs when there is a lack of anti-thrombic and anti-atherogenic properties [8]. The

malfunction of the artery in inhibiting the development of vascular smooth muscle cells (VSMCs) causes excessive growth of VSMCs towards the inside of the blood vessel, resulting in gradual obstruction over time [9]. According to previous research conducted by Fischman et al. in 1994, around 15-20 percent of patients who had stents implanted experienced the need for re-intervention within 6-12 months after the initial implantation due to in-stent restenosis (ISR) associated to bare-metal stents (BMS) [5]. All categories of stents have resolved this problem. Multiple varieties of bare metal stents (BMS) were manufactured in the subsequent decade. Implementing BMS significantly reduced the occurrence of abrupt arterial closure, while some restenosis still persisted. The restenosis rate for treated arteries decreased from 30% to 60% with balloon angioplasty to 10% to 30% with BMS [10]. The advent of drug-eluting stents (DES) marked the beginning of a new age. These stents, such as CypherTM (which releases sirolimus) and TaxusTM (which releases paclitaxel), utilize strong polymers to control the release of drugs. As a result, they have greatly lowered both angiographic and clinical restenosis levels compared to bare metal stents (BMS) [11]. The limitations associated with this revolutionary technology were quickly acknowledged, as is the case with many medical equipment and therapies. Restenosis remains common, and the occurrence of very-late stent thrombosis is more frequent with first-generation drug-eluting stents (DES) compared to bare-metal stents (BMS) due to incomplete healing and re-endothelialization [12].

1.5 Biodegradable/Biocompatible:

Several factors influence the process of re-endothelialization, which may be aided by robust polymer surface coatings [13]. DES programs typically seek to either use biodegradable polymers or drastically reduce the amount of polymer on the stent in order to lessen the artery's sensitivity to the polymer [14]. The active medication is carefully released from the stent backbone by the biodegradable polymer DES. This is accomplished by a biocompatible polymer coating that, after its useful life, gradually decomposes into innocuous organic monomers. This reduces the potential risks associated with having a durable polymer present on the surface of the coronary vessel over a long period of time [15]. Nevertheless, it is crucial to evaluate the possible advantages of biodegradable polymers through an extended period of observation [17].

CHAPTER 2: LITERATURE REVIEW

2.1 Coronary Artery Stents

Over the past two decades, significant advancements have occurred in the field of percutaneous coronary intervention (PCI), starting with the use of balloon angioplasty alone and progressing to the combination of balloon angioplasty and coronary stent implantation. The method was first documented in 1977 and entails inserting a catheter with a balloon tip into a narrowed section of the coronary artery, inflating the balloon, and then removing the catheter once the balloon is deflated. The widespread adoption of balloon angioplasty was initially hindered by two significant complications: the abrupt closure of blood vessels during or immediately after the procedure caused by blood clot formation or damage to the vessel, and the re-narrowing of the vessel due to a combination of the vessel's elastic recoil, the excessive growth of smooth muscle cells, and the thickening of the inner layer of the blood vessel. The advent of coronary stents has significantly reduced both consequences. Stents are placed over a balloon at the site of atheromatous lesions. The enhanced safety and effectiveness of percutaneous coronary intervention (PCI) has resulted in a significant increase in the number of operations being conducted. Currently, over 90% of all PCIs involve the insertion of at least one coronary stent. As a result, a growing subset of individuals with coronary artery disease (CAD) has the placement of a coronary stent and may later need to undergo non-cardiac surgery. The objective of this review is to analyze the challenges related to the perioperative care of patients who have coronary artery stents and provide a concise summary of the existing research, with a specific focus on the role of the anesthesiologist.

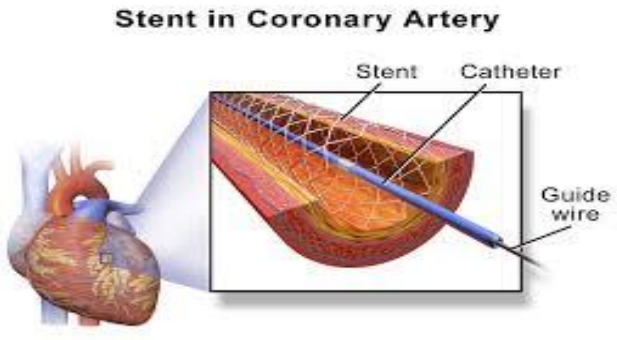


Figure 1: Stents in coronary Artery

2.2 Common Geometry and Design of Stents

Rings and connectors are arranged in a sequential fashion to insert stents. These hoops firmly interlock these chains of rings, providing radial reinforcement and connections to improve longitudinal stability. Large blood arteries usually have stent diameters between 2.5 and 3 mm. The following are some variations of commercial stent designs:

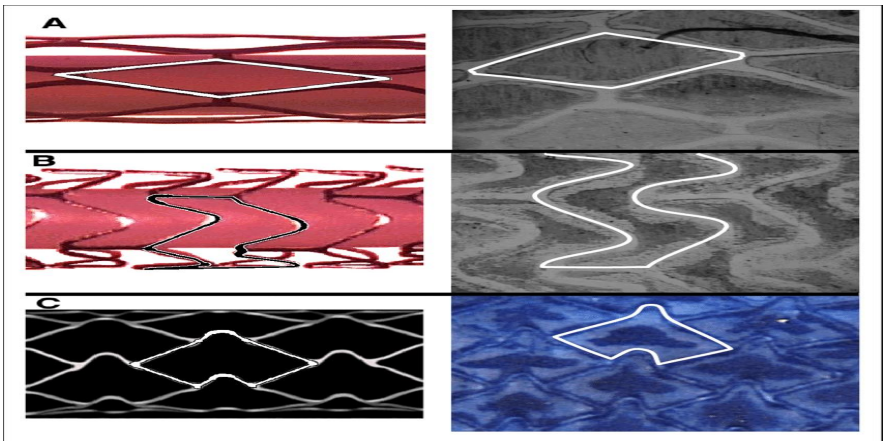


Figure 2: Commercial strut design

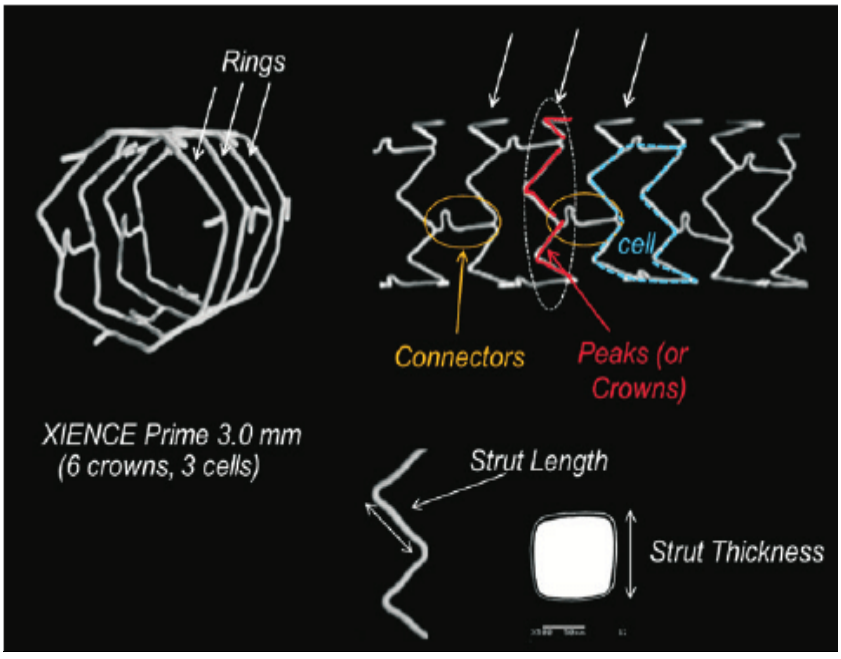


Figure 3: Formations of struts and thickness

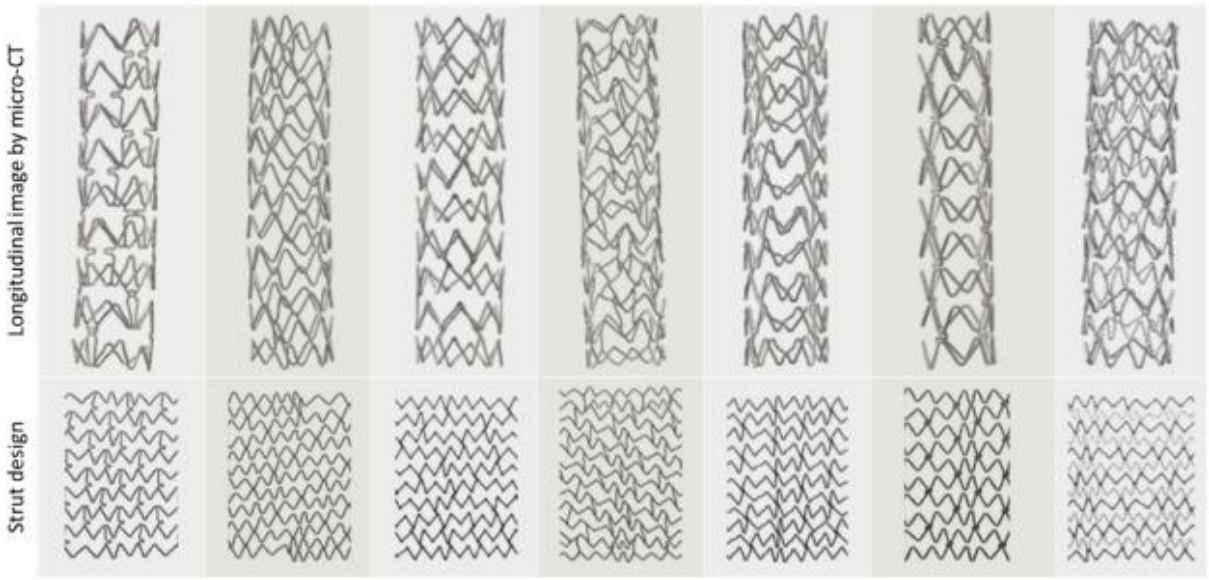


Figure 4: Various designs of struts with varied thickness

2.3 Requirements for efficient working of Strut Thickness

- Reducing the thickness of stent struts increases the flexibility of the devices and decreases the amount of space they occupy within blood vessels.
- The thickness of the strut limits the ability of blood to pass through the vessels and promotes a smooth and efficient flow.
- Recoiling must be avoided as it restricts the flow of blood in the vessels.

2.4 Characteristics of Stents

- Capable of being decomposed by natural processes, such as bacteria or other living organisms-Biodegradable
- Compatible with living organisms-Biocompatible
- Elasticity refers to the property of a material or substance to deform under the influence of an external force and then return to its original shape once the force is
- Stent expansion plasticity
- Highly resistant to rebound/recoiling
- Increased tensile strength
- Adaptability/Flexibility

- Enhanced pharmaceutical administration

2.5 Top Stent Manufacturers in Coronary Market

- Boston Scientific Corporation.
- Abbott Laboratories.
- Medtronic Plc.
- BIOTRONIK SE & Co. KG.
- Biosensors International Group Ltd.

2.6 Various stent materials

Stents can be classified into three types based on the deformation or condition of the material: absorbable, balloon-dilated, and self-expanding. The ability to undergo plastic deformation and maintain the required dimensions after deployment is a prerequisite for balloon-expandable stents [2]. For self-expanding stents to be able to be compressed for transportation and then expand in the intended area, they need to be sufficiently flexible. The following metals are frequently used to make stents: titanium (Ti), cobalt-chromium alloy (605L), tantalum (Ta), nitinol (Ni-Ti), platinum-iridium (Pt-Ir) alloy, and 316L stainless steel (316L SS). The fully biodegradable stent is considered the most ambitious and promising technique in the field of developing stents. The purpose is to offer a steady supportive force in the immediate period; the stent materials will gradually break down inside the body, making the biodegradable stent effective in reducing restenosis caused by vascular recoil, constrictive remodeling, and loose intimal dissection flaps [3]. The components of a biodegradable stent consist of an absorbable polymer and a degradable metal, specifically pure iron (Fe) and magnesium (Mg) alloys.

Polymer coatings are used to enhance biocompatibility and minimize the occurrence of nonspecific adsorption

The ongoing endeavor to find a material that possesses optimal surface qualities and necessary mechanical properties is particularly significant when it comes to materials used for cardiovascular stents. The present generation of stent materials often elicits many negative

responses, including inflammation, fibrosis, thrombosis, and infection. Most of these complications occur because of contact concerns between the surface of the stent and its immediate surroundings. Consequently, the primary emphasis of many research organizations is to alter the surface of materials while keeping the bulk qualities unchanged. Most polymeric materials inherently exhibit desirable bulk characteristics such as a high strength-to-weight ratio, outstanding resistance to corrosion, ease of processing and shaping, and great mechanical properties. Consequently, modifying the surface characteristics of existing polymers is the most pursued method. Several surface modification techniques have been intensively researched, leading to improved compatibility with blood by reducing either the occurrence of late-stage restenosis or acute thrombogenicity.

2.7 Polymeric material for stents

Various stents were employed in medical practice to alleviate obstructions caused by malignant strictures.

2.7.1 Properties of polymers:

Characteristics of matter that may be observed or measured without changing its chemical composition are referred to as physical properties.

Increasing the length of the polymer chain and the degree of cross-linking leads to an increase in the polymer's tensile strength.

Polymers do not undergo melting, but rather undergo a transition from a crystalline state to a semi-crystalline state.

