

**IntechOpen**

IntechOpen Series  
Biomedical Engineering, Volume 36

# **Polymeric Scaffolds**

The Backbone of Modern Tissue Engineering

*Edited by Adnan Haider,  
Sajjad Haider and Sumra Wajid Abbasi*





---

# Polymeric Scaffolds - The Backbone of Modern Tissue Engineering

*Edited by Adnan Haider,  
Sajjad Haider and Sumra Wajid Abbasi*

Published in London, United Kingdom

---

Polymeric Scaffolds – The Backbone of Modern Tissue Engineering

<http://dx.doi.org/10.5772/intechopen.1009723>

Edited by Adnan Haider, Sajjad Haider and Sumra Wajid Abbasi

#### Contributors

Abdusemer Reyimu, Adnan Haider, Aimin Xu, Alimu Keremu, Ankush Kumar, Chuanjiang He, Dhandeep Singh, Dimple Sethi Chopra, Joham Sarfraz Ali, Mamatali Rahman, Mareeswari Balasubramanian, Muhammad Naeem, Navjeet Singh, Nirmal Singh, Pugalanthipandian Sankaralingam, Ravichandran Kandaswamy, Rida Fatima Saeed, Rouzi Kamiliyang, Sajjad Haider, Shaikat Khan, Sumra Wajid Abbasi, Sundara Moorthi Ganesan, Vijayakumar Chinnaswamy Thangavel, Wuerken Jumabayi, Zureguli Tuerxun

#### © The Editor(s) and the Author(s) 2026

The rights of the editor(s) and the author(s) have been asserted in accordance with the Copyright, Designs and Patents Act 1988. All rights to the book as a whole are reserved by INTECHOPEN LIMITED. The book as a whole (compilation) cannot be reproduced, distributed or used for commercial or non-commercial purposes without INTECHOPEN LIMITED's written permission. Enquiries concerning the use of the book should be directed to INTECHOPEN LIMITED rights and permissions department ([permissions@intechopen.com](mailto:permissions@intechopen.com)).

Violations are liable to prosecution under the governing Copyright Law.



Individual chapters of this publication are distributed under the terms of the Creative Commons Attribution 4.0 License which permits commercial use, distribution and reproduction of the individual chapters, provided the original author(s) and source publication are appropriately acknowledged. If so indicated, certain images may not be included under the Creative Commons license. In such cases users will need to obtain permission from the license holder to reproduce the material. More details and guidelines concerning content reuse and adaptation can be found at <http://www.intechopen.com/copyright-policy.html>.

#### Notice

Statements and opinions expressed in the chapters are those of the individual contributors and not necessarily those of the editors or publisher. No responsibility is accepted for the accuracy of information contained in the published chapters. The publisher assumes no responsibility for any damage or injury to persons or property arising out of the use of any materials, instructions, methods or ideas contained in the book.

First published in London, United Kingdom, 2026 by IntechOpen

IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 167-169 Great Portland Street, London, W1W 5PF, United Kingdom

For EU product safety concerns: IN TECH d.o.o., Prolaz Marije Krucifikse Kozulić 3, 51000 Rijeka, Croatia, [info@intechopen.com](mailto:info@intechopen.com) or visit our website at [intechopen.com](http://intechopen.com).

#### British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Polymeric Scaffolds – The Backbone of Modern Tissue Engineering

Edited by Adnan Haider, Sajjad Haider and Sumra Wajid Abbasi

p. cm.

This title is part of the Biomedical Engineering Book Series, Volume 36

Topic: Biotechnology – Biosensors, Biomaterials and Tissue Engineering

Series Editor: Robert Koprowski

Topic Editor: Luis Jesús Villarreal-Gómez

Print ISBN 978-1-83635-938-8

Online ISBN 978-1-83635-937-1

eBook (PDF) ISBN 978-1-83635-939-5

ISSN 2631-5343

If disposing of this product, please recycle the paper responsibly.

IntechOpen Book Series

# Biomedical Engineering

Volume 36

## Aims and Scope of the Series

Biomedical Engineering is one of the fastest-growing interdisciplinary branches of science and industry. The combination of electronics and computer science with biology and medicine has improved patient diagnosis, reduced rehabilitation time, and helped to facilitate a better quality of life. Nowadays, all medical imaging devices, medical instruments, or new laboratory techniques result from the cooperation of specialists in various fields. The series of Biomedical Engineering books covers such areas of knowledge as chemistry, physics, electronics, medicine, and biology. This series is intended for doctors, engineers, and scientists involved in biomedical engineering or those wanting to start working in this field.



# Meet the Series Editor



Robert Koprowski, MD (1997), Ph.D. (2003), Habilitation (2015), is an employee of the University of Silesia, Poland, Institute of Computer Science, Department of Biomedical Computer Systems. For 20 years, he has studied the analysis and processing of biomedical images, emphasizing the full automation of measurement for a large inter-individual variability of patients. Dr. Koprowski has authored more than a hundred research papers with dozens in impact factor (IF) journals and has authored or co-authored six books. Additionally, he is the author of several national and international patents in the field of biomedical devices and imaging. Since 2011, he has been a reviewer of grants and projects (including EU projects) in biomedical engineering.



# Meet the Volume Editors



Dr. Haider has been working as an Associate Professor in the Department of Biological Sciences (Section of Nanomedicine) at the National University of Medical Sciences (NUMS) since 31/01/2020. He also worked at the Department of Chemistry at Kohat University of Science and Technology, Kohat, Pakistan, until August 2019. He taught undergraduate and MS students. He received his Ph.D. from Kyungpook National University and his postdoctoral degree from Yeungnam University in Daegu, South Korea, in polymer science and engineering. His research focuses on electrospun nanofibers, the development of metal nanoparticles, and the synthesis of biopolymer composites for biomedical and environmental applications. Dr. Haider has served as Principal and Co-Principal Investigator on multiple competitively funded research projects and has published 98 high-impact articles, including book chapters and books. Dr. Haider's research has been well-received by the research community. His articles appear on the lists of most-cited and most-downloaded articles in the most prominent journals. Dr. Haider's current citations are 6785 with an h-index of 35 and an i10-index of 62 (07/11/2025, Google Scholar). Dr. Haider's name has been in the top 2% cited list for five consecutive years. The list is compiled by Stanford University and Elsevier. He is also the managing editor of Life and Science Journal.



Dr. Sumra Wajid Abbasi is a Tenured Associate Professor in the Department of Biological Sciences at the National University of Medical Sciences (NUMS), Pakistan. She earned her Ph.D. in Bioinformatics from Quaid-i-Azam University, Islamabad, following earlier degrees in bioinformatics at the undergraduate and postgraduate levels. She also completed international research training at King's College London through the Higher Education Commission of Pakistan's International Research Support Initiative Program. Dr. Abbasi's scholarly work is rooted in bioinformatics and computational biology, with particular emphasis on protein structure modelling, molecular docking, molecular dynamics simulations, genomics, immunoinformatics, and systems-level data analysis. Her research has advanced computational approaches in infectious diseases, cancer genomics, antimicrobial discovery, and vaccine design, integrating structural biology with large-scale biological data. She has served as Principal Investigator and Co-Principal Investigator on multiple competitively funded research projects. She has authored more than 75 international peer-reviewed publications, with a cumulative impact factor exceeding 326, 1,993 citations, an h-index of 21, and an i10-index of 37. Her work has appeared in leading journals across computational biology, molecular medicine, and biomedical sciences. Beyond research, Dr. Abbasi plays an active role in academic leadership and mentorship, holding several administrative and advisory positions at NUMS and supervising undergraduate and postgraduate research. She also contributes to the international scientific community as a topic editor, guest editor, and reviewer for high-impact journals, particularly in computational biology, immunoinformatics, and vaccine development.



Prof. Sajjad Haider is a Professor of Polymer Engineering and Science in the Department of Chemical Engineering at King Saud University (KSU), Riyadh, Saudi Arabia. He has been serving at KSU since May 2009, initially joining the department as an Assistant Professor. He is actively involved in teaching and mentoring graduate and master's students while leading advanced research in polymer science and nanotechnology. His primary research interests include the fabrication of electrospun nanofibers for environmental and biomedical applications, renewable biopolymer composites, polymer hydrogels for controlled release, and the development of metal nanoparticles incorporated into nanofibers for photocatalytic applications. Prof. Sajjad's work integrates materials design with functional performance, addressing key challenges in sustainability, healthcare, and environmental remediation. Prof. Sajjad's research contributions have received significant international recognition. His publications frequently rank among the most-cited and most-downloaded articles in leading international journals. According to Google Scholar, he has accumulated 11,859 citations, with an h-index of 53 and an i10-index of 148. His scholarly output includes more than 250 peer-reviewed publications, 3 patents, 10 edited reference books, and 15 book chapters. Collectively, his research publications have an impact factor exceeding 940 (as of 2025), with several additional manuscripts currently under review or in preparation. In recognition of his sustained scientific impact, Prof. Sajjad has been listed among the Top 2% of scientists worldwide for multiple years (2021, 2022, and 2024). At King Saud University, he has successfully established a fully operational Nanotechnology Research Laboratory, supported by the National Plan for Science, Technology, and Innovation (NPST). Through securing multiple competitive research grants, he has led projects that resulted in high-quality publications, patents, and excellent evaluations by AAA committees. In addition to his academic role at KSU, Prof. Sajjad has contributed to several international research initiatives during his Ph.D. studies. He was actively involved in the preparation and execution of research proposals funded by the Korean government and the Asian Office of Aerospace Research and Development (AOARD) under the U. S. Air Force Research Laboratory (AFRL), forming an integral part of his doctoral research and collaborative scientific activities.

# Contents

|                                                                                                                                                                                                                                                                                                    |             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| <b>Preface</b>                                                                                                                                                                                                                                                                                     | <b>XIII</b> |
| <b>Section 1</b>                                                                                                                                                                                                                                                                                   |             |
| Polymeric Scaffold in Biomedical Engineering                                                                                                                                                                                                                                                       | 1           |
| <b>Chapter 1</b>                                                                                                                                                                                                                                                                                   | <b>3</b>    |
| Introductory Chapter: Polymers and Their Scaffolds – A Biomedical Perspective<br><i>by Sajjad Haider, Adnan Haider and Sumra Wajid Abbasi</i>                                                                                                                                                      |             |
| <b>Chapter 2</b>                                                                                                                                                                                                                                                                                   | <b>7</b>    |
| Polymeric Scaffolds and Their Role in Biomedical Engineering<br><i>by Shaukat Khan, Joham Sarfraz Ali, Rida Fatima Saeed, Muhammad Naeem, Sumra Wajid Abbasi, Sajjad Haider and Adnan Haider</i>                                                                                                   |             |
| <b>Chapter 3</b>                                                                                                                                                                                                                                                                                   | <b>33</b>   |
| Polyhydroxyalkanoate (PHA) Scaffolds in Biomedical Engineering: Fabrication, Properties and Applications<br><i>by Mamatali Rahman, Abdusemer Reyimu, Zureguli Tuerxun, Wuerken Jumabayi, Rouzi Kamilijiang, Chuanjiang He, Alimu Keremu and Aimin Xu</i>                                           |             |
| <b>Section 2</b>                                                                                                                                                                                                                                                                                   |             |
| Advanced Scaffold Design                                                                                                                                                                                                                                                                           | 57          |
| <b>Chapter 4</b>                                                                                                                                                                                                                                                                                   | <b>59</b>   |
| Nanofluorophosphate Glasses as Biocompatible and Bioactive Materials in Porous Biopolymeric Scaffolds for Bone Tissue Engineering<br><i>by Mareeswari Balasubramanian, Sundara Moorthi Ganesan, Vijayakumar Chinnaswamy Thangavel, Pugalanthipandian Sankaralingam and Ravichandran Kandaswamy</i> |             |
| <b>Chapter 5</b>                                                                                                                                                                                                                                                                                   | <b>83</b>   |
| Three-Dimensional Printed Biomimetic Polymer Scaffolds for Wound Healing<br><i>by Ankush Kumar, Navjeet Singh, Dimple Sethi Chopra, Dhandeep Singh and Nirmal Singh</i>                                                                                                                            |             |



# Preface

Tissue engineering is an interdisciplinary field that integrates biology, materials science, and clinical medicine to provide transformative approaches for repairing, replacing, and regenerating damaged tissues and organs. Central to this rapidly advancing discipline are polymeric scaffolds, engineered to provide the physical, chemical, and biological support required to direct cell behaviour and tissue development. *Polymeric Scaffolds - The Backbone of Modern Tissue Engineering* is dedicated to examining the essential contributions of these materials to the current landscape and future directions of regenerative medicine.

Polymeric scaffolds serve a function beyond structure. They influence cell adhesion, proliferation, differentiation, and extracellular matrix deposition while simultaneously addressing critical challenges, including biocompatibility, biodegradability, mechanical integrity, and controlled bioactivity. Advances in polymer chemistry, nanotechnology, additive manufacturing, and biofabrication have enabled the design of scaffolds that closely mimic native tissue architecture and dynamic biological environments. As a result, polymeric scaffolds have become indispensable tools for applications ranging from bone and cartilage regeneration to skin, vascular, neural, and soft tissue engineering.

This book aims to provide a comprehensive perspective on polymeric scaffolds, covering fundamental principles, structure–property relationships, and biological interactions. It also highlights recent innovations, such as 3D bioprinting. Future directions are discussed to bridge the gap between laboratory research and real-world medical applications.

*Polymeric Scaffolds - The Backbone of Modern Tissue Engineering* is intended for graduate students, researchers, academicians, and professionals in biomaterials science, biomedical engineering, biotechnology, and regenerative medicine. By bringing together theoretical foundations and practical insights, this book seeks to inspire innovation and foster a deeper understanding of how polymeric scaffolds can be engineered to meet the complex demands of tissue regeneration.

We hope this book serves not only as a reference but also as a catalyst for continued research and collaboration, advancing tissue engineering and the development of next-generation regenerative therapies.

**Adnan Haider and Sumra Wajid Abbasi**

Department of Biological Sciences,  
National University of Medical Sciences,  
Rawalpindi, Pakistan

**Sajjad Haider**

Department of Chemical Engineering,  
King Saud University,  
Riyadh, Saudi Arabia

---

## Section 1

# Polymeric Scaffold in Biomedical Engineering

---



# Introductory Chapter: Polymers and Their Scaffolds – A Biomedical Perspective

*Sajjad Haider, Adnan Haider and Sumra Wajid Abbasi*

## 1. Introduction

Polymers are macromolecules that are made up of repetitive structural units. Polymers can be obtained naturally or synthetically. Natural polymers include chitosan, collagen, alginate, etc. Synthetic polymers include polylactic acid (PLA), polyglycolic acid (PGA), polycaprolactone (PCL), etc. [1]. Because of their properties, such as flexibility, mechanical tunability, biodegradability, and biocompatibility, polymers have become very important in biomedical applications [2]. Currently, they are widely used in medical devices, controlled drug delivery, wound dressings, and tissue engineering. The polymer's ability to degrade safely within the body or to remain biocompatible without causing an undesirable immune response makes them excellent for application in the field of biomedicine [3]. Furthermore, recent advances in polymer chemistry have also made it possible to develop materials with specified porosity, molecular weight, and surface chemistry to perform highly focused biomedical activities. Among various biomedical applications, a particularly notable one is the construction of polymeric scaffolds. These scaffolds help to repair and regenerate damaged bone by replicating the extracellular matrix (ECM) [4]. In addition to structural support, these scaffolds aid in the regulation of cell adhesion, proliferation, and differentiation, eventually guiding the regeneration of new tissue [5, 6]. Any scaffold's biological performance and therapeutic outcomes can be predicted by its architecture, which encompasses pore size, interconnectivity, and degradation rate [7]. Consequently, polymer-based scaffolds have become an indispensable tool in tissue engineering and regenerative medicine, connecting clinical applications with material science advancements [8].

## 2. Types of polymeric scaffolds for biomedical applications

Polymeric scaffolds can be broadly classified into various categories. Depending on the intended application, each category provides unique benefits, including drug delivery, cartilage restoration, or bone regeneration. **Table 1** shows the different types of polymeric scaffolds and other important information.

| Type                        | Examples                                      | Pros                                                                                                 | Cons                                                          | References |
|-----------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|------------|
| Natural polymer scaffolds   | Collagen, chitosan, alginate, hyaluronic acid | Exceptional biocompatibility, promotes cell attachment, and is bioactive                             | Variability and inadequate mechanical strength                | [9]        |
| Synthetic polymer scaffolds | PLA, PGA, PCL, PEG                            | Tunable strength, reproducible properties, and controlled degradation                                | Deficit of bioactive signals; potential modification required | [10]       |
| Composite scaffolds         | PLA-collagen, PCL-chitosan                    | Combines mechanical robustness with bioactivity                                                      | Intricate fabrication                                         | [11]       |
| Hydrogel-based scaffolds    | PEG-based hydrogels, alginate hydrogels       | It is advantageous for drug delivery due to its high water content, which resembles delicate tissues | Mechanical strength is restricted                             | [12]       |
| Nanofiber scaffolds         | Electrospun PLA, PCL nanofibers               | High surface area, nanostructure that resembles an ECM                                               | In certain instances, mechanical stability is restricted      | [13]       |
| 3D-printed scaffolds        | PLA, PCL, PEGDA constructs                    | Pore size and architecture are precisely managed                                                     | Requires high-tech tools                                      | [8]        |

**Table 1.**  
*Classification of polymeric scaffolds.*

### 3. Future prospects

Polymeric scaffolds are believed to play a vital role in biomedical applications and could produce remarkable outcomes in the future. Polymer-based smart scaffolds are being designed to respond to environmental changes and deliver drugs or growth hormones as needed, allowing clinicians to precisely manage the treatment. Furthermore, 3D bio printing is also significantly contributing to the growth of personalized medicine. This method results in the development of precise tissue structures by making use of polymers and cells obtained from particular patients. Currently, hybrid materials are being developed to speed up tissue healing. Hybrid materials combine bioactive nanoparticles, growth factors, or stem cells. There is also more and more focus on sustainability and biodegradable polymers. Such polymers are being used more often to build biomedical scaffolds that are less detrimental to the environment. Researchers are focusing on fabricating materials, and more specifically, polymeric scaffolds, for overcoming hurdles in delivering drugs and tissue regeneration. In this book, readers will find information about polymers and their pivotal applications in the biomedical field.

## Author details

Sajjad Haider<sup>2</sup>, Adnan Haider<sup>1</sup> and Sumra Wajid Abbasi<sup>1\*</sup>

<sup>1</sup> Department of Biological Sciences, National University of Medical Sciences, Rawalpindi, Pakistan

<sup>2</sup> College of Engineering, Department of Chemical Engineering, King Saud University, Riyadh, Saudi Arabia

\*Address all correspondence to: [sumra.abbasi@numspak.edu.pk](mailto:sumra.abbasi@numspak.edu.pk)

## IntechOpen

---

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Ratner BD, Bryant SJ. Biomaterials: Where we have been and where we are going. *Annual Review of Biomedical Engineering*. 2004;**6**:41–75
- [2] Peppas NA, Hilt JZ, Khademhosseini A, Langer R. Hydrogels in biology and medicine: From molecular principles to bionanotechnology. *Advanced Materials*. 2006;**18**(11):1345–1360
- [3] Middleton JC, Tipton AJ. Synthetic biodegradable polymers as orthopedic devices. *Biomaterials*. 2000;**21**(23):2335–2346
- [4] Khan MUA, Aslam MA, Abdullah MFB, Stojanović GM. Current perspectives of protein in bone tissue engineering: bone structure, ideal scaffolds, fabrication techniques, applications, scopes, and future advances. *Journal of the American Chemical Society*. 2024;**7**:5082–5106
- [5] Ma PX. Biomimetic materials for tissue engineering. *Advanced Drug Delivery Reviews*. 2008;**60**(2):184–198
- [6] O'Brien FJ. Biomaterials & scaffolds for tissue engineering. *Materials Today*. 2011;**14**(3):88–95
- [7] Hollister SJ. Porous scaffold design for tissue engineering. *Nature Materials*. 2005;**4**(7):518–524
- [8] Murphy SV, Atala A. 3D bioprinting of tissues and organs. *Nature Biotechnology*. 2014;**32**(8):773–785
- [9] Drury JL, Mooney DJ. Hydrogels for tissue engineering: Scaffold design variables and applications. *Biomaterials*. 2003;**24**(24):4337–4351
- [10] Rezwan K, Chen QZ, Blaker JJ, Boccaccini AR. Biodegradable and bioactive porous polymer/inorganic composite scaffolds for bone tissue engineering. *Biomaterials*. 2006;**27**(18):3413–3431
- [11] Zhang YS, Khademhosseini A. Advances in engineering hydrogels. *Science*. 2019;**365**(6456):640–643
- [12] Li J, Mooney DJ. Designing hydrogels for controlled drug delivery. *Nature Reviews Materials*. 2016;**112**:16071
- [13] Pham QP, Sharma U, Mikos AG. Electrospinning of polymeric nanofibers for tissue engineering applications: A review. *Tissue Engineering*. 2006;**12**(5):1197–1211

## Chapter 2

# Polymeric Scaffolds and Their Role in Biomedical Engineering

*Shaukat Khan, Joham Sarfraz Ali, Rida Fatima Saeed,  
Muhammad Naeem, Sumra Wajid Abbasi, Sajjad Haider and  
Adnan Haider*

### Abstract

Tissue and organ failure resulting from diseases, aging, injuries, or accidents remains a major global health challenge. This problem is further compounded by the shortage of donor organs, immune rejection of transplanted tissues, and the limited functionality of transplanted organs. Although biomaterials have long been used in medical applications, recent research has increasingly emphasized their role in tissue regeneration. In particular, scaffolds have evolved from being mere structural supports to dynamic platforms that actively influence cell adhesion, proliferation, differentiation, and migration. Both natural and synthetic biopolymers are extensively utilized in scaffold fabrication due to their favorable chemical and biological characteristics, such as biocompatibility and biodegradability. Advances in scaffold fabrication techniques, including electrospinning, freeze-drying, and three-dimensional (3D) bioprinting, have enabled accurate control over porosity, architecture, and mechanical strength, broadening their applicability in biomedical fields. Moreover, polymer-based scaffolds are increasingly explored as drug delivery systems, which are capable of targeting specific sites, controlling drug release rates, and improving therapeutic efficacy through tailored chemical modifications. The integration of drug delivery and tissue engineering highlights the active therapeutic role of scaffolds, positioning them as multifunctional components rather than passive supports. Therefore, this chapter presents a comprehensive overview of various polymeric scaffolds, their fabrication methods, and their potential uses in drug delivery and tissue regeneration. It also discusses current challenges, emerging trends, and future opportunities within this rapidly evolving area of research.

**Keywords:** 3D printing, biodegradable polymers, polymeric scaffolds, tissue engineering, biofabrication, electrospinning, drug delivery systems

### 1. Introduction

One of the primary health concerns in modern medicine is the increasing incidence of tissue and organ failure resulting from diseases, aging, injuries, and

accidents. Despite significant medical advances, issues such as donor organ shortages, immune rejection, and low transplant success rates persist. Traditionally, biomaterials have played a vital role in addressing these problems; however, recent research has shifted toward their use in promoting tissue regeneration. This emerging focus has created a growing demand for advanced biomaterials capable of not only replacing damaged tissues but also facilitating their natural repair and regeneration. Tissue engineering has become a critical approach for maintaining, restoring, or enhancing the function of tissues compromised by disease or trauma. Achieving these objectives requires the development of innovative biological substitutes, underscoring the importance of continued advancements in biomaterials and fabrication technologies [1].

Owing to the diversity in structural topologies and excellent biodegradability, in addition to biocompatibility, polymers are fundamental materials in the development of biomaterials at both the nano- and macroscale levels. Advances in material characterization techniques have enhanced our understanding of fouling phenomena, thereby enabling the design of polymeric materials with improved antifouling properties. Recent studies have particularly emphasized the advantages of synthetic polymers as promising biomaterials in various applications, including sensing, imaging, separation, and antifouling technologies [2]. Owing to their biocompatibility, controlled enzymatic degradability, and ease of chemical modification, bioactive compounds and polymers have gained attention in the development of advanced drug carriers. Natural polymers, including polysaccharides and proteins, are extensively employed in tissue engineering, cancer therapy, and wound healing applications. As therapeutic strategies expand to encompass peptides, proteins, nucleic acids, and antibodies, drug delivery systems (DDS) are continuously evolving to meet the emerging challenges associated with these complex bioactive agents [3].

Nanoparticles offer an effective approach for drug delivery by enabling controlled and sustained release of drugs. However, concerns regarding their potential toxicity and environmental impact have prompted the exploration of safer alternatives. In recent years, polymer-based DDS have gained prominence in biomedical research due to their ability to provide targeted delivery, controlled release, and improved therapeutic outcomes. Additionally, research has expanded toward drug-free macromolecular therapies and biomimetic or bioinspired polymer systems. Polymers, combined with advanced additive manufacturing techniques, hold great promise for improving patient compliance, therapeutic efficacy, and overall medical safety [4, 5], as concisely summarized in **Table 1**.

Recently, researchers have been exploring three-dimensional (3D) scaffolds as potential materials to promote tissue regeneration, resulting in several biomedical applications. 3D scaffolds not only support structural stability but also provide a biomimetic environment that closely resembles natural tissue architecture [9]. When implanted, these scaffolds form a localized bioactive environment that supports the regeneration of damaged or missing tissues. Both natural and synthetic polymers are extensively utilized as biomaterials for fabricating such scaffolds [10]. However, limitations such as the risk of pathogenic contamination, reduced mechanical strength, and potential immunogenicity remain challenges, particularly with natural polymers. In contrast, synthetic polymers and their copolymers offer advantages in terms of controlled degradation and adjustable mechanical properties, rendering them suitable for scaffold fabrication [9].

| Type of polymers                 | Key chemical properties                              | Polymer type                                           | Applications                                      | Examples                                   | References |
|----------------------------------|------------------------------------------------------|--------------------------------------------------------|---------------------------------------------------|--------------------------------------------|------------|
| Hydrogels                        | Hydrophilic, swellable, crosslinked                  | Natural (alginate, chitosan) or synthetic (PHEMA, PEG) | Wound healing, controlled drug release, PEG-based | Hydrogel for insulin delivery              | [6]        |
| Nanoparticles                    | Biodegradable, biocompatible, and surface-modifiable | Biodegradable (PLGA, PCL, chitosan)                    | Cancer therapy, vaccines, and gene delivery       | PLGA-NPs for paclitaxel                    | [7]        |
| Liposomes and polymeric micelles | Self-assembling, hydrophilic-lipophilic balance      | Amphiphilic copolymers (PEG-PLA, PCL-PEG)              | Cancer therapy, antimicrobial delivery            | Doxil (PEGylated liposome for doxorubicin) | [8]        |

**Table 1.**  
*Latest advancements in polymeric drug delivery systems (DDS) and their applications.*

This chapter discusses recent advancements in polymeric drug delivery systems, scaffold materials, their properties, design considerations, and the emerging prospects for clinical applications and personalized medicine.

## 2. Polymers used for scaffold fabrication

Natural and synthetic polymers both serve crucial functions in skin tissue regeneration, each characterized by distinct properties and mechanisms of action. Natural polymers contain physiologically recognizable functional moieties that actively interact with cellular systems and are inherently biodegradable. Conversely, synthetic polymers provide the advantage of extensive control over biodegradability, mechanical stability, and chemical resistance – enabling precise customization of material properties (as illustrated in **Table 2**) [11].