Properties related to the behavior of substances in chemical reactions.

The polymer exhibits enhanced cross-linking strength due to the presence of hydrogen bonding and ionic bonding, in contrast to typical molecules with various side molecules.

The presence of dipole-dipole bonding side chains enhances the polymer's flexibility.

Polymers that are connected by Van der Waals interactions between chains are recognized for their inherent weakness, which results in a relatively low melting point for the polymer.

2.7.2 Polymer degradation:

The term "polymer degradation" describes how exposure to external factors like heat, light, chemicals, or applied force can change a polymer's properties, such as its tensile strength, color, shape, and molecular weight, or those of a product manufactured from the polymer.

2.8 Selection of Chitosan/PCL

2.8.1 Polycaprolactone (PCL)

Polycaprolactone (PCL) is a man-made, partially crystalline, biodegradable polyester that melts at approximately 60 °C and undergoes a glass transition at around -60 °C.
Polycaprolactone (PCL) is a man-made thermoplastic polyester that finds application in the field of biomedicine, specifically in the production of sutures and drug delivery devices. Although PCL has longer degradation durations compared to polylactides and polyglycolides, it has gained research interest in parallel with the advancement of tissue engineering.

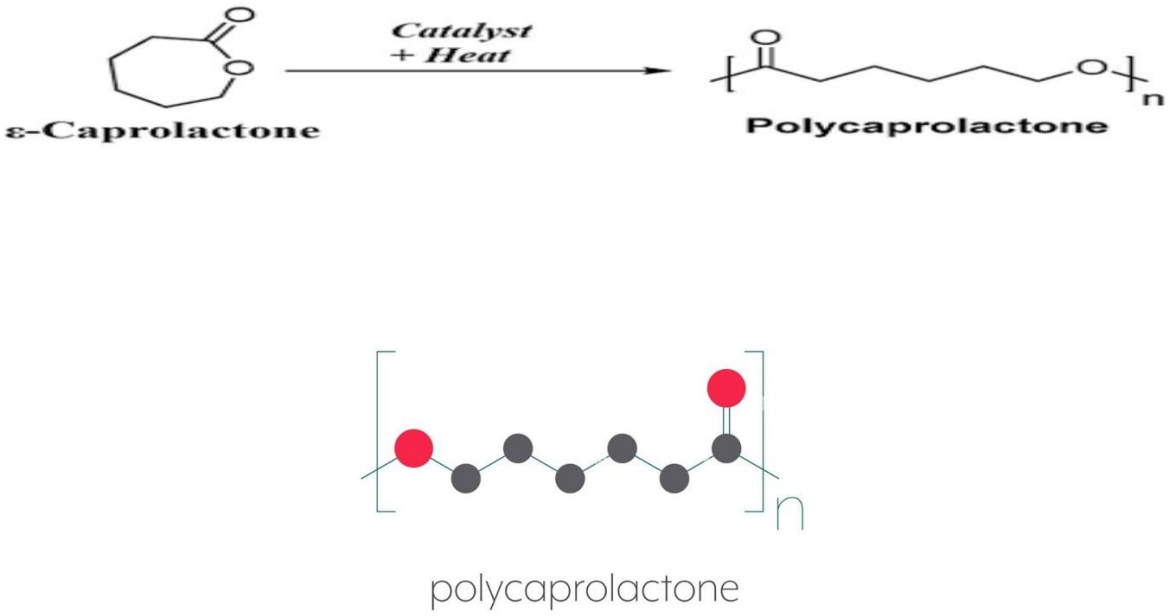


Figure 5: Chemical structure of Polycaprolactone

2.8.2 Chemical properties of PCL

- Biodegradable
- Biocompatible
- Hydrophobic
- Semicrystalline
- Low melting point
- Permeable
- Compatible with copolymers

Poly(ε-caprolactone) possesses numerous benefits, including biocompatibility, biodegradability, and simplicity of modification, which make it well-suited for a wide range of applications, including tissue engineering. PCL can undergo functionalization to attach polymer chains, hence broadening its potential uses in the biological domain.

2.8.3 Applications of PCL

The current expansion in the domain of cardiac tissue engineering holds the capacity to not only mitigate the subsequent consequences of damaged tissues on heart performance and lifespan, but also to reconstruct cardiac function by regenerating contractile tissue. An effective approach to achieve this is by the use of a cellularized patch that can be surgically inserted onto a damaged heart. An important aspect of this field involves utilizing tissue scaffolds to recreate the mechanical and structural conditions of the natural heart. This helps enhance the contractility and functionality of synthetic myocardium. The native heart's high mechanical capabilities and anisotropic structural organization are mostly due to a robust extracellular matrix. However, replicating this strength and structure in cultured tissues has proven challenging. Polycaprolactone (PCL) is a promising candidate for addressing these deficiencies in creating scaffolds that replicate the mechanical properties and structure of the natural heart. Poly(ε-caprolactone) (PCL) is currently being investigated as a scaffold in cardiovascular engineering for the purpose of regenerating the myocardium. This is due to its easy fabrication, favorable mechanical, chemical, and biocompatible characteristics, and most notably, its ability to degrade naturally. These properties make PCL a suitable material for restoring and enhancing heart function following disease or injury.

2.8.4 Chitosan

Chitosan is a polysaccharide made up of D-glucosamine and N-acetyl-D-glucosamine, which are connected in a linear manner through β-linkages. The process involves subjecting the chitin shells of shrimp and other crustaceans to an alkaline material, such as sodium hydroxide. It is utilized for medicinal purposes and in the production of pharmaceutical drugs. Chitosan is a fibrous material that has the potential to decrease the body's absorption of fat and cholesterol from diet.

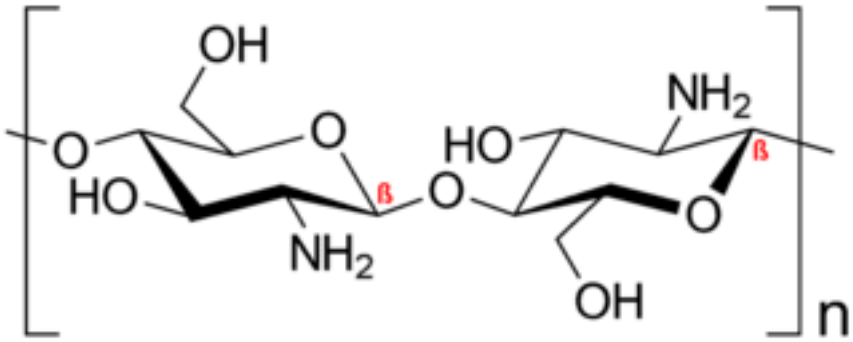


Figure 6: Chemical structure of Chitin

Chitin is a highly prevalent biopolymer present in the exoskeleton of crustaceans, the cuticles of insects, algae, and the cell wall of fungus. Chitosan is a rather rare substance found naturally in certain fungi, specifically those belonging to the Mucoraceae family. In the past, commercial chitosan samples were primarily derived from the chemical deacetylation of chitin obtained from crustacean sources. Currently, there is a growing market interest in chitosan derived from fungi, mostly due to the increasing demand from vegan consumers. Furthermore, these samples are more effectively regulated in terms of low viscosity and have an exceptionally high deacetylation degree [1]. There is a growing interest in producing protein from insect cuticles due to the increased interest in protein production from these sources.

2.8.5 Chemical properties of Chitosan

- Biocompatible
- Highly biodegradable

- Biopolymer
- Mucoadhesive
- Anti-inflammatory
- Antioxidant
- Antimicrobial
- Antifungal
- Wound healing
- Hydrophilic
- Non-toxic

Chitosan is a naturally occurring polymer that is created by removing the acetyl groups from chitin. The primary sources of this substance are primarily crustaceans and fungi. The material possesses several inherent characteristics, including biocompatibility, biodegradability, cationic nature, and nontoxicity.

2.8.6 Applications of Chitosan

Chitosan is a natural polymer derived from chitin through alkaline deacetylation. It is non-toxic, biocompatible, and biodegradable. Recently, it has garnered more attention for its uses in the food and pharmaceutical industries. In recent decades, numerous researchers have directed their attention towards chitosan as a promising reservoir of bioactive substances. The bioactivities outlined in this summary may offer new perspectives on the functions of chitosan and its derivatives. The present fascination with medical uses of chitosan and its derivatives is easily comprehensible. Chitosan is utilized in the production of hydrogels, films, fibers, or sponges, with a majority of these materials being employed in the biomedical field, where biocompatibility is crucial. Chitosan is currently recognized as a novel carrier material in drug delivery systems, wound healing, antibacterial treatment, fat binding, and as a hemostatic agent. It has also shown a hypocholesterolemic effect, as evidenced by numerous recent studies.

Chitosan's polycationic surface allows it to establish hydrogenic and ionic interactions with medicinal molecules, making it highly valuable. Chitosan's biocompatibility makes it suitable for use in drug delivery systems. Chitosan-based nanoparticles have enhanced the importance of chitin as a drug delivery mechanism for topical drug administration. In addition,

chitin can serve as a carrier for targeted delivery of cancer medicines and exhibits an antiproliferative impact by decreasing cell survival. Chitosan can be utilized as a wound dressing to expedite the regeneration of skin epithelial cells and stimulate collagen formation by fibroblasts.

2.9 Polymer Blends

Biodegradable poly(ε-caprolactone) (PCL) and its composites or blends have garnered significant interest in recent years due to their potential uses in human life and environmental cleanup. Considerable endeavors have been undertaken to create biodegradable chemical compounds as adsorbents, which are environmentally non-polluting, with the aim of substituting conventional materials. Out of the many types of materials that might degrade, PCL is currently considered the most promising, popular, and superior material for development. It is often referred to as a "green" and eco-friendly material. Some applications of this biodegradable polymer (PCL) include membranes and adsorbents for water treatment, packaging and compost bags, controlled medication carriers, and biomaterials for tissues such as bone, cartilage, ligament, skeletal muscle, skin, cardiovascular and nerve tissues.

Polymer mixing is a straightforward technique used to create polymeric materials with desired qualities by combining different components for certain uses [30]. Blends of natural polymers have gained significant importance recently due to their high potential for replacing synthetic polymers in various applications. These blends are not only renewable resources, but also non-toxic, cost-effective, and produce biodegradable waste. Chitosan and its mixes have garnered significant attention among natural polymers because of their versatility and adaptability for numerous uses, as previously mentioned. The capabilities of chitosan are improved by combining it with both synthetic and naturally occurring macromolecules. As a result, this field has gained significant interest in recent years on many occasions.

Chitosan's characteristics can be altered by combining it with several natural and synthetic polymers, including zein, curdlan, sodium alginate, konjac, polylactic acid, glucomannan, polycaprolactone, poly(ethylene oxide), graphene oxide, and poly(vinyl pyrollidine) [33,34]. The presence of -NH2 and -OH functional groups in chitosan enables their interaction with other polymers and biological substances. Chitosan, either by itself or in conjunction with other materials, can be used as a suitable base for creating a wide range of

nanocarriers including films, hydrogels, porous foams, beads, in situ gels, nanoparticles, scaffolds, nanofibers, and nanosponges [35,36].

The polymer blending method provides a cost-effective approach that replaces complex chemical operations with straightforward physical procedures. Polymer blends offer a viable solution to address several challenges in formulation and drug delivery, particularly in terms of the time and money required to get regulatory permission for the use of new excipients [13,14]. After analyzing around 13,000 reports from research engines similar to Science Direct and PubMed, it was noted that chitosan-based drug delivery systems that incorporate blending polymer possess various properties of polymers. These properties include the ability to regulate the rate, duration, and site of drug release in the body, ultimately enhancing the safety and effectiveness of the delivery system [15]. At the nanoscale, these potential carriers have the ability to transport bioactive compounds to specific cells and tissues while eliciting a minimum immune response [16].

2.10 PCL/Chitosan Blends

2.10.1 Composition sources:

PCL, or polycaprolactone:
Source: The ring-opening polymerization of the cyclic ester ε-caprolactone yields PCL, a synthetic polymer.
Chemical Structure: Its low melting temperature and flexibility are attributed to the repeating units of the caprolactone monomer.
Qualities: PCL is beneficial in a variety of biological applications due to its outstanding mechanical qualities and slow rate of deterioration.

Chitosan
Source: Mostly present in the exoskeletons of crustaceans like shrimp and crabs, chitosan is a naturally occurring polymer that is produced by deacetylating chitin.
Chemical Structure: β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine make up this linear polysaccharide.
Characteristics: Chitosan has antibacterial, biodegradable, and biocompatible qualities.

2.10.2 Mechanical properties:

Tensile Strength: When compared to pure Chitosan, the PCL and Chitosan blend usually shows better tensile strength. The mechanical performance of the blend is improved by PCL's flexibility.

Elastic Modulus: Adding PCL to chitosan can reduce its elastic modulus, improving its ductility and flexibility.

Impact Resistance: Because PCL is strong and flexible, the blend frequently exhibits higher impact resistance.

Hardness: The blend's hardness, which reflects a mix of rigidity and flexibility, is typically in the middle range between that of pure PCL and pure Chitosan.

2.10.3 Thermal degradation:

Temperature of Degradation: The blend exhibits characteristics of thermal degradation halfway between that of chitosan and pure PCL. PCL usually breaks down at temperatures between 350 and 400°C, whereas chitosan usually breaks down at temperatures between 300 and 400°C.

Degradation Mechanism: PCL breaks down hydrolytically, while chitosan breaks down thermally through the breakdown of its polysaccharide chains and deacetylation.