### 2.1 Alginates

They are naturally anionic polysaccharides with excellent gelling ability, biocompatibility, optimal deflocculation, moisture retention, protein adsorption capacity, biodegradability, and viscoelasticity, owing to their suitability for scaffold fabrication. Their proven safety and biocompatibility have led to extensive applications across several fields, such as food processing, drug delivery systems (DDS), cosmetics, tissue regeneration, and wound care material development. Alginates have been in use as wound dressings for a long time. Such dressings can be successfully commercialized and employed in clinical wound treatments ever since the 1980s, for example, Sorbsan, which is used for treating trophic as well as diabetic ulcers. Several brands of alginate dressings have been developed and marketed in diverse forms and sizes to accommodate specific clinical needs. These dressings are particularly suitable for managing superficial wounds and lacerations. Owing to their high absorbency, alginates are especially recommended for wounds with moderate to heavy exudate [18].

| Natural biomaterials | Key characteristics of tissue repair                                                                                                                                                                                                                                                    | References |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Cellulose            | <ul style="list-style-type: none"> <li>Cellulose degradation rates can be modified to meet wound-healing stages.</li> <li>Cellulose scaffolds' porous texture facilitates the development of blood vessels and cell infiltration.</li> </ul>                                            | [13]       |
| Chitosan             | <ul style="list-style-type: none"> <li>Chitosan regulates the immunological response, facilitating healing and lowering the inflammation.</li> <li>Chitosan can enhance the development of new blood vessels, which are essential for tissue regeneration.</li> </ul>                   | [14]       |
| Alginate             | <ul style="list-style-type: none"> <li>Calcium, a divalent cation, crosslinks alginate, creating a temporary barrier that promotes clotting.</li> <li>A variety of medicinal drugs, such as antibiotics or antifungals, can be applied directly to the wound using alginate.</li> </ul> | [15]       |
| Fibrin               | <ul style="list-style-type: none"> <li>Different cell types that could be involved in wound healing can be drawn to and activated by certain peptides in fibrin.</li> <li>Fibrin eventually degrades, and fresh tissue replaces it during recovery.</li> </ul>                          | [16]       |
| Elastin              | <ul style="list-style-type: none"> <li>Elastin facilitates skin mobility during wound closure, which promotes healing.</li> <li>Elastin may aid in preventing the overproduction of scar tissue.</li> </ul>                                                                             | [17]       |

**Table 2.**  
Natural biomaterials characteristics. Adapted from the study by Sindhi et al. [12].

## 2.2 Fibrin

Fibrin constitutes the primary structural factor of blood coagulates, typically formed during vascular injuries. It plays a critical role in clot contraction, also known as retraction, which refers to the spontaneous reduction in clot size, and thus contributes substantially to wound healing, hemostasis, and the restoration of normal blood flow otherwise blocked by obstructive thrombi. The activated platelets generate the driving force behind clot contraction through intracellular interactions with non-muscle myosin IIa and actin. The fibrin network actively transmits these forces through strong platelet–fibrin interactions facilitated by the platelet adhesive receptor integrin  $\alpha\text{IIb}\beta 3$  [19]. Xu et al. [20] reported an innovative fibrin-loaded polyvinyl alcohol (PVA) scaffold for skin regeneration applications. The findings showed that fibrin-embedded lyophilized PVA-based hydrogel granules had better structural integrity and biocompatibility. Additionally, the hydrogel scaffolds' potential as perfect dressing materials was demonstrated by *in vivo* immunohistochemical and histological investigations, which verified that they promoted optimal tissue development, revascularization, and epithelialization [20].

Owing to their exceptional biocompatibility, hydrogels have gained prominence as alternatives to autografts and allografts in wound healing applications. Burmeister et al. have developed a hydrogel using fibrin that improves the burn-induced wound tissue regeneration mechanism. *In vivo* studies also demonstrated that the aforesaid hydrogel enhanced granulation tissue development and modulated the rate of skin regeneration [21]. Similarly, Natesan et al. [22] showed in their study that they developed a bilayer hydrogel system incorporating polyethylene glycol, collagen, and fibrin, carrying skin adipose stem cells, for severe burn treatment. This

technique is unique in that it uses stem cells isolated directly from the patient's debrided burn tissue, which improves tissue integration with the matrix of the hydrogel. The *in vitro* and *in vivo* data suggested that these adipose stem cell-loaded hydrogels are effective for burn wound healing [22].

### 2.3 Dextran

Dextran has drawn a lot of interest due to its high biocompatibility and low cytotoxicity. Because of its superior permeability properties, dextran has been widely employed in the fabrication of scaffolds. In another study, Du et al. [23] investigated the interaction between oxidized dextran and the hydrophobic alkyl groups of engineered chitosan. The material has outstanding shape fidelity, viscoelastic behavior, no cytotoxicity, and bioadhesive properties, according to a thorough assessment employing cytotoxicity, field emission scanning electron microscopy, rheological analysis, and tissue adhesion testing. Furthermore, antibacterial assays against *Staphylococcus aureus* and *Pseudomonas aeruginosa* indicated potent bactericidal activity. Additionally, an *in vivo* study revealed that the engineered hydrogels accelerated wound healing, confirming their therapeutic potential. Burn injuries pose significant clinical challenges, such as infection risk and excessive scar formation, both of which impede wound repair and contribute to complications. Conventional treatments, such as autologous skin grafts and transplants, are often limited by inadequate revascularization and epithelialization [23]. In this context, chemical-based therapeutic approaches offer an alternative strategy by modulating immune responses and enhancing tissue repair. Shen et al. [24] reported a hydrogel using dextran for the effective restoration of burn-induced skin damage. The study employed a three-dimensional hydrogel framework to evaluate the therapeutic potential of hydrogel-mediated treatment and the underlying tissue rejuvenation mechanisms. The early anti-inflammatory response induced by the dextran hydrogel was found to stimulate angiogenesis, followed by enhanced epithelialization, thereby improving the overall healing efficacy. Eventually, the hydrogel (dextran) facilitated skin restoration in addition to tissue regeneration, which highlighted its promise for clinical translation to improve burn wound healing [24].

### 2.4 Hyaluronic acid

The disaccharide monomers of D-glucuronic acid, in addition to N-acetyl-D-glucosamine, join to form the natural polysaccharide polymer known as hyaluronic acid (HA). Large levels of HA are found throughout the human body, particularly in the connective tissues, vitreous humor, dermal layers, umbilical cord, and synovial fluid. HA constitutes a fundamental component of the extracellular matrix (ECM), contributing significantly to structural and biological functions. The molecular structure of HA contains numerous carboxyl and hydroxyl functional groups, which enable it to hold water up to 1,000 times its own weight. This remarkable water-retention capacity allows HA to hydrate the ECM effectively and maintain tissue homeostasis. Beyond its hydration properties, HA forms a protective pericellular coat that supports intercellular communication and regulates cell proliferation and migration. It is also present intracellularly, where it participates in modulating inflammatory responses. Importantly, HA exhibits non-toxic, non-immunogenic, and

non-inflammatory properties, elevating its value as a biomedical material. Through its multifunctional biological activities, HA contributes to wound healing, immunomodulation, tissue regeneration, anticancer responses, and cosmetic skin treatments, while also sustaining overall physiological homeostasis [25]. HA is also a central player in inflammatory regulation, cellular activation, and wound repair. Skin injury disrupts tissue architecture and triggers hemorrhage, initiating the inflammatory phase of wound repair. During this stage, platelets release large amounts of high molecular weight-HA (HMW-HA), which facilitates fibrinogen aggregation and restores fluid balance necessary for edema formation and hemostasis. The accumulation of HMW-HA in edema fluid promotes neutrophil migration, enhances phagocytosis, and stimulates the secretion of pro-inflammatory cytokines, such as tumor necrosis factor- $\alpha$ , interleukin-1  $\beta$ , and interleukin-8. Additionally, HMW-HA modifies several intracellular signaling pathways by interacting with CD44 receptors on monocytes and granulocytes [26].

## **2.5 Synthetic polymers**

Synthetic and natural polymers, each with their own special qualities and uses, are essential to the regeneration of skin tissue. Natural polymers have biologically identifiable components that actively participate in cellular functions and are naturally biodegradable. Synthetic polymers, on the other hand, provide the benefit of significant control over the structural characteristics, for example, biodegradation, durability, and chemical resistance, enabling customized modifications (see **Table 3**).

### *2.5.1 Polyvinyl alcohol*

PVA, a synthetic hydrophilic polymer, is used as a potent material for scaffold fabrication owing to its excellent biocompatibility, bio adhesive, and film-forming features. Zhang et al. [27] formulated a composite scaffold made of PVA, lignin, and chitosan, which exhibited pronounced antibacterial and antioxidant activities, making it a promising candidate for skin regeneration. Regardless of its advantageous antibacterial performance and biocompatibility, the mechanical strength of the PVA–chitosan composite scaffolds remains a limiting factor for its clinical application as a wound dressing [27]. Recent advances in tissue engineering have underscored the potential of hydrophilic scaffolds for the repair of injured skin tissues. In particular, topically applied hydrogels have shown excellent efficiency in burn wound treatment and tissue restoration due to their 3D network structure and water-retaining properties. Uppuluri et al. [28] demonstrated the development of an icariin-loaded PVA agar hydrogel scaffold and utilized it as an implant on burn-induced skin wounds to facilitate ECM repair. The physicochemical characteristics of the hydrogel, including melting enthalpy, component compatibility, and chemical structure, were systematically analyzed through DSC, FTIR, and XRD. In addition, FESEM revealed a highly interconnected porous network, confirming the homogeneous diffusion of icariin throughout the scaffold. Histological assessments conducted 21 days post-implantation demonstrated substantial reepithelialization and tissue regeneration, providing direct evidence of the healing potential of the hydrogel scaffold [28].

| Polymers | Functional characteristics found in wound repair                                                                                                                                                                                                                                | Advantages                                                                                                                                                                           | References |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| PCL      | <ul style="list-style-type: none"><li>• Slow degradation results in long-term support for tissue formation and cell growth.</li><li>• Can be altered to provide growth factors or drugs in a regulated manner.</li></ul>                                                        | <ul style="list-style-type: none"><li>• Providing a stable frame-work for cell activity.</li><li>• Encourages long-term wound healing.</li></ul>                                     | [33]       |
| PEG      | <ul style="list-style-type: none"><li>• Increases in wound hydration, decreasing dryness, result in promoting a favorable healing environment.</li><li>• Decreases scar formation.</li><li>• Can be utilized to make hydrogels for continuous drug delivery or cells.</li></ul> | <ul style="list-style-type: none"><li>• Produces a moist environment that encourages cell activity.</li><li>• Allows targeted delivery of therapeutic agents.</li></ul>              | [34]       |
| PGA      | <ul style="list-style-type: none"><li>• By promoting cell adhesion and proliferation, a rapid disintegration rate facilitates quick tissue regeneration.</li></ul>                                                                                                              | <ul style="list-style-type: none"><li>• Promotes early cell adhesion and growth.</li><li>• Allows the formation of tissue over time.</li></ul>                                       | [35]       |
| PHA      | <ul style="list-style-type: none"><li>• To modify tunable mechanical properties to suit the requirements of various skin tissues.</li><li>• May possess innate bioactivity that encourages tissue development and cell growth.</li></ul>                                        | <ul style="list-style-type: none"><li>• May have innate qualities that promote regeneration.</li><li>• Enables customization of scaffolding properties.</li></ul>                    | [36]       |
| PLA      | <ul style="list-style-type: none"><li>• Easily modifiable to enhance functioning with additional biomaterials or bioactive chemicals.</li></ul>                                                                                                                                 | <ul style="list-style-type: none"><li>• Allows robust support for tissue reconstruction.</li><li>• Supports the incorporation of therapeutic agents for targeted benefits.</li></ul> | [37]       |

**Table 3.**  
*Functional characteristics of synthetic polymers and associated advantages. Modified from the study by Sindhi et al. [12].*

### 2.5.2 Polyvinylpyrrolidone

A synthetic hydrophilic polymer, polyvinylpyrrolidone (PVP), has attracted considerable attention due to its crosslinking capacity, biocompatibility, and excellent response to diverse physical and chemical stimuli, elevating its value as a hydrogel material for scaffold fabrication. Kim et al. [29] developed a film forming PVP-based hydrogel incorporating sodium fusidate, with ethanol, PVA, and propylene glycol to improve properties and wound-healing efficacy. Through systematic optimization, a 2:12 PVA/PVP ratio was identified as optimal, demonstrating rapid film formation, efficient drug release, and excellent flexibility. Histological studies and stability tests confirmed that the sodium fusidate-loaded hydrogel achieved enhanced reepithelialization, scarless tissue regeneration, and long-term thermal stability (up to six months at 45°C) compared to commercial formulations, establishing its efficacy for advanced wound therapy [29]. Similarly, Choi et al. [30] reported that a PVA and PVP hydrogel with a neomycin sulfate additive exhibited superior bio-adhesive strength, fluid retention, and tensile resilience. Minimal molecular interaction between the drug and polymeric matrix facilitated uniform drug dispersion within four hours. The formulation demonstrated enhanced wound regeneration efficiency relative to conventional

treatments, indicating that PVA/PVP composite hydrogels offer a robust platform for skin tissue repair and management [30].

### *2.5.3 Poloxamer*

Poloxamer is an amphiphilic triblock copolymer containing poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide), acknowledged for its role as a polymer surfactant. It functions effectively as an antifoaming agent, thickener, wetting agent, and emulsifier, and has been increasingly explored in hydrogel scaffolds for wound healing due to its biocompatibility, non-toxicity, localized drug delivery capability, and thermoreversible gelation properties. Additionally, Soriano-Ruiz et al. [31] developed an HA–poloxamer composite hydrogel combined with antioxidants to enhance wound healing. Furthermore, the formulation's acidic pH (4.6) inhibited bacterial proliferation and shortened healing time. Physicochemical and biological evaluations demonstrated excellent structural integrity, antibacterial activity, and wound-repair performance, confirming its safety and potential as a vitamin-loaded therapeutic platform for future clinical wound-healing applications [31].

In a related study, Li et al. [32] fabricated a biodegradable hydrogel using poloxamer and evaluated its wound healing efficacy using an *in vivo* (rat) model. Also, the hydrogel exhibited high water retention, air permeability, and antimicrobial activity, effectively accelerating the healing process. Histological analyses revealed that the poloxamer hydrogel enhanced angiogenesis, revascularization, and reepithelialization, resulting in improved skin tissue regeneration [32].

## **3. Fabrication techniques**

The polymeric scaffold fabrication method for tissue engineering necessitates precise regulation of structural parameters, for example, porosity, mechanical strength, and architecture. Various fabrication methodologies have been developed to achieve these design specifications, with the most prevalent techniques including 3D printing, electrospinning, freeze-drying, and solvent casting [38].

### **3.1 Three-dimensional printing**

Also referred to as additive manufacturing [39], it represents an extremely versatile and precise fabrication strategy capable of generating scaffolds with complex geometries and controlled pore architectures [40]. Here, a layer-by-layer deposition of a polymer melt or solution takes place in accordance with a computer-aided digital design, allowing precise regulation of the scaffold's overall structure. Such control facilitates the fabrication of scaffolds with customized porosity, interconnectivity, and mechanical strength, optimized for specific tissue engineering applications. Moreover, this technique enables the direct incorporation of bioactive agents or living cells during the fabrication process, thereby enhancing the biofunctionality and regenerative potential of the resultant scaffold [41].

### **3.2 Electrospinning**

This is a well-established technique for producing nanofibrous scaffolds, thoroughly replicating the fibrous architecture of biological ECM. This method creates continuous threads that are collected onto a surface by ejecting a charged polymer solution through a tiny nozzle. The obtained scaffold exhibits a high surface area-to-volume ratio, leading to better cell adhesion, proliferation, and differentiation. However, precise control over pore size remains challenging, often hindering tissue ingrowth [42]. Key operational parameters such as tip-to-collector distance, applied voltage, and solution flow rate strongly affect the fiber diameter, orientation, and overall porosity.

### **3.3 Freeze-drying**

Freeze-drying is a versatile fabrication method for producing highly porous scaffolds with interconnected pore networks. A polymer solution is frozen, and the solvent is then sublimated using a vacuum, leading to a lightweight, porous matrix. Scaffold porosity is tailored by manipulating the rate of freezing and polymer concentration. Additionally, scaffolds that are freeze-dried are frequently used in tissue engineering because high porosity facilitates nutrient diffusion, cell infiltration, and vascularization. However, this method often yields scaffolds with relatively weak mechanical strength [43, 44]. Typically, freezing is carried out at a temperature range of  $-20^{\circ}\text{C}$  to  $-80^{\circ}\text{C}$ , with slower freezing rates resulting in high porosity.

### **3.4 Solvent casting and particulate leaching**

This method is widely used and is a cost-effective approach for the fabrication of polymeric scaffolds. In this technique, a porogen such as salt, sugar, or paraffin spheres is mixed into a polymer solution, followed by casting in a mold. Then, after solvent evaporation, the porogen is filtered out through dissolution, resulting in a porous scaffold. The porosity is primarily governed by the size, shape, and concentration of the porogens. Despite its simplicity and scalability, this method offers limited control over pore interconnectivity and mechanical properties, which may restrict its application in load-bearing tissues [45].

## **4. Drug delivery systems and strategies**

In biomedical engineering, polymeric scaffolds have drawn a lot of interest as efficient drug delivery platforms due to their tunable physical and chemical properties, biodegradability, and structural similarity to the ECM. These scaffolds are capable of encapsulating, protecting, and releasing therapeutic agents in a controlled manner, which is particularly beneficial for treating chronic diseases, cancer, and tissue regeneration [46]. The release behavior of these systems can be tailored by selecting appropriate polymers and fabrication methods, allowing either sustained, gradual release over time or stimuli-responsive release triggered by specific physiological conditions. Among various polymeric structures, hydrogels and electrospun nanofibers are especially prominent, as they facilitate uniform drug

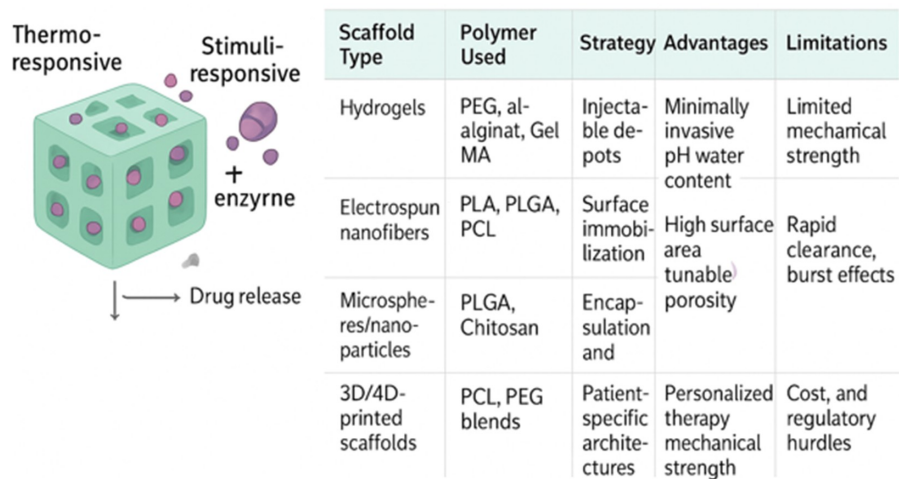
incorporation and controlled diffusion, thereby enhancing therapeutic efficacy and treatment outcomes [47]. Several drug delivery strategies have been integrated into polymeric scaffolds to achieve controlled and efficient therapeutic outcomes. Among these, diffusion-controlled release is the most extensively studied approach, where drugs gradually diffuse via the polymer matrix over time. Degradation-controlled release employs hydrolytically or enzymatically degradable polymers – such as poly (lactic-co-glycolic acid) (PLGA) – allowing drugs to be released progressively as the scaffold breaks down [48]. Stimuli-responsive scaffolds represent a more advanced strategy, wherein drug release is triggered by internal physiological indications (e.g., temperature, pH, or enzyme activity) or external stimuli (e.g., ultrasound, light, or magnetic fields) [49]. These “smart” scaffolds enable precise spatiotemporal control over drug delivery, reducing side effects and enhancing clinical efficacy. Targeted delivery systems further refine therapeutic precision by functionalizing scaffolds with targeting moieties such as peptides, antibodies, or aptamers, thereby directing drugs precisely to diseased tissues or cells [50]. In addition, hybrid systems that integrate nanoparticles within polymeric scaffolds have been developed to combine the advantages of nanoscale carriers with the structural and mechanical support of scaffolds. Such systems facilitate localized, multimodal treatments – for example, simultaneous drug delivery and diagnostic imaging (theranostics) [51]. **Table 4** presents a comparative overview of various scaffold-based drug delivery systems, while **Figure 1** illustrates the primary mechanisms of drug release in polymeric scaffolds.

## 5. Polymer-based drug delivery system

Polymers are composed of repeating structural units, ranging in size from small molecules containing only a few monomer units to macromolecules consisting of thousands or even millions of monomers [57]. The development of polymer-based DDS has revolutionized the pharmaceutical industry by enabling more effective and

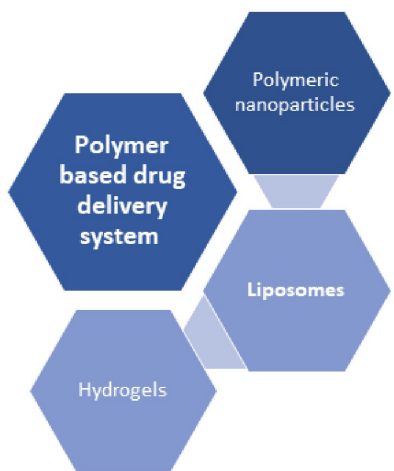
| Scaffold type                              | Drug delivery strategy                       | Key features                            | Representative applications        | References |
|--------------------------------------------|----------------------------------------------|-----------------------------------------|------------------------------------|------------|
| Hydrogels                                  | Diffusion-controlled release                 | High water content, tunable porosity    | Wound healing, cancer therapy      | [52]       |
| Electrospun nanofibers                     | Surface immobilization, nanoparticle loading | High surface area, mechanical strength  | Tissue engineering, antibiotics    | [53]       |
| PLGA scaffolds                             | Degradation-controlled release               | Biodegradable, FDA-approved             | Cancer, sustained protein delivery | [54]       |
| Smart polymers                             | Stimuli-responsive (pH, temperature, enzyme) | Controlled release, precision targeting | Diabetes, localized chemotherapy   | [55]       |
| Hybrid scaffolds (polymer + nanoparticles) | Theranostics, targeted delivery              | Multifunctional, imaging + therapy      | Cancer, regenerative medicine      | [56]       |

**Table 4.**  
*Current polymeric scaffold types and their drug-delivery strategies.*



**Figure 1.**  
Schematic representation of drug delivery strategies for polymeric scaffolds, including diffusion-controlled, degradation-mediated, stimuli-responsive, and targeted/theranostic approaches.

safer therapeutic approaches. These systems take advantage of polymers’ special physicochemical characteristics to achieve controlled and targeted drug release, thereby enhancing drug efficacy and minimizing adverse effects [58]. Polymers can be categorized according to their physical characteristics, biodegradability, and place of origin. Their versatility, biocompatibility, and ability to be surface-modified make them highly suitable for diverse biomedical uses. Some of these categories and their key characteristics are illustrated in **Figure 2**.



**Figure 2.**  
Diagrammatic presentation of polymer-based drug delivery system.

## **5.1 Polymeric nanoparticles**

Polymeric nanoparticles (PNPs) have emerged as multipurpose platforms aimed at drug delivery, capable of encapsulating therapeutic agents to enhance bioavailability and enable controlled release. This controlled delivery improves treatment efficacy while diminishing potential side effects [59]. During PNP preparation, surfactants are often employed to reduce particle size and simultaneously act as cryoprotectants, preserving nanoparticle stability during storage [60]. Among numerous polymers, PLGA is the most widely utilized due to its proven biodegradability, biocompatibility, and regulatory approval by the U.S. Food and Drug Administration (FDA) in 1989 [61]. PLGA has been broadly explored for sustained drug delivery applications, frequently in combination with PVA to optimize particle stability and performance. Furthermore, PNPs are increasingly explored as innovative alternatives to traditional contrast agents, owing to their tunable surface properties and capacity to enhance the solubility of encapsulated compounds. These attributes make them particularly valuable for advanced imaging applications, such as improved visualization of tumors and other pathological tissues in cancer diagnostics.

## **5.2 Liposomes**

Liposome-based DDS have gained considerable prominence in modern therapeutics, effectively integrating advancements in nanotechnology with pharmaceutical innovation [61, 62]. Liposomes are spherical vesicles composed of phospholipid bilayers capable of encapsulating a wide variety of drugs – hydrophobic, hydrophilic, or amphiphilic – either within their aqueous core or lipid membrane [63]. Because their structure closely mimics that of biological membranes, liposomes exhibit excellent biocompatibility and are particularly well-suited for delivering diverse therapeutic agents, including nucleic acids. Depending on their formulation, polymers can either serve as surface coatings on liposomes or be incorporated within the phospholipid bilayer, resulting in polymer-lipid hybrid structures with enhanced stability and functionality. These versatile systems have shown great potential in tumor-targeted drug delivery, offering improved pharmacokinetics, reduced systemic toxicity, and more effective localization of therapeutic agents [64].

## **5.3 Hydrogels**

Hydrogels formed through physical crosslinking exhibit distinctive properties such as a glassy structure, high water retention capacity, and responsiveness to environmental stimuli like temperature or pH. These physically crosslinked hydrogels are typically reversible, allowing transitions between sol and gel states depending on external conditions. In contrast, chemically crosslinked hydrogels demonstrate superior structural stability because covalent bonds are formed between polymer chains, enhancing their mechanical strength and durability [65]. The functional groups present within polymers, such as hydroxyl (–OH), amino (–NH<sub>2</sub>), and carboxyl (–COOH), play a crucial role in determining the solubility and hydrophilicity of hydrogels and can be tailored to achieve specific material characteristics. Based on their synthesis methods, hydrogels are generally

categorized into four types: homopolymers, which consist of a single monomer type with a crosslinked backbone determined by the polymerization process; copolymers, which are composed of two or more different monomers; semi-interpenetrating networks (semi-IPNs), in which a linear polymer infiltrates a crosslinked network without forming chemical bonds; and interpenetrating networks (IPNs), formed by two polymers where at least one is crosslinked in the presence of the other [66].

Among hydrogel-forming polymers, PVA stands out for its non-toxicity, biodegradability [67], and biocompatibility. PVA-based hydrogels are being extensively investigated for biomedical applications, including the treatment of infections due to their antibacterial properties [68] and their use in wound dressings [69]. Beyond serving as three-dimensional support matrices, hydrogels and scaffolds are vital for guiding essential cellular processes such as adhesion, growth, proliferation, differentiation, and migration, ultimately promoting effective tissue regeneration.

## **6. Regulatory facets of nanomaterial-based scaffolds**

The regulatory process for nanomaterial (NM)-based scaffolds is often lengthy, costly, and complex, necessitating careful consideration before commercialization. Researchers typically adhere to the standards established by major regulatory bodies to ensure compliance in biomedical applications involving NMs. However, regulatory progress has been considerably hindered by the heavy workload of agencies, limited interdisciplinary communication, and insufficient understanding across scientific and regulatory domains. Moreover, market expectations regarding the practical utility of hybrid NM-based systems introduce an additional layer of complexity.

At present, there are no comprehensive FDA or EMA guidelines specifically dedicated to NM-based bone tissue regeneration (BTR) products, nor are there standardized databases for large-scale *in vivo* testing or GMP scalability benchmarks. Although the FDA has issued several guidance documents, current evaluations are primarily conducted through conventional review pathways and product classifications according to risk categories. Nevertheless, explicit regulatory frameworks for NM-based BTR remain limited. A major challenge lies in the absence of long-term preclinical and clinical data necessary to assess chronic toxicity, carcinogenicity, and excretion of NMs – issues that significantly constrain clinical translation and industrial production of NM-based scaffolds. Furthermore, the deficiency of reliable computational models to predict NM behavior within complex scaffold matrices, coupled with uncertainties in scalability, further slows research advancement. The absence of a standardized toxicity index for evaluating NMs under physiological conditions also impedes translational success [70].

Therefore, NM-based scaffolds intended for BTR must undergo rigorous case-by-case evaluation and follow harmonized safety protocols to accelerate their clinical adoption. Greater global coordination and transparency among regulatory authorities are essential to expedite licensing procedures and ensure consistent safety evaluation. The establishment of standardized long-term safety and efficacy testing methods would facilitate this process, while early

consultation with regulatory bodies to classify raw materials could streamline approval pathways.