Stability: Compared to pure PCL, the blend may have less thermal stability, but it usually remains stable under normal processing circumstances.

2.10.4 Crystallization Behavior:

Crystallinity: Chitosan is mostly amorphous, whereas PCL is recognized for being semi-crystalline. There are usually a combination of crystalline and amorphous zones in the blend.

Crystallization Temperature: The component ratio affects the blend's crystallization temperature, with PCL contributing to greater temperatures than Chitosan.

Morphology: The ratio of PCL to Chitosan can affect the crystalline structure of the mix; a higher PCL component often yields more noticeable crystallinity.

2.10.5 Biocompatibility:

- **Cellular Response:** Both PCL and Chitosan are biocompatible; their blend is generally well-tolerated by cells, making it suitable for biomedical applications such as tissue engineering and drug delivery.

- **Cytotoxicity:** The blend shows low cytotoxicity, with minimal adverse effects on cell viability and function, attributed to Chitosan's natural origin and PCL's established safety profile.
- **Integration with Biological Tissues:** The blend supports cellular adhesion and proliferation, aiding in tissue regeneration and repair.

2.10.6 Biodegradability:

Degradation Mechanism: The mixture breaks down by both enzymatic and hydrolytic processes. PCL is broken down by hydrolysis, whereas chitosan is broken down by microbes and enzymes.
Degradation Rate: By modifying the blend composition, the rate of degradation can be adjusted. In general, the combination breaks down more slowly than pure Chitosan but faster than pure PCL.
Environmental Impact: The blend's biodegradability reduces long-term waste accumulation and encourages sustainable material use, making it environmentally benign.

2.10.7 Benefits:

Enhanced Mechanical Properties: By fusing the strength and natural origin of chitosan with the flexibility of PCL, the blend improves overall mechanical performance.
Customizable Properties: The blend's properties can be tailored for specific purposes, including scaffolds in tissue engineering or controlled-release drug delivery systems, by adjusting the ratio of PCL to Chitosan.
Safety and Biocompatibility: The blend's improved integration into biological tissues is facilitated by its biocompatibility, which guarantees its safe usage in pharmaceutical and medical applications.
Environmental Sustainability: By providing a workable substitute for traditional non-degradable polymers, the blend's biodegradability promotes environmental sustainability and pressures encountered during the stenting procedure.

2.11 Limitations of PCL via ABBOT Stent review

Limited biocompatibility: Although PCL is generally regarded as biocompatible, in certain patients it can nevertheless trigger an inflammatory response that might result in problems like restenosis and thrombosis.

Variable PCL degradation rates: The overall performance and safety of the scaffold can be impacted by a number of factors, including the molecular weight, crystallinity, and manufacturing circumstances.

Possibility of particle matter: PCL can fragment into tiny pieces during its degradation, which may result in inflammation and other issues.

It's important to note that the Absorb BRS uses a relatively modest amount of PCL in comparison to the other components, and that the scaffold's general composition and design probably lessen its drawbacks.

CHAPTER 3: EXPERIMENTAL METHODS

3.1 Polymer Blends/PB

A blend consisting of a minimum of two macromolecular compounds, such as polymers or copolymers, with an ingredient concentration above 2 weight percent. Polymer blends are currently highly significant materials in polymer science, both in theory and practice. They are progressively utilized to develop innovative and high-performance polymeric goods. To enhance the overall performance of the product, numerous polymers with different qualities have been extensively mixed, eliminating the need to design specialized polymer systems. Polymer blends are gaining popularity due to their distinct characteristics compared to individual polymers. Polymer blends offer the benefits of cost-effectiveness and superior material qualities and can be further enhanced by combining polymers that are chemically or physically compatible. Polymer blends [14,15], graft copolymers [16], and block copolymers [17] exemplify the diverse ways in which two types of polymer molecules can be combined to create fascinating structures. Polymer mixing is an efficient and adaptable technique for managing the properties of polymeric materials produced from easily accessible polymers. The thermal stability of individual polymers is affected by polymer blends [18,19]. Blending is an effective approach for enhancing polymer properties because of its practicality and straightforwardness [20,21].

Polymer mixes possess the subsequent attributes:

- The distinct characteristics of each polymer contribute to the overall attributes of a system consisting of multiple components.
- Blends exhibit a wide range of maximum values in several physical and mechanical properties when in a solid form.
- The miscibility condition significantly affects the mechanical, thermal, rheological, and otherproperties.

Here are several distinct attributes that can influence the behaviors of polymer blends:

- The dimensions and shape of polymer chains, which are determined by factors such as the molecular weight and presence of chain branching.
- The polymerization mechanism governs the consistency of the chain and the repetition of its units.
- The impact of the organization of polymer molecules resulting from the intermolecular interactions between polymer chains.

3.2 Types of Polymer Blends

3.2.1 Miscible polymer blend:

A polymer blend that is uniform at the molecular level, characterized by a negative free energy of mixing (ΔGm) which is approximately equal to or less than zero (ΔHm≤ 0), and a positive second derivative ($\partial 2\Delta Gm/\partial \varphi 2 > 0$). The structure is monophasic, exhibiting qualities that are intermediate between the properties of its individual components, and possesses a single glass transition temperature(Tg).

3.2.2 Immiscible polymer blend:

A mixture demonstrates the presence of more than two distinct stages. The blend has a positive free energy of mixing, where ΔGm ≈ ΔHm > 0. Typically, there are two transition temperatures (Tg's) since the two components are divided into different phases.

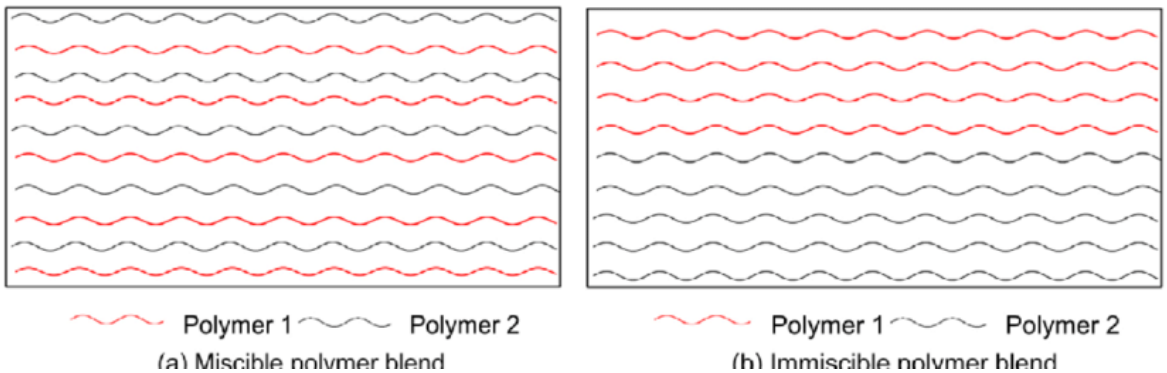


Figure 7: Difference between miscible and immiscible polymer blend.

Scientists frequently determine the glass transition temperature (Tg) of a blend to ascertain its miscibility or immiscibility. If there are two Tgs present, then the blend is considered immiscible. If only one transition glass (Tg) is seen, it indicates that the blend is likely to be miscible.

3.2.3 Homologous polymer Blend:

It refers to a mixture of multiple fractions of the same polymer, where each fraction has a distinct molecular weight distribution.

3.2.4 Isomorphic polymer Blend:

It refers to a blend of two or more distinct semi-crystalline polymers that are capable of mixing together both in their crystalline condition and when melted.

3.2.5 Compatible Blends:

A polymer blend is considered compatible when it is a usable blend despite having multiple phases that are not mixed. The inhomogeneity generated by these separate phases is so minor that it is not noticeable during use.

Figure 8: Schematic illustration of compatibilized blend

3.2.6 Polymer alloy:

It refers to a blend of polymers that are not soluble in each other but have been made compatible through modifications to their interface and structure.

3.2.7 Distinguishing Polymer Blend from Polymer Alloy:

Blending or alloying two or more polymers can significantly alter the characteristics of many plastics. These terms are sometimes used interchangeably, although strictly speaking, blends refer to mixtures that are not completely compatible, while alloys refer to mixtures that are fully compatible. A polymer alloy is a distinct category within polymer blends, encompassing nearly all high-performance engineering blends.

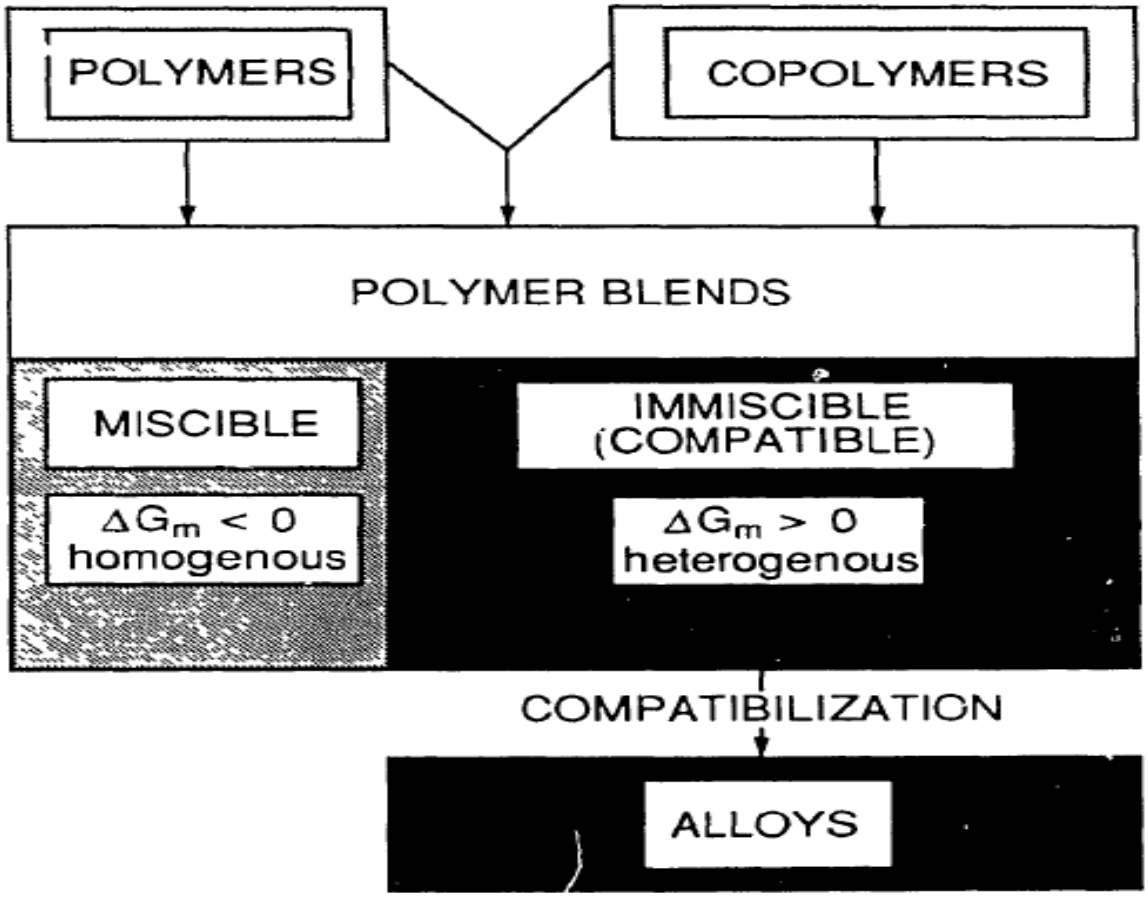


Figure 9: Difference between polymer blend and polymer alloy.

3.3 Applications of Polymer Blends

Medical textile materials cater to a wide range of applications with diverse end-use needs, and improved processing technologies have been created to address the growing complexity of technical challenges. This chapter provides a concise overview of the advancements made in altering the properties and functions of polymers, fibers, and textile materials. The work

provides an overview of the technology, product capabilities, and uses of medical textile products created using polymer blending, composite materials, tissue engineering, and artificial organs. Through the application of chemical, physical, and biological treatment methods, it is feasible to improve the performance of textile materials such as polymers, fibers, and composites. This can lead to the development of medical textile products that possess desirable qualities such as high absorbency, antimicrobial properties, protection against ultraviolet radiation, drug release capabilities, and other functions that are highly valuable in the field of biomedical materials and functional medical textiles.

3.4 Methods pf Blending

Various techniques can be employed to synthesis and/or prepare polymer blends [42]. Each strategy possesses its own advantages and disadvantages. Below, we give a concise overview of many viable ways for producing polymer blends.

3.4.1 Melt Mixing

This process is quite popular for preparing polymer blends without any contamination, and it is frequently utilized [42]. Specialized equipment, such as various extruders and temperature control systems, are utilized to handle and liquefy each unique component. The raw ingredients are introduced into a specialized chamber equipped with extruders to ensure a homogeneous combination of all the raw elements. The temperature is raised to an optimal threshold, causing all additional substances to melt accordingly. In addition to the content of the components, process parameters such as the time of blending, operating temperature, and pressure all play a crucial role in achieving the desired qualities of the blend. This process is generally regarded as a viable technology; however, it can be costly at times and may yield non-uniform polymer blends if not managed properly, resulting in mechanically inferior products[42].