On a positive note, several NM-based bone scaffolds have successfully reached the market with FDA approval. For instance, NanoFUSE<sup>®</sup> combines demineralized bone matrix (DBM) with 45S5 bioactive glass and is used for repairing bone voids. Upon contact with biological fluids, NanoFUSE releases Na<sup>+</sup>, Ca<sup>2+</sup>, PO<sub>4</sub><sup>3-</sup>, and Si<sup>2+</sup> ions, elevating local pH and stimulating HA formation [71]. Similarly, Actifuse<sup>®</sup>, an FDA-cleared NM-based scaffold, demonstrated superior fusion efficiency compared to conventional hydroxyapatite scaffolds [72]. NanoBone<sup>®</sup> Putty represents another key advancement; it integrates hydroxyapatite within a porous silica gel matrix, enhancing osteoconductivity, cell adhesion, and controlled degradation [73]. OsteoFlo-NanoPutty<sup>®</sup> employs a quad-phasic composite of bioglass,  $\alpha$ -TCP,  $\beta$ -TCP, and hydroxyapatite, facilitating cell activity through a synergistic resorption mechanism.

Conversely, several products, such as NanOss<sup>®</sup>, Op-1 Putty<sup>®</sup>, and OSTEOTRANS-MX<sup>®</sup>, have failed to meet clinical or commercial expectations. NanOss<sup>®</sup> was originally fabricated to replicate the bone mineral phase by increasing scaffold surface area; however, preclinical studies revealed a difference between tissue regeneration and scaffold degradation rates, leading to its failure [74]. The optimized NanOss<sup>®</sup> 3D Plus, incorporating super-fine HAp crystals to better emulate natural bone, has since demonstrated a 97% fusion rate [75]. Op-1 Putty<sup>®</sup>, which utilized a collagen/carboxymethyl cellulose matrix for controlled recombinant BMP-7 delivery, suffered from insufficient mechanical stability, uncontrolled BMP release, and immune complications. Similarly, OSTEOTRANS-MX<sup>®</sup>, a biphasic composite scaffold of organic and inorganic NMs, failed due to pore heterogeneity, uneven NM distribution, and inconsistent degradation behavior [76].

Overall, the successful translation of NM-based scaffolds from preclinical research to clinical and commercial use depends on both regulatory alignment and market acceptance. The regenerative medicine sector is currently valued at USD 43.8 billion and has been projected to grow to USD 212.8 billion by 2034. Furthermore, tissue engineering constitutes approximately 28.84% of this market (2024), reflecting the expanding role of scaffolds in regenerative applications. Coherent Market Insights suggests that the scaffold technology market is expected to grow from USD 2.31 billion in 2025 to USD 5.34 billion by 2032 (<https://www.ihealthcareanalyst.com/global-regenerative-medicines-market/>; accessed on 29 July 2025). **Table 5** characterizes a few of the recent patents on tissue engineering scaffolds and was taken from [76]. **Table 6** represents the FDA-approved/commercialized NMs-based scaffolds.

## 7. Future prospects

The future of drug delivery using polymer-based scaffolds is being shaped by developing technologies such as nanomedicine, artificial intelligence, and advanced bioprinting. AI has been shown to play an essential role in optimizing scaffold design by forecasting drug release kinetics and enabling the development of personalized treatment strategies tailored to individual patients [77]. By combining machine learning and materials science, scientists may improve drug release profiles and scaffold design with less experimental work, thereby hastening the development of these systems for use in clinical settings.

| Sr. no | Publication number | Title                                                                                                         | Year |
|--------|--------------------|---------------------------------------------------------------------------------------------------------------|------|
| 1.     | US10058514B2       | A scaffold platform made of silk for creating tissue constructions                                            | 2018 |
| 2.     | US10117967B2       | Skin tissue engineering scaffold and its synthesis process                                                    | 2018 |
| 3.     | CN106110401B       | Micro-nano composite double-layer dermal scaffold and its preparation technique                               | 2016 |
| 4.     | US20160354515A1    | Scaffold for the development and repair of tissues                                                            | 2019 |
| 5.     | US20160106782A1    | Wound healing and tissue engineering                                                                          | 2022 |
| 6.     | CN107998451A       | Skin tissue engineering scaffold creation using 3D printing and the stent's in vitro cytotoxicity test method | 2018 |
| 7.     | AU2008315318A1     | Biodegradable polymer scaffold and its preparation method                                                     | 2014 |

**Table 5.**  
*Recent developments in tissue-engineered scaffold patents.*

| Scaffold/Product                | Composition/Technology                                    | Manufacturer/Status                | Regulatory approval                     | Clinical/Commercial notes                                                                                                        |
|---------------------------------|-----------------------------------------------------------|------------------------------------|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| NanoFUSE <sup>®</sup> DBM       | Demineralized bone matrix + 45S5 bioactive glass          | Surgical Orthopedic Products (USA) | FDA-approved                            | Releases Ca <sup>2+</sup> , Na <sup>+</sup> , Si <sup>2+</sup> , PO <sub>4</sub> <sup>3-</sup> ; stimulates HA and cell activity |
| Actifuse <sup>®</sup>           | Silicate-substituted calcium phosphate                    | Apatech Ltd./Baxter Healthcare     | FDA-cleared (withdrawn)                 | Enhanced bone fusion; withdrawn due to market competition                                                                        |
| NanoBone <sup>®</sup> Putty     | Nano-hydroxyapatite in silica gel matrix                  | Artoss GmbH (Germany)              | CE-marked, FDA-approved (Putty version) | High osteoconductivity, improved cell attachment, and biodegradation.                                                            |
| OsteoFlo <sup>®</sup> NanoPutty | Bioglass + $\alpha$ -TCP + $\beta$ -TCP + HA (quad-phase) | Ceramed Corp.                      | FDA-cleared                             | Promotes osteointegration via nano-surface technology                                                                            |
| NanOss <sup>®</sup> 3D Plus     | Nano-HAP crystals mimicking bone mineral                  | Medtronic                          | FDA-cleared (optimized version)         | 97% fusion rate; improved degradation kinetics                                                                                   |
| Op-1 Putty                      | Collagen/CMC matrix + recombinant BMP-7                   | Stryker Biotech                    | FDA-approved (withdrawn)                | Failure due to uncontrolled BMP release and poor mechanics                                                                       |
| OSTEOTRANS-MX                   | Organic/inorganic nanocomposite                           | Olympus Terumo Biomaterials        | Not approved (failed trials)            | Issues: pore inconsistency, degradation control                                                                                  |

**Table 6.**  
*FDA-approved/commercialized nanomaterials-based scaffolds.*

Another promising innovation is four-dimensional (4D) bioprinting, which combines smart, stimuli-responsive polymers with traditional 3D printing techniques [78]. These dynamic scaffolds can modify their shape or properties in response to physiological or environmental changes, allowing for precise drug

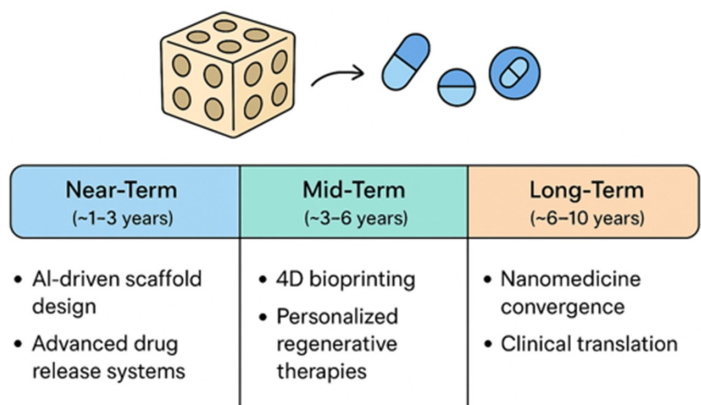
delivery and enhanced tissue regeneration [79]. The incorporation of bioinks containing stem cells and bioactive molecules further enhances functionality, enabling scaffolds to simultaneously deliver therapeutics and support tissue repair. Such multifunctional systems hold great potential for applications in bone regeneration, cardiovascular repair, and even organ bioprinting [80].

The integration of nanotechnology into polymeric scaffolds signifies another major advancement. Researchers are developing hybrid systems that incorporate nanoparticles, exosomes, or magnetic NMs for theranostic uses, uniting therapy and diagnosis in a single platform. These intelligent scaffolds can provide sustained drug release while enabling real-time monitoring of therapeutic progress through imaging or sensing functionalities [81]. However, before these advanced systems can be adopted in clinical practice, it is essential to ensure their long-term safety. This includes addressing concerns such as nanoparticles persisting in the body or accumulating in unintended tissues, which could pose toxicity or biocompatibility risks. Ensuring precise control over degradation and clearance pathways will be crucial for the safe and effective implementation of these next-generation scaffold-based drug delivery technologies.

Translating these innovative concepts into clinical applications presents several significant challenges. Although polymeric scaffolds have demonstrated excellent performance in laboratory settings, issues such as achieving consistent reproducibility, reducing manufacturing costs, and scaling up production for widespread use remain major obstacles [82]. Addressing these challenges requires coordinated international efforts to establish standardized testing protocols and harmonize regulatory frameworks, ensuring safety, quality, and efficacy across different healthcare systems. **Table 7** provides a summary of the emerging trends in this field, while **Figure 3** illustrates a conceptual framework for integrating new technologies into scaffold-based DDS to facilitate their transition from research to clinical practice.

| Future direction                    | Key approach                                   | Advantages                                                  | Challenges                                      | References |
|-------------------------------------|------------------------------------------------|-------------------------------------------------------------|-------------------------------------------------|------------|
| AI-driven scaffold design           | Machine learning and predictive modeling       | Personalized release kinetics, reduced trial-and-error      | Requires large datasets, regulatory uncertainty | [83]       |
| 4D bioprinting                      | Smart polymers with shape-shifting ability     | Dynamic scaffolds, responsive to stimuli, precision therapy | High cost, material limitations                 | [84]       |
| Nanomedicine integration            | Exosomes, magnetic nanoparticles, quantum dots | Multifunctional scaffolds with imaging and therapy          | Long-term safety concerns                       | [85]       |
| Bioink-based regenerative scaffolds | Living cells with bioactive molecules          | Simultaneous tissue repair and drug delivery                | Immunogenicity, scale-up                        | [11]       |
| Clinical translation                | Standardized protocols, regulatory alignment   | Faster bench-to-bedside adoption                            | Complex validation, ethical concerns            | [86]       |

**Table 7.**  
*Emerging future prospects and directions for polymeric scaffold-based drug delivery systems.*



**Figure 3.**  
*Conceptual roadmap of future directions in polymeric scaffold-based drug delivery, including AI-driven design, 4D bioprinting, nanomedicine integration, and clinical translation.*

**8. Conclusion**

Polymeric materials have become fundamental to regenerative medicine and modern drug delivery systems. They play a vigorous role in supporting cell-based therapies and enabling accurate drug release control, thus enhancing drug efficacy, stability, and overall therapeutic performance while minimizing adverse side effects. These materials serve two primary functions: providing three-dimensional frameworks that facilitate tissue regeneration and acting as platforms for targeted and controlled drug delivery. This dual functionality positions them at the forefront of biomedical innovation.

Recent progress in chemical engineering, surface modification, and the development of smart polymers has expanded their applications in fields such as cancer therapy, wound healing, skincare, and personalized medicine. When designing or selecting polymers, critical factors include biocompatibility, degradation behavior, safety profile, cost-effectiveness, and scalability – each of which influences their clinical viability. Furthermore, the integration of nanotechnology, 3D bioprinting, and bioresponsive polymer systems is paving the way for customized, patient-specific scaffolds and advanced drug delivery platforms.

The creation of affordable, biodegradable, and multipurpose polymeric systems that can close the gap between lab discovery and clinical translation should be a top priority for future research. Achieving this goal will depend on continued interdisciplinary collaboration among chemists, materials scientists, biotechnologists, and clinicians. As regulatory frameworks evolve to accommodate emerging biofabrication technologies, polymer-based scaffolds are expected not only to strengthen existing therapeutic strategies but also to drive the creation of safer, more effective, and patient-centered medical solutions.

**Abbreviations**

- |    |    |                         |
|----|----|-------------------------|
| N  | 23 | Amino                   |
| AI |    | Artificial intelligence |

|        |                                                          |
|--------|----------------------------------------------------------|
| COOH   | Carboxyl                                                 |
| DDS    | Drug delivery systems                                    |
| ECM    | Extracellular matrix                                     |
| FDA    | Food and Drug Administration                             |
| 4D     | Four-dimensional (time-responsive systems)               |
| Gel MA | Gelatin methacryloyl                                     |
| HA     | Hyaluronic acid                                          |
| OH     | Hydroxyl                                                 |
| NPs    | Nanoparticles                                            |
| PCL    | Polycaprolactone                                         |
| PEG    | Polyethylene glycol                                      |
| PLA    | Poly(lactic acid) (sometimes referred to as polylactide) |
| PLGA   | Poly(lactic-co-glycolic acid)                            |
| PNPs   | Polymeric nanoparticles                                  |
| PVA    | Polyvinyl alcohol                                        |
| PVP    | Polyvinylpyrrolidone                                     |

## Author details

Shaukat Khan<sup>1</sup>, Joham Sarfraz Ali<sup>2</sup>, Rida Fatima Saeed<sup>2</sup>, Muhammad Naeem<sup>2</sup>, Sumra Wajid Abbasi<sup>2\*</sup>, Sajjad Haider<sup>3</sup> and Adnan Haider<sup>2</sup>

<sup>1</sup> Department of Chemical Engineering, College of Engineering, Dhofar University, Salalah, Sultanate of Oman

<sup>2</sup> Department of Biological Sciences, National University of Medical Sciences, Rawalpindi, Pakistan

<sup>3</sup> Department of Chemical Engineering, College of Engineering, King Saud University, Riyadh, Saudi Arabia

\*Address all correspondence to: sumra.abbasi@numspak.edu.pk

## IntechOpen

---

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Baptista R, Guedes MJM. Morphological and mechanical characterization of 3D printed PLA scaffolds with controlled porosity for trabecular bone tissue replacement. *Materials Science and Engineering: C*. 2021;**118**:111528
- [2] Trowbridge AJ, Bennett NT, Reimer TM, Fu KX. Bridging the gap: Polymer materials with controlled architecture and precise functionalization to overcome biofouling challenges for biosensing, drug delivery, and bioseparation. *Polymer*. 2024;**307**:127230
- [3] Vargason AM, Anselmo AC, Mitragotri S. The evolution of commercial drug delivery technologies. *Nature Biomedical Engineering*. 2021;**5**(9):951–967
- [4] Ukwubile C, Ikpefan E, Olatu O, Njidda S, Angyu A, Menkiti N, et al. Nanoencapsulation of phthalate from melastomastrum capitatum (Fern.) in chitosan-nps as a target mediated drug delivery for multi-drug resistant pathogen. *International Journal of Advanced Biological and Biomedical Research* 2021;**9**:160–180
- [5] Borandeh S, van Bochove B, Teotia A, Seppälä J. Polymeric drug delivery systems by additive manufacturing. *Advanced Drug Delivery Reviews*. 2021;**173**:349–373
- [6] Mansoor S, Kondiah PP, Choonara YE. Advanced hydrogels for the controlled delivery of insulin. *Pharmaceutics*. 2021;**13**(12):2113
- [7] Fonseca C, Simoes S, Gaspar R. Paclitaxel-loaded PLGA nanoparticles: Preparation, physicochemical characterization and in vitro anti-tumoral activity. *Journal of Controlled Release*. 2002;**83**(2):273–286
- [8] Gabizon AA. Pegylated liposomal doxorubicin: Metamorphosis of an old drug into a new form of chemotherapy. *Cancer Investigation*. 2001;**19**(4): 424–436
- [9] Kumari S, Katiyar S, Darshna, Anand A, Singh D, Singh BN, et al. Design strategies for composite matrix and multifunctional polymeric scaffolds with enhanced bioactivity for bone tissue engineering. *Frontiers in Chemistry*. 2022;**10**:1051678
- [10] Stratton S, Shelke NB, Hoshino K, Rudraiah S, Kumbar SG. Bioactive polymeric scaffolds for tissue engineering. *Bioactive Materials*. 2016;**1**(2):93–108
- [11] Chandra DK, Reis RL, Kundu SC, Kumar A, Mahapatra C. Nanomaterials-based hybrid bioink platforms in advancing 3D bioprinting technologies for regenerative medicine. *JABS Engineering*. 2024;**10**(7):4145–4174
- [12] Sindhi K, Pingili RB, Beldar V, Bhattacharya S, Rahaman J, Mukherjee D. The role of biomaterials-based scaffolds in advancing skin tissue construct. *Journal of Tissue Viability*. 2025;**34**(2):100858
- [13] Loh EYX, Mohamad N, Fauzi MB, Ng MH, Ng SF, Mohd Amin MC. Development of a bacterial cellulose-based hydrogel cell carrier containing keratinocytes and fibroblasts for full-thickness wound healing. *Scientific Reports*. 2018;**8**(1):2875

- [14] Sheikholeslam M, Wright ME, Jeschke MG, Amini-Nik S. Biomaterials for skin substitutes. *Advanced Healthcare Materials*. 2018;**7**(5):1700897
- [15] Kurakula M, Rao GK, Kiran V, Hasnain MS, Nayak AK. Alginate-based hydrogel systems for drug releasing in wound healing. *Alginates in Drug Delivery*: Elsevier. 2020;**1**:323–358
- [16] Bencherif S, Gsib O, Egles C. Fibrin: An underrated biopolymer for skin tissue engineering. *Journal of Molecular Biology and Biotechnology*. 2017;**2**(1):1–4
- [17] Wen Q, Mithieux SM, Weiss AS. Elastin biomaterials in dermal repair. *Trends in Biotechnology*. 2020;**38**(3):280–291
- [18] Froelich A, Jakubowska E, Wojtyłko M, Jadach B, Gackowski M, Gadziński P, et al. Alginate-based materials loaded with nanoparticles in wound healing. *Pharmaceutics* 2023;**15**:1142
- [19] Litvinov RI, Weisel JW, editors. What Is the Biological and Clinical Relevance of Fibrin? *Seminars in Thrombosis and Hemostasis*. Published in final edited form as: *Semin Thromb Hemost*. 2016;**42**(4):333–343
- [20] Xu F, Zou D, Dai T, Xu H, An R, Liu Y, et al. Effects of incorporation of granule-lyophilised platelet-rich fibrin into polyvinyl alcohol hydrogel on wound healing. *Scientific Reports*. 2018;**8**:14042
- [21] Burmeister DM, Roy DC, Becerra SC, Natesan S, Christy RJ. In situ delivery of fibrin-based hydrogels prevents contraction and reduces inflammation. *Journal of Burn Care & Research*. 2017;**39**(1):40–53
- [22] Natesan S, Zamora DO, Wrice NL, Baer DG, Christy RJ. Bilayer hydrogel with autologous stem cells derived from debrided human burn skin for improved skin regeneration. *Journal of Burn Care & Research*. 2013;**34**(1):18–30
- [23] Du X, Liu Y, Wang X, Yan H, Wang L, Qu L, et al. Injectable hydrogel composed of hydrophobically modified chitosan/oxidized-dextran for wound healing. *Materials Science and Engineering: C, Materials for Biological Applications*. 2019;**104**:109930
- [24] Shen Y-I, Song -H-HG, Papa AE, Burke JA, Volk SW, Gerecht S. Acellular hydrogels for regenerative burn wound healing: Translation from a porcine model. *Journal of Investigative Dermatology*. 2015;**135**(10):2519–2529
- [25] Alkabli J. Recent advances in the development of chitosan/hyaluronic acid-based hybrid materials for skin protection, regeneration, and healing: A review. *International Journal of Biological Macromolecules*. 2024;**279**:135357
- [26] Shang L, Li M, Xu A, Zhuo F. Recent applications and molecular mechanisms of hyaluronic acid in skin aging and wound healing. *Medicine in Novel Technology and Devices*. 2024;**23**:100320
- [27] Zhang Y, Jiang M, Zhang Y, Cao Q, Wang X, Han Y, et al. Novel lignin–chitosan–PVA composite hydrogel for wound dressing. *Materials Science and Engineering: C*. 2019;**104**:110002
- [28] Uppuluri VNVA, Shanmugarajan TS. Icaritin-loaded polyvinyl alcohol/agar hydrogel:

Development, characterization, and in vivo evaluation in a full-thickness burn model. *The International Journal of Lower Extremity Wounds*. 2019;**18**(3):323–335

[29] Jin SG, Kim KS, Kim DW, Kim DS, Seo YG, Go TG, et al. Development of a novel sodium fusidate-loaded triple polymer hydrogel wound dressing: Mechanical properties and effects on wound repair. *International Journal of Pharmaceutics*. 2016;**497**(1–2):114–122

[30] Choi JS, Kim DW, Kim DS, Kim JO, Yong CS, Cho KH, et al. Novel neomycin sulfate-loaded hydrogel dressing with enhanced physical dressing properties and wound-curing effect. *Drug Delivery*. 2016;**23**:2806–2812

[31] Soriano-Ruiz JL, Calpena-Campmany AC, Silva-Abreu M, Halbout-Bellowa L, Bozal-de Febrer N, Rodriguez-Lagunas MJ, et al. Design and evaluation of a multifunctional thermosensitive poloxamer-chitosan-hyaluronic acid gel for the treatment of skin burns. *International Journal of Biological Macromolecules*. 2020;**142**:412–422

[32] Li X, Li A, Feng F, Jiang Q, Sun H, Chai Y, et al. Effect of the hyaluronic acid-poloxamer hydrogel on skin-wound healing: In vitro and in vivo studies. *Animal Models and Experimental Medicine*. 2019;**2**:107–113

[33] Mondal D, Griffith M, Venkatraman SS. Polycaprolactone-based biomaterials for tissue engineering and drug delivery: Current scenario and challenges. *International Journal of Polymeric Materials and Polymeric Biomaterials*. 2016;**65**(5):255–265

[34] Masood N, Ahmed R, Tariq M, Ahmed Z, Masoud MS, Ali I, et al. Silver nanoparticle impregnated chitosan-PEG hydrogel enhances wound healing in diabetes induced rabbits. *International Journal of Pharmaceutics*. 2019;**559**:23–36

[35] Foong CY, Hamzah MSA, Razak SIA, Saidin S, Nayan NH. Influence of poly (lactic acid) layer on the physical and antibacterial properties of dry bacterial cellulose sheet for potential acute wound healing materials. *Fibers and Polymers*. 2018;**19**(2):263–271

[36] Datta S, Menon G. Nanofibers from polyhydroxyalkanoates and their applications in tissue engineering. In: *Biotechnological Applications of Polyhydroxyalkanoates*. Springer: nature link; 2019. p. 409–420

[37] Renuka RR, Julius A, Yoganandham ST, Umopathy D, Ramadoss R, Samrot AV, et al. Diverse nanocomposites as a potential dressing for diabetic wound healing. *Frontiers in Endocrinology*. 2023;**13**:1074568

[38] Liu T, Wang Y, Kuang T. Oriented Porous Polymer Scaffolds in Tissue Engineering: A Comprehensive Review of Preparation Strategies and Applications. *Macromolecular Materials and Engineering*. 2024;**309**(1):2300246

[39] Xu Y, Zhang F, Zhai W, Cheng S, Li J, Wang Y. Unraveling of advances in 3D-printed polymer-based bone scaffolds. *Polymers*. 2022;**14**(3):566

[40] Tavasolikejani S, Farazin A. The effect of increasing temperature on simulated nanocomposites reinforced with SWBNNs and its effect on characteristics related to mechanics and the physical attributes using the MDs approach. *Heliyon*. 2023;**9**(10):e21022

- [41] Mirkhalaf M, Men Y, Wang R, No Y, Zreiqat H. Personalized 3D printed bone scaffolds: A review. *Acta Biomaterialia*. 2023;**156**:110–124
- [42] Arash A, Dehgan F, Zamanlui Benisi S, Jafari-Nodoushan M, Pezeshki-Modaress M. Polysaccharide base electrospun nanofibrous scaffolds for cartilage tissue engineering: Challenges and opportunities. *International Journal of Biological Macromolecules*. 2024;**277** (Pt 1):134054
- [43] Farazin A, Aghadavoudi F, Motififard M, Saber-Samandari S, Khandan A. Nanostructure, molecular dynamics simulation and mechanical performance of PCL membranes reinforced with antibacterial nanoparticles. *Journal of Applied and Computational Mechanics*. 2021;**7** (4):1907–1915
- [44] Farazin A, Aghdam HA, Motififard M, Aghadavoudi F, Kordjamshidi A, Saber-Samandari S, et al. A polycaprolactone bio-nanocomposite bone substitute fabricated for femoral fracture approaches: Molecular dynamic and micro-mechanical Investigation. *J Nanoanalysis*. 2019;**6**:172–184
- [45] Kumar M, Sidpara AM, Racherla V. Finishing performance of polyurethane-based flexible tools fabricated using solvent casting and particulate leaching method. *Journal of Manufacturing Processes*. 2023;**90**: 166–179
- [46] Zhao L, Zhou Y, Zhang J, Liang H, Chen X, Tan H. Natural polymer-based hydrogels: From polymer to biomedical applications. *Pharmaceutics*. 2023;**15** (10):2514
- [47] Abdullah KK, Molnár K. Current trends and future prospects of integrating electrospinning with 3D printing techniques for mimicking bone extracellular matrix scaffolds. *Journal of Polymer Science*. 2025;**63** (6):1481–1504
- [48] Ansari MAA, Golebiowska AA, Dash M, Kumar P, Jain PK, Nukavarapu SP, et al. Engineering biomaterials to 3D-print scaffolds for bone regeneration: Practical and theoretical consideration. *Biomaterials Science*. 2022;**10**:2789–2816
- [49] Liu Y, Li C, Yang X, Yang B, Q F. Stimuli-responsive polymer-based nanosystems for cardiovascular disease theranostics. *Biomaterials Science*. 2024;**12**(15):3805–3825
- [50] Veselov VV, Nosyrev AE, Jicsinszky L, Alyautdin RN, Cravotto G. Targeted delivery methods for anticancer drugs. *Cancers*. 2022;**14** (3):622
- [51] Saberian E, Jenča A, Petrášová A, Zare-Zardini H, Ebrahimifar M. Application of scaffold-based drug delivery in oral cancer treatment: A novel approach. *Pharmaceutics*. 2024;**16**(6):802
- [52] Yang P, Yang J-L, Liu K, HJ F. Hydrogels enable future smart batteries. *ACS Nano*. 2022;**16**(10):15528–15536
- [53] Nadaf A, Gupta A, Hasan N, Ahmad S, Kesharwani P, Fj A. Recent update on electrospinning and electrospun nanofibers: Current trends and their applications. *RSC Advances*. 2022;**12**(37):23808–23828
- [54] Wei J, Yan Y, Gao J, Li Y, Wang R, Wang J, Zou Q, Zou Y, Zhu M, Li J.