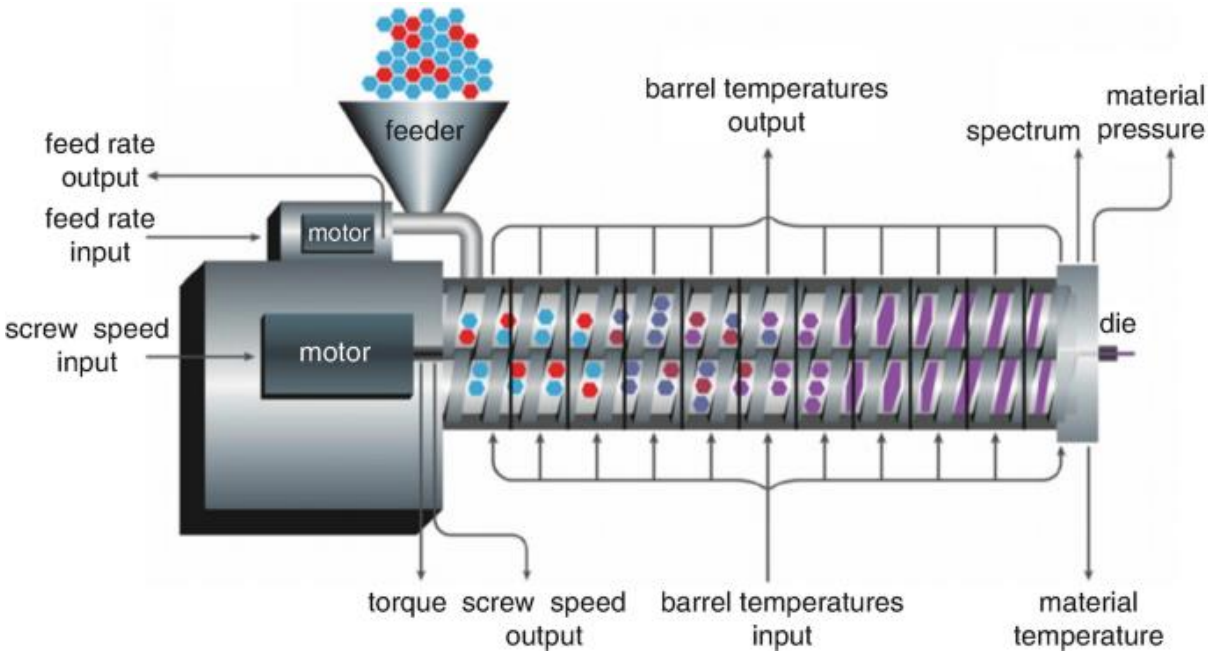


Figure 10: Schematic illustration of melt mixing

3.4.2 Mill Mixing/Fine Powder Mixing Method

A straightforward technique involves the combination of blending components through the process of milling and grinding. Various types of milling equipment and grinders are utilized for this purpose. The raw components are ground to obtain the finest powder, which is then combined to create homogeneous mixing at a microscopic level. Afterwards, the product undergoes further procedures to obtain the appropriate polymer mix products [43,44]. The Bunbury mixer, often referred to as the Master Mixer, is commonly utilized for mechanically mixing polymer materials. It is particularly suitable for synthesizing polymer blends [44].

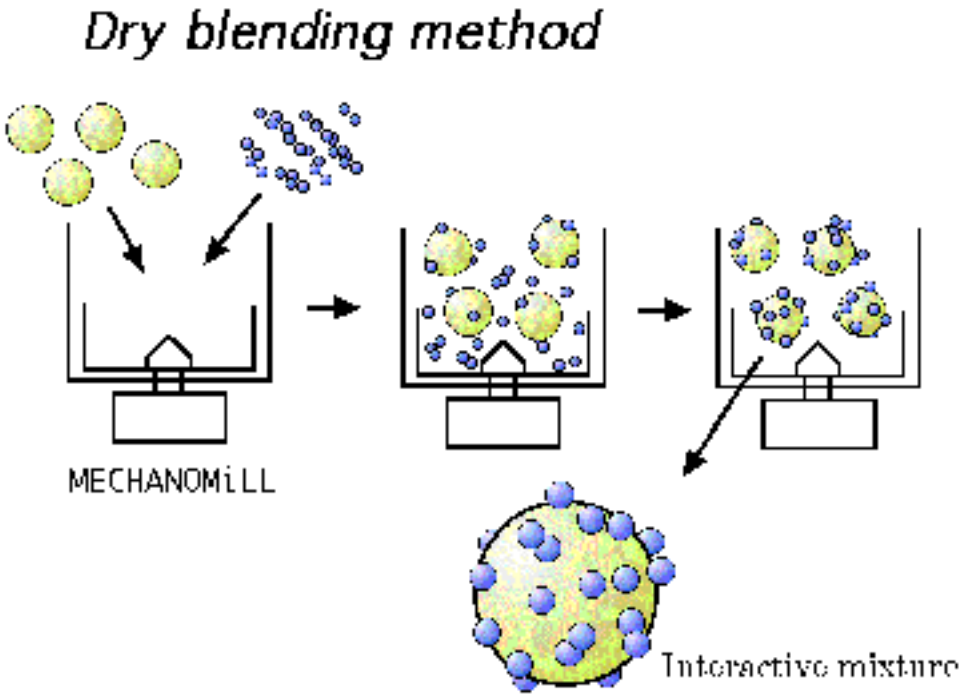


Figure 11: Schematic illustration of dry blending method

3.4.3 Solution Casting Method

This technique is one of the most straightforward and often used methods. This approach involves casting the blend using a shared solvent and includes the following steps:

- The chosen component polymers are selected for the purpose of blending.
- The chosen polymers are dissolved in a designated solvent. The choice of solvent is crucial and significantly influences the solution casting procedure.
- The solution mixture should be continuously stirred for a specific duration in order to achieve a homogeneous solution.
- The binders and compatibilizers are included if necessary.5. The final product is gathered at the conclusion of the procedure and analyzed.

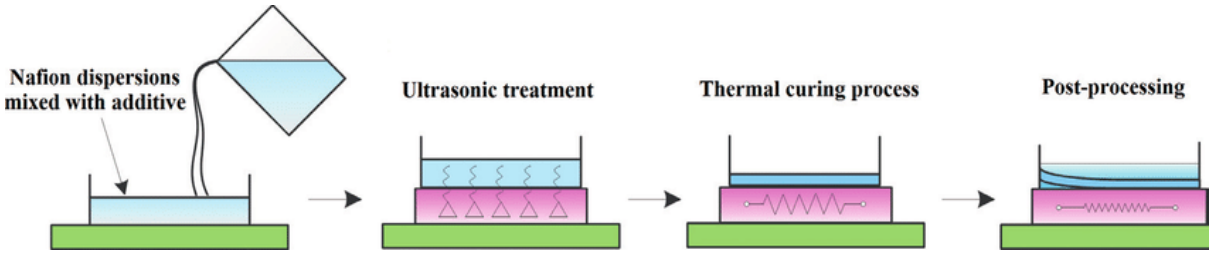


Figure 12: Schematic illustration of solution casting method

3.4.4 Freeze Drying Method

Quenching is a well-known method in any chemical laboratory operations, also used in freeze-drying method. In freeze-drying, the component polymers are quenched down to a suitable (normally very low) temperature, and the solution got frozen. The component polymers will have a very least chance to agglomerate and thus all frozen solvent can be collected very easily. The solvent is then removed by the application of sublimation. This method is the best when symmetrical solvents are used in the solution[47-49].

Quenching is a widely recognized technique used in various chemical laboratory procedures, including freeze-drying. During freeze-drying, the constituent polymers are rapidly cooled to an appropriate, typically extremely low, temperature, causing the solution to solidify into ice. The individual polymers comprising the component will have a minimal likelihood of forming clusters, allowing for the straightforward collection of all solidified solvent. The solvent is subsequently eliminated by the process of sublimation. This approach is most effective when symmetrical solvents are utilized in the solution [47–49].

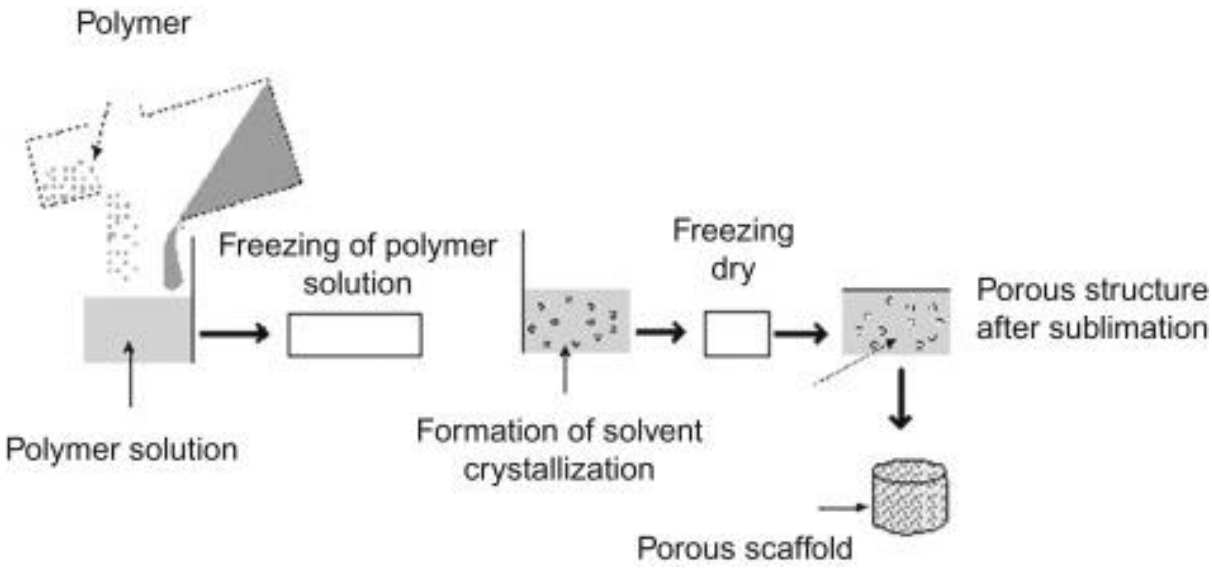


Figure 13: Schematic illustration of Freeze-drying method.

3.4.5 Latex Blending Method

The term "latex" holds significant importance and carries a specific meaning within the polymer sector. It is utilized to achieve a steady dispersion (emulsion phase) of polymer particles at a microscopic level in a specific aqueous media. Therefore, latex blending is a distinctive method used for combining polymers and other polymerization procedures. This technique resulted in the creation of plastic blends that were reinforced with rubber. In order to create these blends, the polymers that contribute to the mixture should be in either latex or emulsion form, and then they should be mixed together. The mixing step is crucial as it results in the production of micro-sized homogeneous latex and the distribution of distinct phases [50,51].

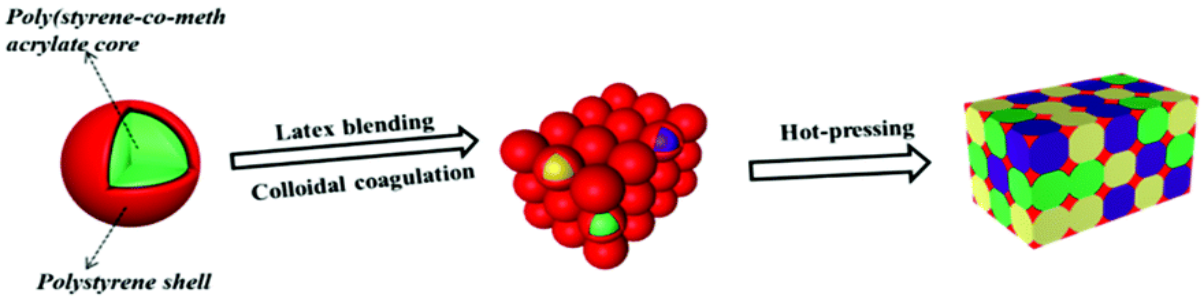


Figure 14: Schematic illustration of latex blend method

3.5 Advantages of Polymer Mixing/ Blending

Advantages of blending can be divided into two categories:

Improved resin performance and Improved process ability.

3.5.1 Improved resin performance

Mixing can increase a resin's or product's efficiency in the following ways:

- It provides valuable ingredients at comparatively low cost that accurately meet the desired set of properties.
- Adding less expensive polymers to prepared resins to extend their useful life or boost their efficiency.
- Enhancement of specific qualities such as:

i. Brittleness
ii. Toughness
iii. Elastic modulus
iv. Chemical and solvent resistance
v. Flame resistance
vi. Biodegradability

3.5.2 Improved Process ability

Blending enhances process ability:

- By processing prepared resins at a temperature significantly below the thermal degradation time span or limit,
- Minimal reduction in pressure across runners.
- Blends have a regulated level of continuous hardening.
- Preserving the foaming procedure

  We shall now talk about our polymer mixing approach.

3.6 Blend Preparation

Blends were made with the Intense Blend Mixer utilizing the melt mixing method. Various blend compositions were made in accordance with the mixer's feed.

3.6.1 Preparation PCL/CS Blends:

PCL/CS mixes are made utilizing the Hot Melt Extrusion Process on the compositions shown in Table 1. As indicated in Table 1, all the compositions are melt-blended in the HAAKE PolyLab OS internal engineering mixer, which entails a rigorous mixing procedure. This mixer has two triangle-shaped rotors that rotate counter-clockwise at a ratio of 1.25:1. The rotational speed of the screws was first adjusted to 10 rpm and subsequently increased to 70 rpm for blending. Samples were blended for ten minutes at various temperatures. Because PCL melts at a lower temperature than CS, it must be blended at a lower temperature to prevent burning. The software of HAAKE Polysoft was supplied the processing conditions necessary for the necessary blending operation. The samples were cooled at room temperature without squeezing.