- 3D-printed hydroxyapatite microspheres reinforced PLGA scaffolds for bone regeneration. *Biomaterials Advances*. 2022;**133** (2021):112618
- [55] Ussia M, Pumera M. Towards micromachine intelligence: Potential of polymers. *Chemical Society Reviews*. 2022;**51**(5):1558–1572
- [56] Asl SK, Rahimzadegan M, Asl AK. Progress in cardiac tissue engineering and regeneration: Implications of gelatin-based hybrid scaffolds. *International Journal of Biological Macromolecules*. 2024;**261**:129924
- [57] Pires PC, Mascarenhas-Melo F, Pedrosa K, Lopes D, Lopes J, Macário-Soares A, et al. Polymer-based biomaterials for pharmaceutical and biomedical applications: A focus on topical drug administration. *European Polymer Journal*. 2023;**187**:111868
- [58] Tudu M, Samanta A. Natural polysaccharides: Chemical properties and application in pharmaceutical formulations. *European Polymer Journal*. 2023;**184**:111801
- [59] Eltaib L. Polymeric nanoparticles in targeted drug delivery: Unveiling the impact of polymer characterization and fabrication. *Polymers*. 2025;**17**(7):833
- [60] Bonaccorso A, Musumeci T, Carbone C, Vicari L, Lauro MR, Puglisi G, et al. Revisiting the role of sucrose in PLGA-PEG nanocarrier for potential intranasal delivery. *Pharmaceutical Development and Technology*. 2018;**23**:265–274
- [61] Park K, Skidmore S, Hadar J, Garner J, Park H, Otte A, et al. Injectable, long-acting PLGA formulations: Analyzing PLGA and understanding microparticle formation. *Journal of Controlled Release*. 2019;**304**:125–134
- [62] Basak S, Das TK. Zwitterionic, stimuli-responsive liposomes for curcumin drug delivery: Enhancing M2 macrophage polarization and reducing oxidative stress through enzyme-specific and hyperthermia-triggered release. *ACS Applied Bio Materials*. 2024;**8**(1):726–740
- [63] Miles CM, Cullen S, Kenaan H, Gu W, Andrews GP, Sosso GC, et al. Unravelling the interactions between small molecules and liposomal bilayers via molecular dynamics and thermodynamic modelling. *International Journal of Pharmaceutics*. 2024;**660**:124367
- [64] De Leo V, Milano F, Agostiano A, Catucci L. Recent advancements in polymer/liposome assembly for drug delivery: From surface modifications to hybrid vesicles. *Polymers*. 2021;**13** (7):1027
- [65] Haugen HJ, Basu P, Sukul M, Mano JF, Reseland JE. Injectable biomaterials for dental tissue regeneration. *International Journal of Molecular Sciences*. 2020;**21**(10):3442
- [66] Ha JH, Lim JH, Lee JM, Chung BG. Electro-responsive conductive blended hydrogel patch. *Polymers*. 2023;**15** (12):2608
- [67] Jung H, Kim MK, Lee JY, Choi SW, Kim J. Adhesive hydrogel patch with enhanced strength and adhesiveness to skin for transdermal drug delivery. *Advanced Functional Materials*. 2020;**30**(42):2004407

- [68] Hanif W, Hardiansyah A, Randy A, Asri LATW. Physically crosslinked PVA/graphene-based materials/aloe vera hydrogel with antibacterial activity. *RSC Advances*. 2021;**11**(46):29029–29041
- [69] Kamoun EA, Kenawy E-RS, Tamer TM, El-Meligy MA, Eldin MS. Poly (vinyl alcohol)-alginate physically crosslinked hydrogel membranes for wound dressing applications: Characterization and bio-evaluation. *Arabian Journal of Chemistry*. 2015;**8**(1):38–47
- [70] Kumarasamy RV, Natarajan PM, Umapathy VR, Roy JR, Mironescu M, Palanisamy CP. Clinical applications and therapeutic potentials of advanced nanoparticles: A comprehensive review on completed human clinical trials. *Frontiers in Nanotechnology*. 2024;**6**(2024):1479993
- [71] Kirk JF, Ritter G, Waters C, Narisawa S, Millán JL, Talton JD. Osteoconductivity and osteoinductivity of NanoFUSE(®) DBM. *Cell and Tissue Banking*. 2013;**14**(1):33–44
- [72] Sekhon L, Tomlinson A, Allen B, Lynch J. 64. Immediate postoperative complications and radiological features of interbody fusion between INFUSE BMP and actifuse: A randomized prospective trial. *The Spine Journal*. 2009;**9**(10):32S–3S
- [73] Tian X-B, Sun L, Yang S-H, Zhang Y-K, Hu R-Y, Fu D-H. Osteogenic potential of the human bone morphogenetic protein 2 gene activated nanobone putty. *Chinese Medical Journal*. 2008;**121**(8):745–751
- [74] Epstein NE. Preliminary study showing safety/efficacy of nanoss bioactive versus vitoss as bone graft expanders for lumbar noninstrumented fusions. *Surgical Neurology International*. 2015;**6**(Suppl 10):S318–22
- [75] Epstein NE. High lumbar noninstrumented fusion rates using lamina autograft and Nanoss/bone marrow aspirate. *Surgical Neurology International*. 2017;**8**:153
- [76] Sukegawa S, Kanno T, Katase N, Shibata A, Takahashi Y, Furuki Y. Clinical evaluation of an unsintered hydroxyapatite/poly-L-lactide osteoconductive composite device for the internal fixation of maxillofacial fractures. *The Journal of Craniofacial Surgery*. 2016;**27**(6):1391–1397
- [77] Vora L, Gholap A, Jetha K, Thakur R, Solanki H, Chavda V. Artificial intelligence in pharmaceutical technology and drug delivery design. *Pharmaceutics*. 2023;**15**:1916
- [78] Yang Q, Gao B, Xu F. Recent advances in 4D bioprinting. *Biotechnology Journal*. 2020;**15**(1):e1900086
- [79] Percival KM, Paul V, Husseini GA. Recent Advancements in Bone Tissue Engineering: Integrating Smart Scaffold Technologies and Bio-Responsive Systems for Enhanced Regeneration. *International Journal of Molecular Sciences*. 2024;**25**(11):6012
- [80] Moghaddam AS, Khonakdar HA, Arjmand M, Jafari SH, Bagher Z, Moghaddam ZS, et al. Review of bioprinting in regenerative medicine: Naturally derived bioinks and stem cells. *ACS Applied Bio Materials*. 2021;**4**:4049–4070
- [81] Won C, Kwon C, Park K, Seo J, Lee T. Electronic drugs: Spatial and

temporal medical treatment of human diseases. *Advanced Materials*. 2021;**33**(47):2005930

[82] Rosellini E, Cascone MG. Microfluidic fabrication of natural polymer-based scaffolds for tissue engineering applications: A review. *Biomimetics* (Basel, Switzerland). 2023;**8**(1):8010074

[83] Kapoor DU, Sharma JB, Gandhi SM, Prajapati BG, Thanawuth K, Limmatvapirat S, et al. AI-driven design and optimization of nanoparticle-based drug delivery systems. *Advanced Materials*. 2024;**18**:24010003–24010013

[84] Willemen NG, Morsink MA, Veerman D, Da Silva CF, Cardoso JC, Souto EB, et al. From oral formulations to drug-eluting implants: Using 3D and 4D printing to develop drug delivery systems and personalized medicine. *Bio-Design and Manufacturing*. 2022;**5**: 85–106

[85] Zeng M, Guo D, Fernández-Varo G, Zhang X, Fu S, Ju S, et al. The integration of nanomedicine with traditional Chinese medicine: Drug delivery of natural products and other opportunities. *Molecular Pharmaceutics*. 2022;**20**:886–904

[86] Li W, Tang J, Lee D, Tice TR, Schwendeman SP, Prausnitz MR. Clinical translation of long-acting drug delivery formulations. *Nature Reviews Materials*. 2022;**7**(5):406–420



## Chapter 3

# Polyhydroxyalkanoate (PHA) Scaffolds in Biomedical Engineering: Fabrication, Properties and Applications

*Mamatali Rahman, Abdusemer Reyimu, Zureguli Tuerxun, Wuerken Jumabayi, Rouzi Kamilijiang, Chuanjiang He, Alimu Keremu and Aimin Xu*

### Abstract

Polyhydroxyalkanoates (PHAs), a versatile family of microbially synthesized biodegradable polyesters, are characterized by their excellent biocompatibility, tunable mechanical properties, and controllable degradation rates. These properties make them highly attractive for biomedical applications, particularly in tissue regeneration and drug delivery systems. This chapter provides a comprehensive overview of PHA-based scaffolds, beginning with their biosynthesis and structural diversity. It subsequently explores advanced fabrication techniques – such as electrospinning, 3D printing, and salt leaching – for processing PHAs into functional scaffolds. The chapter also highlights the expanding applications of PHA scaffolds in various tissue engineering fields, including bone, cartilage, nerve, and skin regeneration. Furthermore, it examines the role of PHA composites (e.g., with hydroxyapatite) and functionalized scaffolds (e.g., RGD-modified surfaces) in promoting cellular interactions and tissue repair. Current challenges related to production costs and degradation kinetics are discussed, alongside prospects for smart scaffolds and integrated stem cell therapies. In conclusion, PHAs demonstrate significant potential as next-generation biomaterials for regenerative medicine and advanced medical devices.

**Keywords:** polyhydroxyalkanoates (PHAs), biodegradable scaffolds, tissue engineering, bone regeneration, cartilage repair, nerve regeneration, drug delivery, electrospinning, 3D printing, biocompatibility

### 1. Introduction

The regeneration of complex tissues following injury or disease remains a significant challenge in modern medicine. Tissue engineering, which combines

cells, signaling molecules, and scaffolds, offers a promising solution. However, the quest for an ideal scaffold material that can seamlessly integrate with biological systems is ongoing [1]. An ideal scaffold should not only provide structural support but also actively promote healing without causing adverse reactions [2].

Among various biomaterials, polyhydroxyalkanoates (PHAs) have shown considerable promise. These biopolymers are natural polyesters synthesized by microorganisms under nutrient-limited conditions [3]. They possess a unique combination of properties ideal for biomedical use: excellent biocompatibility, which minimizes immune rejection and inflammation; tunable biodegradability that can be aligned with tissue regeneration rates; and versatile mechanical properties that can be designed to resemble those of native tissues. Moreover, PHAs support sustainability goals, as they are derived from renewable resources and degrade completely into natural metabolites [4, 5].

The structural diversity of PHAs allows for precise customization of their chemical, physical, and biological characteristics. By adjusting monomer composition, molecular weight, and copolymer ratios, researchers can tailor PHA-based materials to achieve specific mechanical strength, degradation behavior, and surface properties for particular clinical needs. This chapter provides a thorough overview of PHA scaffolds in biomedical engineering. It begins with their biosynthesis and fundamental properties, proceeds to advanced fabrication methods, and concludes with their applications in diverse tissue engineering areas, including bone, cartilage, nerve, tendon, and skin regeneration. Finally, current challenges and future directions for translating PHA technologies from the laboratory to the clinic are discussed.

## **2. Biosynthesis and types of PHAs**

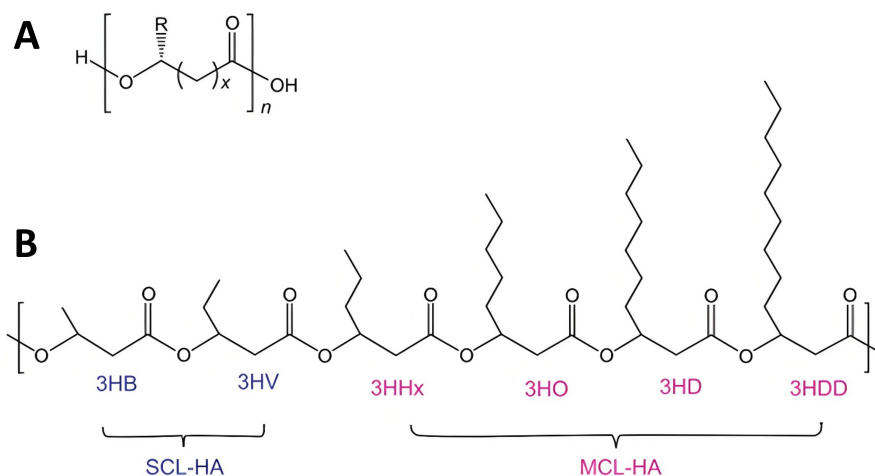
PHAs represent a diverse class of biodegradable polyesters synthesized by microorganisms under nutrient-limited conditions. These biopolymers have attracted considerable scientific and industrial interest due to their tunable material properties, biocompatibility, and sustainability [6, 7]. PHAs are linear polyesters composed of hydroxy fatty acid monomers (**Figure 1A**), with over 150 different monomers identified to date, enabling a wide spectrum of material characteristics [8, 9].

### **2.1 Structural classification of PHAs**

PHAs are broadly categorized into three groups based on the number of carbon atoms in their monomer units:

Short-chain-length PHAs (scl-PHAs) contain 3–5 carbon atoms, as found in poly(3-hydroxybutyrate) (PHB) and its copolymer with hydroxyvalerate (PHBV) [10]. These semicrystalline polymers feature high melting points, stiffness, and brittleness (**Figure 1B**).

mcl-PHAs possess 6–14 carbon atoms, exemplified by polymers such as poly(3-hydroxyoctanoate) (PHO) and poly(3-hydroxybutyrate-co-3-hydroxyhexanoate) (PHBHHx) [11]. mcl-PHAs are characterized by lower crystallinity, reduced melting temperatures (typically 39–65°C), and elastomeric



**Figure 1.**  
 (A) General molecular formula of PHAs. Typically,  $x = 1-8$ , and  $n$  ranges from 100 to 1,000. (B) Some commonly synthesized short-chain-length PHA monomers (scl-PHAs) and middle-chain-length PHA monomers (mcl-PHAs). Adapted from Reference [13].

properties, making them suitable for flexible applications like nerve regeneration and soft tissue engineering (**Figure 1B**).

Long-chain-length PHAs, with 15 or more carbon atoms, are less common but provide distinct material properties [8].

Commonly used PHA types in biomedical applications include P3HB, PHBV, PHBHHx, P(3HB-co-4HB), and terpolymers such as PHBVHHx, each offering distinct mechanical and degradation profiles tailored to specific tissue engineering needs [12].

## 2.2 Biosynthesis pathways and microbial production

PHA biosynthesis occurs through diverse microbial metabolic pathways, influenced by carbon source, enzymatic activity, and genetic regulation. For instance, Wei et al. demonstrated that enzymatic regulation, particularly the deficiency of short-chain thioesterases in *Escherichia coli*, significantly affects the copolymer composition and yield of P(3HB-co-LA) [6]. Cai et al. showed that *Cupriavidus necator* can efficiently synthesize PHBV using volatile fatty acids (VFAs) as the sole carbon source, highlighting the role of metabolic adaptability in PHA production [7].

Recent research has expanded the range of microbial producers to include extremophiles and genetically engineered strains. For example, *Halomonas halophila* 18 H has been identified as an efficient producer of PHB, offering advantages for low-cost production under nonsterile conditions [14].

Thermophilic genera, including *Caldimonas* and *Schlegelella*, have been genomically characterized to elucidate the genetic determinants of PHA synthesis, facilitating strain optimization via metabolic engineering [15].

### 2.3 Sustainable substrates and production strategies

The use of renewable and waste-derived carbon sources – such as plant biomass, food waste, and animal by-products – further enhances the sustainability of PHA production. Lactic acid bacteria (LAB) and other microbial systems have been employed to convert these substrates into PHAs, emphasizing the ecological and economic benefits of integrated bioprocessing [16].

Advances in synthetic biology and fermentation technology continue to improve the scalability and cost-effectiveness of PHA production. Strategies such as constructing artificial microbial consortia and implementing high-density fermentation processes have shown promise for enhancing the yield of mcl-PHAs and other valuable copolymers [8].