Table 1: Different blend compositions prepared with varied factors

Blends	**PCL %**	**CS%**	**Drug %**	**RPM**	**T ˚C**	**Mixing time**
B-1	80	20	30	80	180	25
B-1a	80	20	30	75	175	20
B-2	70	30	30	75	165	25
B-2a	70	30	30	70	160	20
B-3	50	50	30	65	165	20
B-3a	50	50	30	60	160	20
B-4	30	70	30	55	155	25
B-4a	30	70	30	50	150	20
B-5	100	0	30	60	150	20

Above mentioned nine different blend compositions were prepared by varying the process parameters involved in this reaction like:

- Temperature
- RPM
- Mixing time
- Drug quantity to be kept constant in all blends since we can vary either of the two parameters.

Every composition is created by changing these specifications. From all this composition,four were deemed to have the best surface morphologywith less phase separation and greater homogeneity. Table 2 lists the compositions that were most wellchosen. Given th at the goal of blending was to coat, we chose compositions that exhibit consistent mixing at el evated temperatures. All of the mix compositions listed above were created asblend sheets. Ev ery sheet mix sheet film had a thickness of 0.5 mm. SEM was used to examine the mix films' surface morphologies.

Table 2: Four standard samples chosen after initial characterization

Sample No.	**PCL%**	**CS%**	**Drug%**
1	80	20	30
2	70	30	30
3	60	40	30
4	50	50	30

Figure 15: (a) Intense Mixer used for blending (b) HAAKE Intense Mixer at UET Lahore

To create the solid, mushy gobs, the mixture was combined in the feed mixer at 165-degree Celsius. The stiff, brittle, glossy surface of the mushy gobs revealed the mixture of two polymers, polycaprolactone and chitosan (copolymer).

Hot presser

Once the mushy gobs formed, they were put into a hot presser that had been prepared to 160 ˚ C for six minutes. The pressure was then kept at 100 bar. Five to ten minutes were spent hot pressing the gobs. Figure 15 depicts the hot presser that was used for this operation.

Figure 16: Hot presser used for making films

Cold presser

Films were hot-pressed and then cold-pressed for five to ten minutes to create 0.5 mm sheets in a cold presser. The cold presser that was used for this assignment is shown in Figure 17.

Figure 17: Cold presser used for making sheets

The many sheet forms that occur from combining polymers are listed below.Pictures with varying missicibility clearly demonstrate the various compositions. In order to analyze the surface uniformity of all the blends, heat pressing and then cold pressing were used to turn the blends into blend sheets. Out of nine compositions, the surface investigation revealed that four appear to have less phase separation than the remaining compositions where the immiscibility factor was observed in the blend sheet films.

Figure 18: Films obtained after cold pressing a) F1: 80% PCL & 20 % CS b) F2 : 70% PCL & 30% CS C) F3: 60% PLA & 40% CS d) F4: 50% PCL & 50% CS

Subsequently, the produced films underwent experimental testing employing several characterization methods. A thorough explanation of every characterization strategy employed in this study methodology will be provided in Chapter 4.

CHAPTER 4: CHARACTERIZATION TECHNIQUES

4.1 Scanning electron microscope (SEM):

This method involves focusing a narrow electron beam onto the surface of a material. Electrons interact with the surface of the sample, causing the ejection of photons or electrons from the material's surface. The detector subsequently directs its attention to these dislodged electrons [70]. The output of the detector amplifies the brightness level of the cathode ray tube (CRT). The interaction between the surfaces of the electrons enables the release of secondary electrons (SE), back-scattered electrons (BSE), and X-rays. A commonly used approach for detecting SEM is by utilizing secondary electrons (SE). The emission of these secondary electrons occurs near the surface of the sample. Therefore, a distinct and unambiguous image of the sample is acquired. It has the capability to disclose minute details of samples that are smaller than 1 nm. In addition, the incident electrons undergo elastic scattering, resulting in the emission of backscattered electrons. They originate from more profound sites in contrast to secondary electrons. Therefore, their resolution is relatively low. Figure depicts the scanning electron microscope (SEM) apparatus, namely the JSM 6490LA model, which is located in the SCME department of the School of Chemical and Materials Engineering at NUST in Islamabad. Additionally, figure 15 b provides a schematic illustration of a SEM.

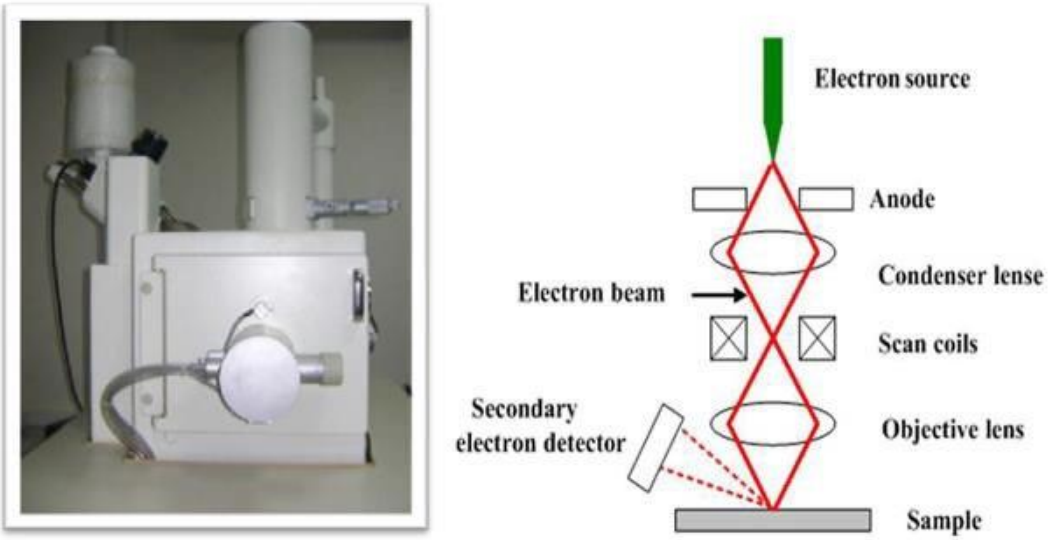


Figure 19: (a) SEM (JOEL JSM-6490LA) present at SCME, NUST (b) Schematic representation of SEM

The approach is highly adaptable and strong for analyzing substances at the nano scale. It has the capability to generate a three-dimensional representation of the surface features and can accurately measure the elevation and dimensions of nano materials. When the tip of the cantilever approaches the surface of the sample, both the surface and the tip deflect the cantilever towards the sample. When the tip touches the sample, repulsive forces occur, causing the cantilever to move away from the surface.

The mix films were subjected to surface electron microscopy at the School of Chemicals and Materials Engineering (SCME), NUST.

4.2 UV-Vis spectroscopy:

This method is employed to ascertain the optical properties of materials. This approach can analyze the properties of absorbance, transmittance, and resistance. It quantifies the degree to which a light beam is absorbed after it traverses through a sample. This absorption might occur at a single wavelength or across a broad spectrum. A UV spectrophotometer utilizes collimated electromagnetic (EM) light spanning from the UV region to the far infrared (IR) portion of the EM spectrum. The radiations are directed at the sample. The intensity of the transmitted light beam is determined concurrently. This equipment contains a spectrometer that measures the extent of absorption exhibited by a prepared sample at different wavelengths. The plot of absorbance produced as a function of wavelength (λ) is referred to as a spectrum [53].

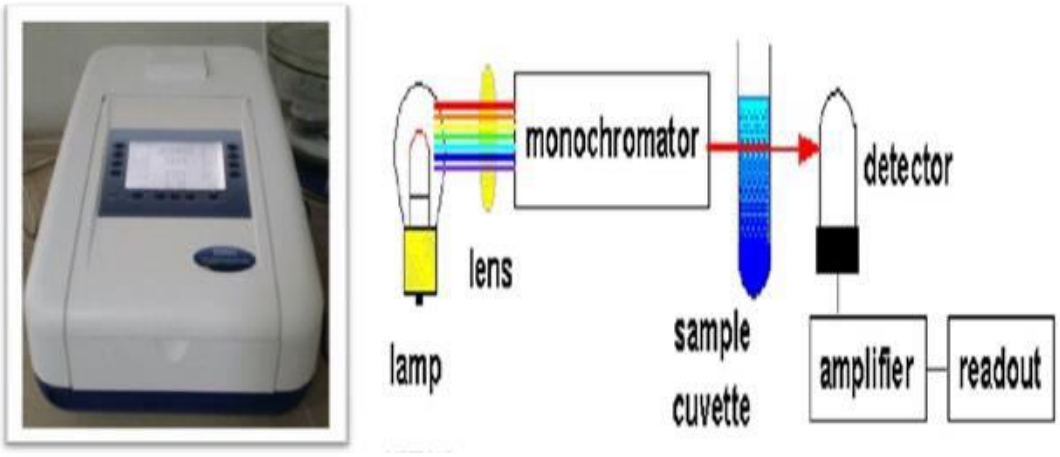


Figure 20: UV-Vis spectrophotometer in SCME, NUST (b) Schematics of UV-Vis spectrophotometer

The absorption and percentage transmission data of the drug released samples in vitro were acquired using the Jenway (7315) UV-Vis spectrometer within the wavelength range of 200-800 nm.

4.3 TGA (Thermogravimetric Analysis)

Thermo quantitative analysis, commonly known as thermal quantitative analysis (TGA), is a method of heat analysis in which the mass of a sample is assessed at various time intervals due to temperature fluctuations. This process gives knowledge pertaining to the tangible things that occur in the physical world, such as:

- Molecular transitions
- Thermal absorption
- Surface assimilation
- Surface desorption
- Chemisorptions,
- Thermal decomposition
- Solid-gas reactions

The thermal processes necessary for this procedure can take place under many atmospheres, such as ambient air, vacuum, or inert gas. The number 72 is enclosed in square brackets [72].

Figure 21: Thermogravimetric Analysis (TGA) Tester.

4.4 FTIR SPECTROSOPY

FT-IR Bruker Alpha spectrometer was used to obtain an FTIR spectrum for the blend films. The spectrum obtained from Bruker Alpha spectrometer was analyzed and studied using the FTIR essential software to determine the type of peaks.

The word infrared spectroscopy Fourier-transform originates from the fact that a Fourier transformation method (a mathematical process) is required to convert the raw information obtained from data into the real spectrum form. FTIR of the blend samples was done to know about the bonds stretching in structures of PLA/EVE blends. An FTIR spectrometer is shown in figure [73].

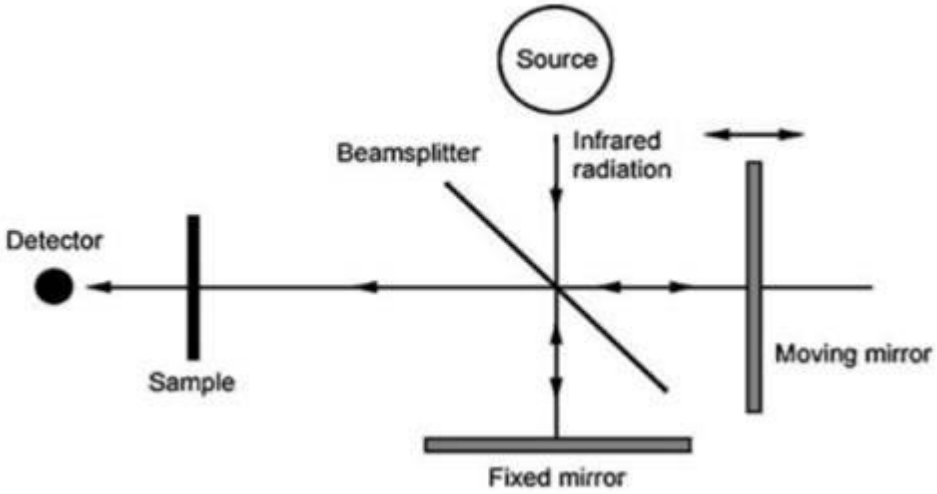


Figure 22: Schematics of an FTIR spectrometer

4.5 In Vitro Biodegradation tests

4.5.1 Weight loss test

The films were divided into circular disks with a diameter of 1cm and subsequently weighed with precision in order to determine their initial mass, Wo. Subsequently, each film sample was inserted into a cylindrical tube with a lengthened shape, which contained 50 ml of Phosphate buffer solution (PBS) with a pH of 7.4, in order to replicate the conditions of the human blood environment. The tubes were placed in an orbital shaker bath set at a temperature of 37°C with a shaking speed of 75 rpm (rotations per minute). After a period of 4 days, the samples were removed from the tube.

The collected samples were thereafter rinsed with distilled water delicately and dried with filter paper. Subsequently, they were subjected to a vacuum drying process at a temperature of 25°C for a duration of 48 hours. Subsequently, the immediate measurement of the dry mass, denoted as W1, was conducted for each film.

Figure 23: Schematic illustration

- Blend disk 1cm in flask.
- Test tube containing 50ml PBS solution at a pH 7.4.
- Placed in orbital shaker at 75 rpm and 37'C temp.
- Disks removed after a time interval of 4 days, dried and weighed.

The degree of weight loss percent (wt %) for these films was calculated using the following equation:

Weight loss; $wt\% = W_0 - W_1 / W_0 * 100$

4.5.2 In Vitro drug release using Absorbance spectra of Uv-Vis spectroscopy:

The drug-laden films were divided into various discs, each measuring around 1 cm in diameter. Each disc was placed in a 15 mL elongated tube filled with 15 mL of phosphate buffer solution (PBS) with a pH of 7.4, as previously determined to match the pH conditions of the human body. Subsequently, the tubes were transferred to an orbital shaker bath set at a predetermined temperature of 37°C ± 0.5°C.

At certain time intervals of 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, and 48 hours, the release medium was removed and replaced with an equivalent volume of 50 mL of new PBS media with a pH of 7.4.

The collected release medium was analyzed using Uv-vis spectroscopy to determine the homogeneity of drug concentration based on the absorption spectra. The resultant figures were compared to the absorption spectra of pure aspirin [57].

4.6 Choosing suitable blend for coating

4.6.1 Dip coating

Following the biodegradation test, the film that demonstrated the highest level of effectiveness was chosen for the purpose of coating the stent.The stent utilized in this procedure was a cobalt-chromium stent. A solution of 40mL was created by dissolving film 3 in a chloroform solution. The solution was

then placed on a magnetic stirrer for 24 hours to ensure complete and even dissolution for the purpose of coating.

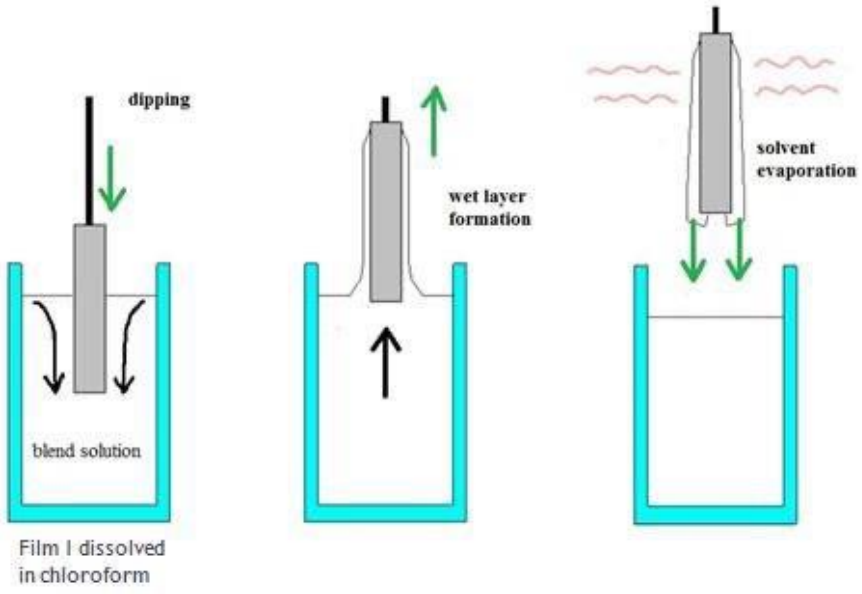


Figure 24: Dip Coating technique done on BMS Stent

Dip coating involves five main steps:

- Immersion
- Startup
- Drainage
- Deposition
- Evaporation

In the initial stage of immersion, the substrate is placed into a solution containing the desired coating material, while maintaining a consistent pace. The substrate must undergo movement or rotation within the coating substance solution before being removed. The extracted specimen is removed from the coating solution at a predetermined and consistent velocity to prevent any form anxiety or lack of consistency. The rate at which the substrate is removed determines the thickness of the coating. The surplus liquid from the surface of the substrate will be removed. The solvent employed in the coating solution subsequently volatilizes off the surface of the substrate, resulting in the formation of a thin layer. In the iterative process, the phases are executed in order to get the intended outcomes.

CHAPTER 5: RESULTS AND DISCUSSIONS

5.1 Blend sheet Samples

5.1.1 Prepared PCL/CS blends

Various sheets of the blends were prepared under different temperatures according to the varying PCL concentrations as discussed in chapter 3. Blends prepared are listed in the chapter in table 3.1. Following figures represent the different blends:

a.

b.

c.

d.

Figure 25: It shows SEM micrographs of a) (80% PCL and 20% CS), b). (70% PCL and 30% CS), c) (50% PCL and 50% CS), and d). (60% PCL and 40% CS) respectively.

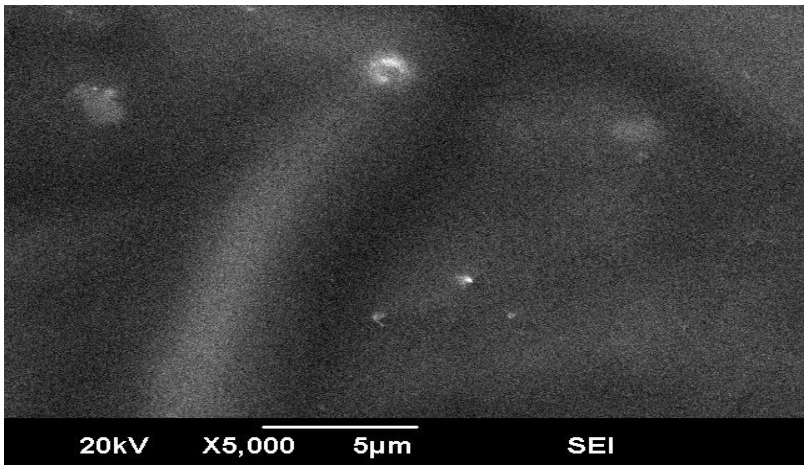
Figure a and b represent the soft sheets of PCL/CS blends without any visible and noticeable traces of Chitosan and show the complete melting. Whereas, looking at the figures c and d, we can clearly see the white non-melted particles of chitosan.

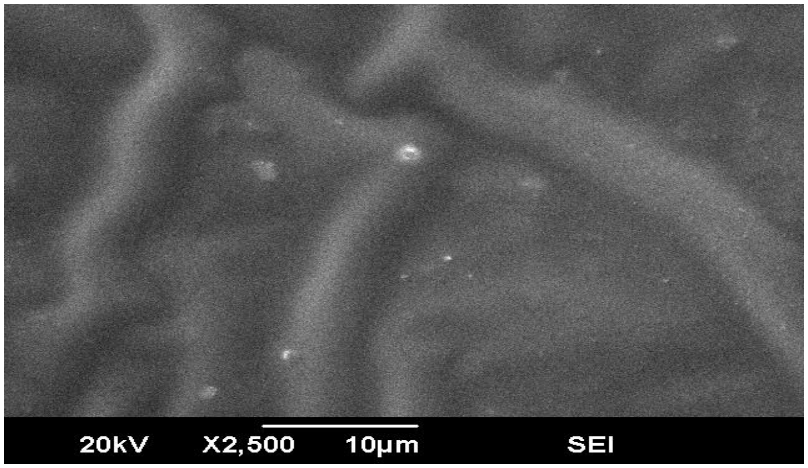
Chitosan, which melts at about 105°C, is responsible for the apparent non-homogenous surface that resulted from the low mixing temperature of 90°C (PCL melts at 70°C). Consequently, the Chitosan filaments were unable to completely melt and break down into smaller pieces.

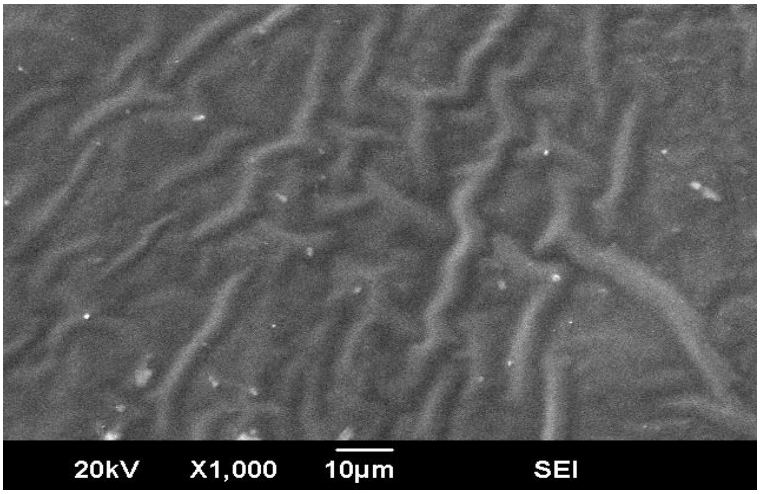
The blend films' morphological and structural properties were examined using scanning electron microscopy (SEM; Joel JSM-6490A). Using this technique, a gold film was sputtered onto each blend film [74].

5.2 SEM Analysis of PCL/CS blends

To observe the morphological changes in the blends, sem analysis was performed on the blend sheets. The SEM study produced the data listed below. The outcomes demonstrate how blending changes the surface structure. The surface of PCL exhibits toughening as the amount of CS increases; this toughening is seen in the SEM pictures as traces. The SEM morphological study allows one to conclude about the impact of CS on PCL as a compatible material. The diverse outcomes of the SEM analysis are listed below. These photos make the distinctions in physical characteristics quite evident. The characteristics of PCL also change as the amount of CS copolymer rises.







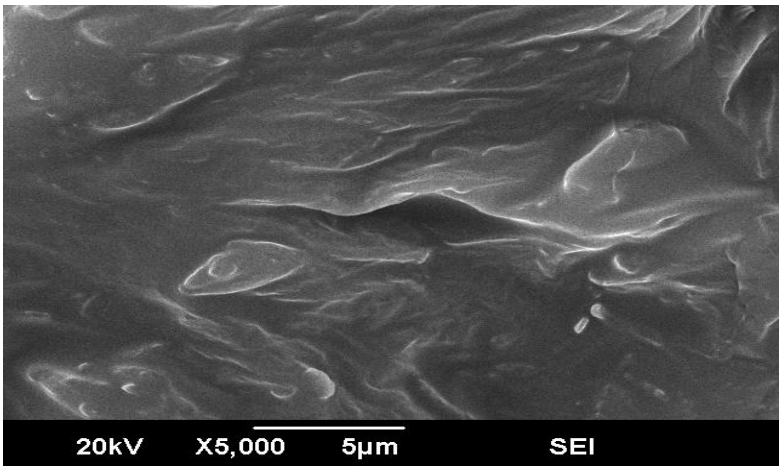
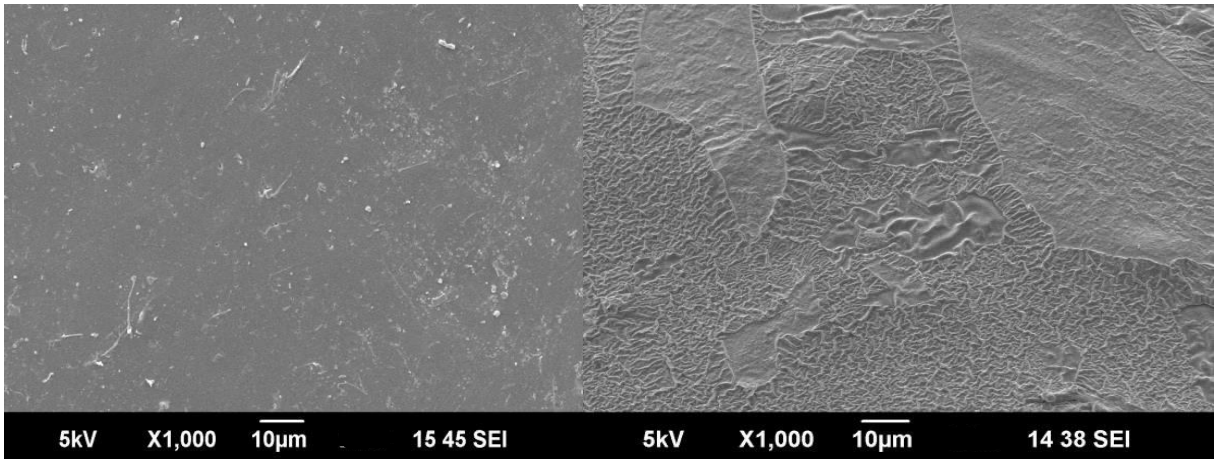
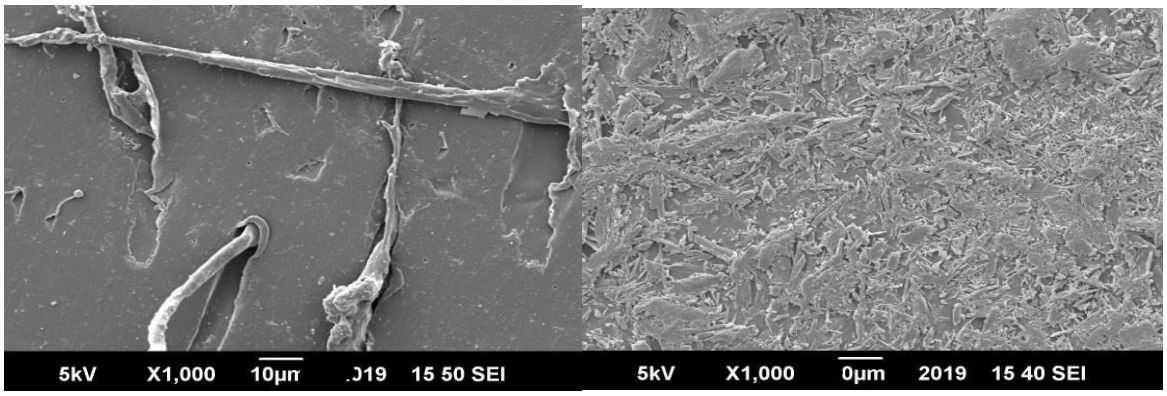


Figure 26: It shows SEM micrographs of a) (80% PCL and 20% CS), b). (70% PCL and 30% CS), c) (50% PCL and 50% CS), and d). (60% PCL and 40% CS) respectively.



(a) **(b)**



(c) **(d)**

Figure 27: SEM micrographs of a) (80% PCL and 20% CS), b). (70% PCL and 30% CS), c) (50% PCL and 50% CS), and d). (60% PCL and 40% CS) respectively.

In comparison to the other sample surfaces, the surfaces of samples 1 and 2 have the smoothest surfaces. No evidence of particles or pores are discernible. The surfaces in Fig. an appear to have a structure like a grain boundary at lower magnification, which suggests that this sample obtained the most optimal homogeneous blend [74].

In contrast to samples 3 and 4, which showed filaments, sample 2's surface was scattered with tiny flake-like particles as the CS level rose. This implied that the filaments and flakes were most likely made of solid carbon that had not had enough time to melt at low

temperatures. Compared to sample 3, where the PCL filaments remained longer, sample 4's higher CS level caused the PCL filaments to break into smaller fragments in the figure.

5.3 FTIR Spectroscopy Analysis

Formation of PCL, CS polymeric blend can be confirmed by FTIR Spectroscopy. The stretching vibrations of PCL's O-H and Chitosan's C-H are responsible for the peaks at 3421.21 cm-1 and 2927.12 cm-1, respectively. PCL's C=O and chitosan's N-H stretching vibrations are responsible for the peaks at 1727.96 cm-1 and 1658.90 cm-1, respectively. The C=O and C=C stretching vibrations of PCL and chitosan, respectively, are responsible for the peaks at 1730 cm-1 and 1500–1600 cm-1, respectively. Peaks at 1600–1700 cm-1 are thought to be caused by Chitosan's N–H bending vibrations. PCL's and chitosan's C-O-C stretching vibrations are responsible for the peaks at 1200 and 1300 cm-1, respectively. PCL's and chitosan's C-O-C stretching vibrations are responsible for the peaks at 1000 and 1100 cm-1, respectively. PCL and chitosan's C-H bending vibrations are responsible for the peaks at 700 and 900 cm-1, respectively. O-H and C-H groups are present in both PCL and chitosan, as indicated by the existence of peaks at 3421.21 cm-1 and 2927.12 cm-1. The existence of C=O and N-H groups in PCL and chitosan is shown by the appearance of peaks at 1727.96 cm-1 and 1658.90 cm-1. The existence of C=O and C=C groups in PCL and chitosan is shown by the occurrence of peaks at 1730 cm-1 and 1500–1600 cm-1.

N-H bending vibrations in Chitosan are indicated by the occurrence of peaks at 1600–1700 cm-1. In both PCL and chitosan, the appearance of peaks at 1200–1300 cm–1 suggests the presence of C–O–C stretching vibrations. In both PCL and chitosan, the occurrence of peaks at 1000–1100 cm–1 suggests the presence of C–O–C stretching vibrations.

O-H, C-H, C=O, N-H, C=C, C-O-C, and C-H groups are present in both PCL and Chitosan, according to the blend's FTIR spectra. These groups' existence suggests that PCL and chitosan are both present in the blend.

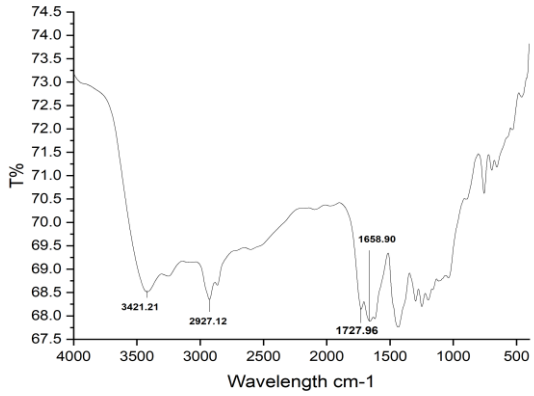


Figure 28: The presence of peaks illustrates the formation of PCL and chitosan.

5.4 Thermogravimetric Analysis (TGA)

Blends were subjected to thermal testing using gravimetric analysis (TGA).
Blend formation was checked using the optimal composition determined by the biodegradation analysis. The different mixes' thermal stability.
Three stages are involved in the heat degradation of PCL and CS [53].

- The intermolecular Trans etherification reaction is responsible for the breakdown or breaking of bonds that occurs in the 200–250 °C temperature range.
- Following that, the temperature range of 250–310 °C clearly shows the following stage of degradation. The absence of acetic acid from the blend's CS co-polymer is the cause of this variation or deterioration.
- In conclusion, unsaturated butane and other chemical components that are in vapor form escape during the last stage of thermal degradation of these blends, which is visible in the temperature range of 310 to 360 °C.

Thus, the decomposition in the region of 310 to 360 °C confirms the formation of PCL CS blend.

5.5 In Vitro Drug Release using UV-Vis Spectroscopy:

The subsequent drug samples were acquired after immersion in PBS (pH 7.4) at varying time intervals.

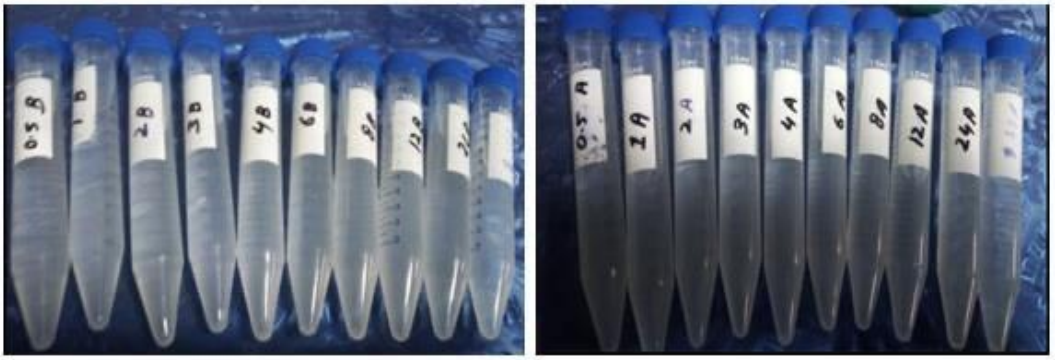


Figure 29: Samples obtained after placing 1X1 cm films in PBS for time intervals (1/2 hour to 48 hours)

A standard stock solution of the desired volume was generated by diluting 5 mg of active aspirin in 50 mL of phosphate buffer (PBS) at pH 7.4 at room temperature. The dilution was subjected to the bath sonicator for 20 minutes.1 ml of PBS has 100 µg of drug; therefore, 5 ml of PBS will contain 500 µg of drug. The subsequent calibration curve was derived after the preparation of stock solutions and appropriate dilutions.

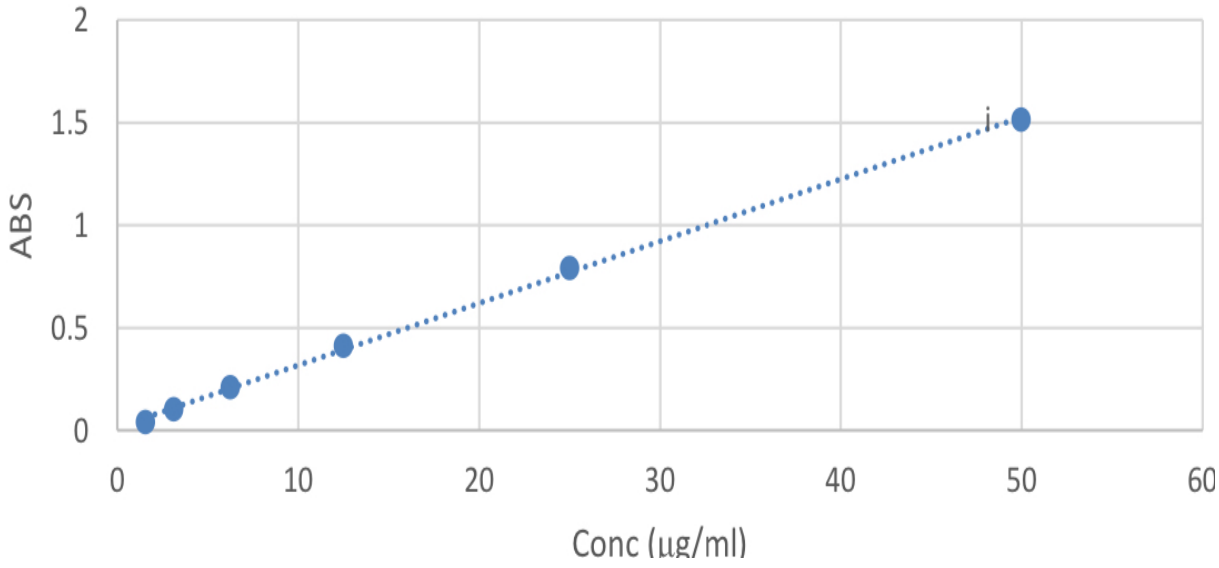


Figure 30: Calibration curve of Aspirin in PBS 7.4

The regression value from the calibration curve is kept at 0.99, indicating that aspirin is released at a controlled interval during the in vitro release research.

5.6 Biodegradation Tests

5.6.1 Weight Loss test of PCL/CS blends

The Weight Loss test is conducted to assess the biodegradability of PCL-CS. Variations in the amounts of both polymers resulted in diverse outcomes across different samples.

- Sample 1, with 80% PCL, had the most rapid degradation rate of 0.5%, resulting in total weight loss in approximately 2 years.
- Sample 2, containing 70% PCL, exhibited a degradation rate of 0.2% and is projected to complete degradation in 5 years.
- Samples 3 and 4, which contain higher CS concentration, had the slowest deterioration, approaching less than 0.01%.

Weight loss is computed based on the difference in percentage, and the data is presented in Table 3.

Table 3: Computed data of weight loss based on the difference of percentages

Sample (w_0-w_1)/g				
Time (days)				
Time	**sample 1**	**sample 2**	**sample 3**	**sample4**
0	0	0	0	0
4	0.25	0.2	0.1	0.1
8	0.45	0.3	0.2	0.13
16	0.5	0.5	0.25	0.2
28	0.9	0.7	0.4	0.28

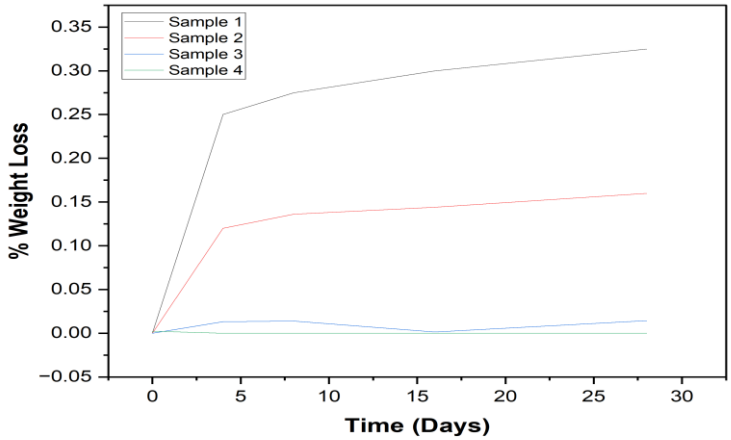


Figure 31: Biodegradation curves for F1(80% PCL and 20 % CS) F2 (70% PCL and 30% CS) F3(50% PCL and 50% CS) and F4 (30% PCL and 70% CS) respectively.

This demonstrates PCL's degradability. The burst release mechanism, in which PCL collects water and bursts along with the medication, is responsible for the first four days of weight reduction. Based on these findings, the ideal composition for drug-eluting polymeric cardiac stents should include less than 30% CS. Additionally, the br degradation test revealed that while CS slows down the rate of degradation, the degradability increased with an increase in PCL concentration.

The thermal stability of PCL/CS blends was evaluated by thermogravimetric analysis, which demonstrates the degradation time of the various polymers involved in the blend creation.

The TGA test indicates that the blend remains thermally stable up to 300°C, with all thermal changes occurring beyond this temperature, signifying that the mix may function in the body without experiencing thermal stress or degradation.

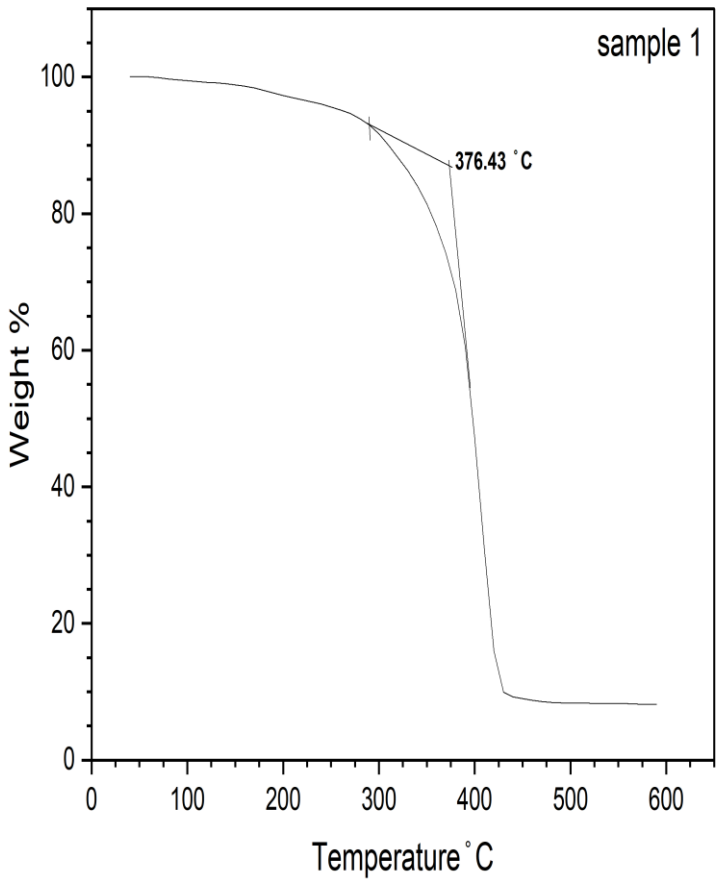


Figure 32: Thermogravimetric Analysis of Film 1.

Achieving thermal stability is the primary challenge in blends due to their composition of two or more polymers. The thermal stability indicates that an optimal composition has been attained in blends suitable for the coating of drug-eluting stents.

5.7 Practical Application

Using Optimum blend composition for drug eluting stent coating material:

The use of PCL effectively addressed our primary worry regarding the brittleness and elongation of CS. Consequently, this research indicates that the ideal composition of the PCL/CS blend for biodegradable stents comprises CS in the range of 15-30% and PCL at 70-85%. We utilized this optimal blend composition (sample 1: 80% PCL and 20% CS) as a coating material for the stent employing the dip coating method.

For the dip coating procedure, a 40 ml solution was made by dissolving the optimal film 1 in chloroform, including 10 g of aspirin. The quantity of medication utilized in the blend that coated the stent from 40 ml was estimated.

40 ml of solution contains aspirin =10 grams

2ml of solution contains aspirin = x

X x 40 = 10 x 2

X = $^{10 \times 2/40}$ = 0.5 grams

Amount of drug coated on stent = 0.5 grams

5.7.1 In Vitro release study of drug loaded stent:

The aspirin-coated stent was immersed in a buffer with a pH of 7.4 for 48 hours in an orbital shaker bath. After various time intervals, the PBS was substituted with fresh PBS. We constructed a graph depicting the cumulative proportion of medication release in relation to time.

The drug concentration was determined using the equation:

$y = 0.0302x + 0.0146$

$y-0.0146/0.0302 = x$

We substituted the corresponding absorbance values obtained from UV-Vis spectroscopy for "y" to get the drug concentration.The acquired graph was subsequently compared with the usual drug models. The most suitable model was the Korsmeyer-Peppas model.

The subsequent graph was derived from the in vitro drug release investigation of an aspirin-coated stent after predetermined time intervals.

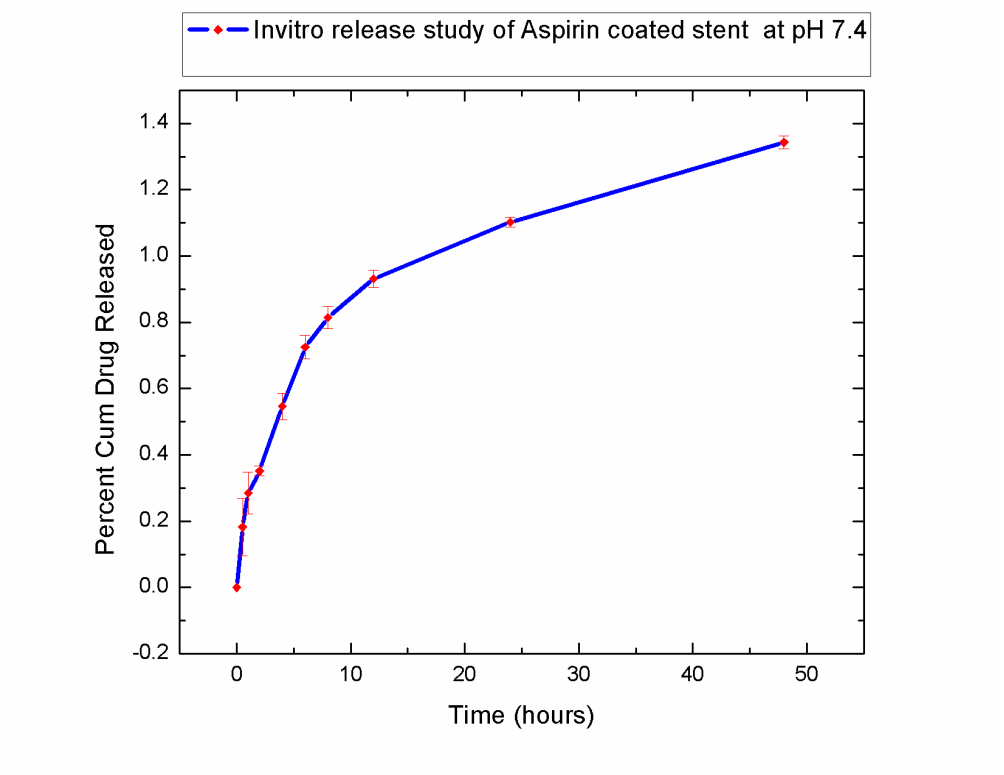


Figure 33: In vitro drug release study of aspirin coated stent

The graph indicates that 1.34 µg of the medication was released over a period of 48 hours. The curve illustrates the regulated release of the medication. To calculate the total quantity of medication coated for release.

Drug released in 48 hours = 1.34 %

Drug released in x hours = 100 %

48 ×100/1.34 = x

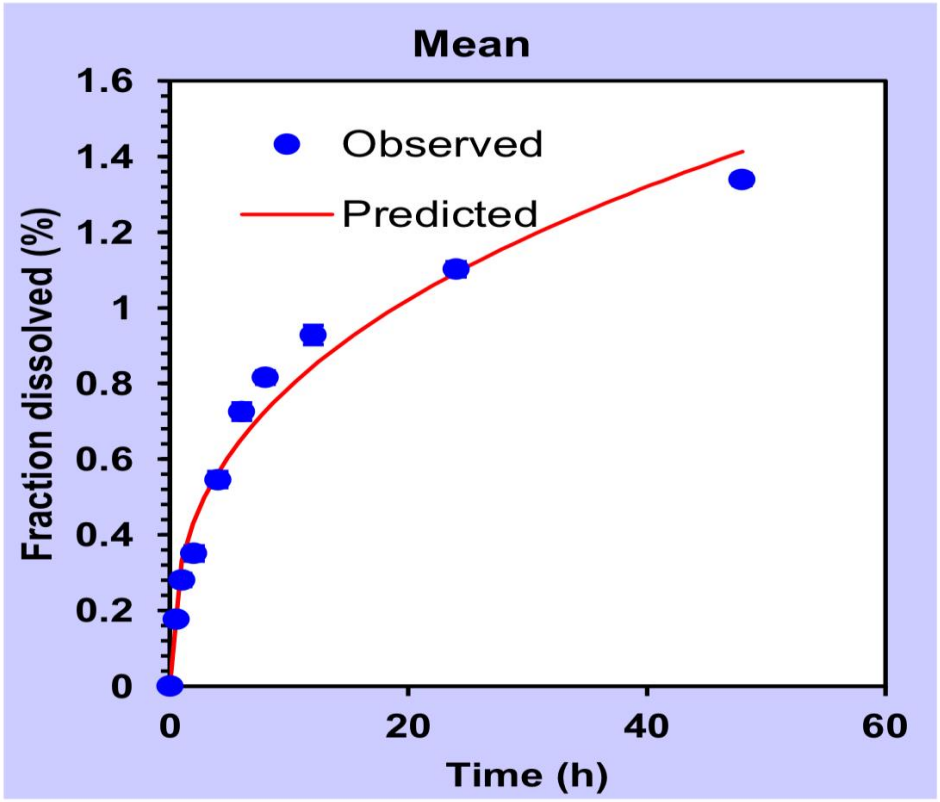
x = 3582 h*our*s

So, 100% of drug will be released in 3582 hours i.e 149.25 days (~ 4 months and 27 days).

5.7.2 Comparison with the standard drug release models:

The mathematical drug release models are employed to validate the mechanics of drug release from a drug-eluting stent tube. Following the application of the coating on the BMS stent, an in vitro drug release study was conducted. As previously stated, entirely distinct kinetic models were utilized to examine the drug release mechanisms from a drug coated BMS stent.

The most effective fitted model in this instance was the "Korsmeyer-Peppas" model. This model is mostly utilized to elucidate the drug release mechanisms of chemical or polymer solutions.



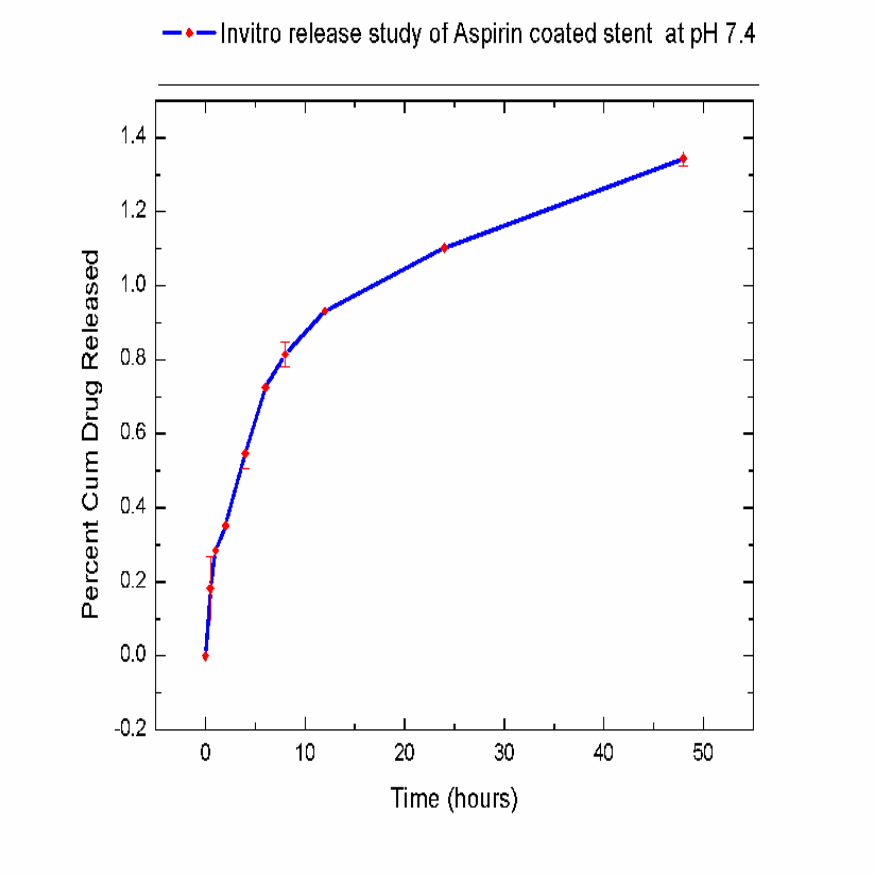


Figure 34: Comparison of observed values with Kerseymere Peppa's Model

The stand equation for the Korsmeyer-Peppas model is given as:

$$M^t / M^a = kt^n$$

- (Mt / M∞) gives the fraction of drug getting released at time "t".
- "k" states the release rate constant.
- "n" refers to the release exponent.
- The value of "n" is used to find values for various polymer concentrations.

CONCLUSION AND FUTURE ASPECTS

Using the hot melting vigorous mixing method, PCL/CS blends were effectively synthesized without the need for any chemical or non-chemical compatibilizers. This demonstrates that PCL adheres well to CS and that, from a thermodynamic perspective, its interaction parameter with CS is insignificant. We were able to address our main worry of changing the brittleness and elongation of CS by blending with PCL. A higher PCL concentration raised the percentage of elongation and reduced brittleness. For samples 1 and 2, the best mechanical results were obtained with 20% and 30% CS, respectively. The strength of these samples was almost 10 MPa, which is close to the needed strength. There was also a notable increase in % elongation from 10% to 160%, and a decrease in brittleness from 12 GPa to 4 GPa.

FTIR examination of all four compositions revealed the presence of a C=O link, indicating the establishment of a chemical bond between PCL and CS. Therefore, it may be asserted that thermodynamic mixes were effectively synthesized. The biodegradation test indicated that sample 1, containing 85% PCL, exhibited the most rapid disintegration over a two-year period, whereas sample 4, having the greatest CS concentration, demonstrated the slowest degradation rate. The optimal degradation period for an effective stent should range from 1.5 to 3 years, and based on our biodegradation findings, this can be accomplished by maintaining the concentration of CS in PLA below 30%.

The TGA results demonstrated that our blends remain stable up to 300 °C, indicating that these blends can function in the body without experiencing heat stress or degradation. SEM analysis further corroborates the aforementioned conclusions that sample 1 exhibited the creation of homogeneous blends. The SEM photos of sample 1, including 80% PCL and 10% CS, exhibited the smoothest surface, devoid of any discernible flakes or particles in comparison to other compositions.

Consequently, this research indicates that the ideal composition of the PCL/CS blend for biodegradable stents comprises CS in the range of 15-30% and PCL at 70-85%.
The future direction of this research involves developing stent coatings with the optimal PCL/CS blend composition while altering the drug content to assess the impact of drug elution in stents.

The third element involves designing a stent utilizing this optimal mixture. A 10-month in vitro release study is necessary to verify that 100% of the medicine will be released within 9.25 months.

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