### 2.4 Functionalization and tailored properties

Beyond their native production, PHAs can be functionalized to introduce additional properties such as antibacterial activity, enhanced biocompatibility, or targeted biodegradability. For instance, Cruz-Romero et al. functionalized PHAs with silver nanoparticles to impart antimicrobial functionality, expanding their applicability in medical devices and wound dressings [17].

The incorporation of different monomer units enables precise modulation of mechanical properties, crystallinity, and degradation rates, making PHAs highly versatile for applications ranging from bone scaffolds to elastic nerve conduits (Table 1).

## 3. Properties of PHAs for biomedical applications

PHAs have garnered significant attention in biomedical engineering due to their exceptional and tunable material properties, which can be tailored to

| PHA type/<br>copolymer | Chain<br>length | Crystallinity | Mechanical<br>properties | Degradation<br>rate | Key tissue engineering<br>applications          | References |
|------------------------|-----------------|---------------|--------------------------|---------------------|-------------------------------------------------|------------|
| PHB                    | scl-<br>PHA     | High          | Brittle, stiff           | Slow                | Bone tissue engineering, stiff scaffolds        | [18]       |
| PHBV                   | scl-<br>PHA     | Medium        | Ductile, tough           | Moderate            | Bone and cartilage repair                       | [19]       |
| P(3HB-co-4HB)          | scl-<br>PHA     | Low to medium | Flexible, elastic        | Fast to moderate    | Soft tissue repair, cardiovascular patches      | [20]       |
| PHBHHx                 | mcl-<br>PHA     | Low           | Elastomeric, tough       | Moderate            | Nerve regeneration, tendon/ligament scaffolds   | [21]       |
| PHO                    | mcl-<br>PHA     | Low           | Highly elastic, soft     | Moderate to Fast    | Soft tissue engineering, drug delivery matrices | [22]       |

*In summary, the biosynthesis of PHAs is a dynamically evolving field, driven by microbial diversity, metabolic engineering, and sustainable bioprocessing. The ability to tailor PHA structures and properties at the molecular level offers unprecedented opportunities for designing advanced biomaterials for regenerative medicine and environmentally friendly plastics.*

**Table 1.**  
*Characteristics and biomedical applications of representative PHAs.*

meet the demanding requirements of various medical applications. Recent advances in synthesis, functionalization, and composite design have further expanded their utility in tissue engineering [2], drug delivery [23], and implantable devices [24].

### **3.1 Biocompatibility**

PHAs demonstrate outstanding biocompatibility, evidenced by minimal inflammatory response and high tissue tolerance upon implantation. Their natural origin and metabolic resorbability promote excellent cellular acceptance, supporting their use in long-term in vivo applications [25]. The lack of cytotoxic leachates further validates their safety in sensitive physiological environments.

Surface morphology is a key factor affecting cellular responses to these biopolymers. For instance, Yu et al. showed that tailored surface properties significantly improve biocompatibility by enhancing interactions with human mesenchymal stem cells (MSCs) [26]. Beyond intrinsic properties, incorporating bioactive additives can further enhance PHA performance. Hsu et al. reported that incorporating hyaluronic acid (HA) into PHAs improved cytocompatibility with human foreskin fibroblasts, suggesting that composites with natural polymers positively influence cellular behavior [27]. Similarly, Chan et al. found that blending PHAs with low-molecular-weight polyethylene glycol (PEG) enhanced both biocompatibility and degradability, underscoring how physicochemical modifications can fine-tune biological properties [28].

Designing composite materials represents another effective strategy for improving biocompatibility. Wu et al. developed PHA composites reinforced with chestnut shell fibers, which exhibited good biocompatibility along with enhanced mechanical and degradation properties [29]. In another study, Aguilar-Rabiela et al. integrated mesoporous bioactive glass nanoparticles into PHBV microspheres, creating drug delivery systems that combine improved biocompatibility with functional performance [30].

Advances in processing techniques have further broadened the biomedical applications of PHAs. Lukaszewicz et al. created binary PHA systems with oligomeric plasticizers, yielding flexible biomaterials for soft tissue engineering that overcome brittleness while maintaining biocompatibility [31]. Additionally, Wu et al. produced functional PHA microspheres loaded with growth factors; these spheres exhibited antibacterial activity without compromising biocompatibility, highlighting the potential of multifunctional PHA platforms [32].

In summary, the biocompatibility of PHAs can be effectively enhanced through surface engineering, forming composites with natural polymers and bioactive fillers, and employing advanced processing methods. These strategies collectively widen the scope of PHA applications in tissue engineering, drug delivery, and regenerative medicine.

### **3.2 Biodegradability**

A defining characteristic of PHAs is their predictable and controllable biodegradation, which occurs mainly through surface erosion driven by hydrolysis

and enzymatic activity. As microbial biopolyesters, PHAs are inherently biodegradable, a property that distinguishes them from conventional plastics and aligns with sustainability objectives [33]. Degradation kinetics can be finely modulated by varying monomer composition, copolymer ratios, and crystallinity. For instance, scl-PHAs, such as PHB, typically degrade more slowly than mcl-PHAs or copolymers containing 4-hydroxybutyrate (4HB) [20]. Crucially, the degradation products – primarily hydroxy acid monomers – are nontoxic and can be metabolized via endogenous biochemical pathways, eliminating the need for surgical removal [34].

The biodegradation behavior of PHAs is strongly influenced by environmental conditions. Anunciado et al. demonstrated that ambient soil exposure and composting conditions significantly affect the degradation of biodegradable plastic mulches, underscoring the importance of context-specific assessments in evaluating biodegradation performance [35]. In marine environments, the biodegradation of PHAs, such as poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), follows standardized protocols (e.g., ASTM D7991-15), with studies showing that the incorporation of natural fillers, like *Miscanthus* fibers or distillers' dried grains with solubles (DDGS), can modulate degradation rates [36].

Chemical modification offers another avenue for tuning PHA biodegradability. Qie et al. reported that oxidizing copolymer films containing 2-hydroxy-4-methylthiobutyrate enhanced their breakdown in seawater, suggesting that targeted molecular alterations can accelerate environmental degradation [37].

In biomedical contexts, the controlled biodegradation of PHAs is essential for applications such as resorbable implants and tissue engineering scaffolds. For example, Miu et al. developed polyhydroxyoctanoate-hydroxyapatite composites that exhibit tailored biodegradability alongside biocompatibility and bioresorbability, highlighting the functional integration of degradation properties in advanced biomedical materials [38].

In summary, the biodegradability of PHAs is governed by a complex interplay of material factors – including chemical structure, composite formulation, and surface modification – and environmental conditions. This tunable degradation profile supports their use across ecological and medical applications, where controlled breakdown and environmental compatibility are required.

### **3.3 Mechanical properties**

PHA-based materials exhibit a broad range of mechanical behaviors – from rigid and brittle to soft and elastomeric – making them suitable for diverse biomedical and industrial applications. scl-PHAs, such as poly PHB, exhibit high tensile strength and stiffness comparable to polypropylene, rendering them suitable for bone tissue engineering and load-bearing applications. In contrast, mcl-PHAs, including PHO and PHBHHx, display a reduced Young's modulus, high elongation at break, and rubber-like elasticity, making them ideal for soft tissue engineering, cardiovascular implants, and neural guides. This intrinsic tunability is further enhanced through copolymerization, blending, and advanced material processing.

Recent advances in modifying the mechanical properties of PHAs focus on surface and interfacial engineering. Jo et al. demonstrated that the silanization of cellulose nanocrystals (CNCs) significantly influences the morphology and mechanical behavior of PHA composites processed via melt extrusion, underscoring

the role of nanofiller surface chemistry in enhancing composite performance [39]. Molecular dynamics simulations by Bejagam et al. provided atomistic insights into structure-property relationships, offering a predictive framework for tailoring mechanical characteristics through rational molecular design [40].

Processing techniques critically affect the mechanical performance of PHAs. Mustafa et al. optimized fused filament fabrication (FFF) parameters for polylactic acid (PLA)/PHA blends, achieving superior mechanical properties through precise control of printing conditions [41]. Similarly, Aziz et al. employed gray relational analysis to enhance the mechanical performance of 3D-printed PLA/PHBV/polycaprolactone (PCL) blends for orthopedic applications [42].

The development of PHA-based composites and nanocomposites represents a prominent strategy for mechanical enhancement. Najah et al. reported that calcium phosphate (CaP) reinforcement tunes the mechanical properties of PHA biocomposites for bone scaffold applications [43]. Champa-Bujaico et al. utilized machine learning to predict the mechanical behavior of PHA nanocomposites reinforced with graphene oxide and nanoclay, highlighting the growing role of computational tools in materials design [44]. Buntinx et al. further reviewed how ZnO nanofillers and processing advancements improve the mechanical integrity of PHA nanocomposites in packaging contexts [45].

Blending PHAs with other biodegradable polymers – such as PLA, poly(butylene succinate-co-adipate) (PBSA), and PCL – enables the fabrication of materials with balanced and application-specific mechanical profiles. Sabalina et al. illustrated that binary and ternary blends allow fine-tuning of thermomechanical properties [46], supporting their use in diverse biomedical and environmental applications.

In summary, the mechanical properties of PHAs are highly customizable through molecular design, surface modification, processing optimization, composite formation, and blending. These strategies, supported by emerging computational and machine learning approaches, facilitate the rational design of PHA-based materials with tailored mechanical performance for use in tissue engineering, medical devices, sustainable packaging, and beyond.

### **3.4 Processability**

The processability of PHAs is crucial for their use in tissue engineering and regenerative medicine, building on their inherent biodegradability and biocompatibility. These biopolymers can be shaped into various structures using both conventional and advanced techniques, allowing the creation of scaffolds tailored to specific biomedical needs [47]. Common methods include electrospinning for nanofibrous scaffolds that mimic the extracellular matrix, salt leaching for interconnected porous 3D constructs, solvent casting for thin films, melt extrusion for filaments and fibers, and additive manufacturing (AM) (e.g., 3D printing) for patient-specific implants [48, 49].

Electrospinning is particularly valuable for creating PHA nanofibrous scaffolds with high surface-area-to-volume ratios and adjustable porosity, which promote cell adhesion, proliferation, and tissue integration [50, 51]. However, electrospinning microbial PHAs requires careful control of parameters such as solution concentration, viscosity, and temperature due to their narrow thermal processing window [51]. Recent improvements in nozzle design and solvent systems have facilitated the production of defect-free PHA nanofibers.

Beyond fibers, PHAs can also be processed into hydrogels for bioprinting and mold-based fabrication. Li et al. developed printable hydrogel inks from PHA composites, including blends with polyvinyl alcohol (PVA), which offer improved printability and mechanical stability while maintaining biodegradability [50, 52]. Such hydrogel systems show promise for building complex, cell-laden constructs for soft tissue engineering.

Downstream processing steps – including purification, blending, and functionalization – significantly affect the final properties of PHA scaffolds [53]. For example, incorporating bioactive fillers or other polymers can enhance melt strength, thermal stability, and interfacial properties, thereby widening the processing window and enabling the fabrication of more complex shapes [52]. Techniques like particulate leaching, gas foaming, and phase separation have also been employed to create porous PHA scaffolds with controlled pore size and connectivity, which are vital for nutrient diffusion and vascularization in tissue engineering [48, 52].

Looking ahead, emerging processing technologies – such as melt electrowriting, microfluidic spinning, and multimaterial 3D printing – are expected to further advance the architectural and functional quality of PHA-based scaffolds [8]. These advances, coupled with a better understanding of process-structure-property relationships, will continue to establish PHAs as versatile, sustainable, and clinically useful biomaterials.

### **3.5 Surface modifiability**

The surface characteristics of PHAs – including their chemistry and topography – critically influence biological performance and integration with host tissues. Surface modification methods can significantly enhance the biofunctionality of PHA materials, enabling customized cellular responses such as improved adhesion, differentiation, and tissue-specific regeneration [54, 55]. Standard approaches include plasma treatment, chemical grafting, physical adsorption, and biomolecular conjugation, which allow the immobilization of bioactive elements such as RGD peptides, collagen, heparin, and growth factors to promote targeted biological interactions.

Plasma surface modification offers an efficient, solvent-free method to introduce functional groups and improve surface energy without affecting bulk material properties. Mohammadali pour et al. demonstrated that plasma treatment improves the surface properties of electrospun PHB nanofibers, enhancing their potential for bone tissue engineering by increasing hydrophilicity and cell attachment [18].

The incorporation of inorganic phases and nanoparticles further expands the possibilities for functionalization. For example, CaP-reinforced PHA biocomposites exhibit enhanced surface bioactivity and osteoconductivity, supporting mineral deposition and improving integration in bone regeneration [29]. Similarly, incorporating silver nanoparticles imparts antibacterial properties to PHAs, broadening their use in infection prevention for wound dressings and implant coatings [56].

Micro- and nano-scale topological modifications also help guide cellular behavior. Wu et al. created functional PHA microspheres with controlled surface features – such as rough microporous or smooth granular structures – to regulate the release of bioactive molecules like BMP-2 and enhance antimicrobial and osteogenic effects

[32]. Chen et al. used phase-separation methods to adjust the surface architecture of PHA microspheres, improving their bone regeneration performance through enhanced cell-material interactions and controlled growth factor delivery [57].

Furthermore, advanced surface engineering methods utilizing nanoscale patterning and dynamic bio-interfaces can better mimic the natural extracellular matrix. Du et al. emphasized that rationally designed surface nanostructures and chemical functionalities can significantly improve the biocompatibility and bioactivity of synthetic biomaterials, indicating strong potential for applying these strategies to PHAs [58].

In summary, the ability to modify PHA surfaces through physical, chemical, and biological methods provides a powerful means to customize their interactions with biological environments. These modifications are crucial for developing advanced PHA-based scaffolds and delivery systems with improved integration capacity, therapeutic function, and clinical relevance in regenerative medicine.

### **3.6 Composite and functional enhancements**

PHAs serve as versatile matrix materials for advanced composites in biomedical engineering, helping overcome inherent limitations such as brittleness, limited bioactivity, and lack of electrical conductivity. By integrating functional fillers, nanoscale modifiers, and other polymers, the performance of PHA-based materials can be substantially improved while maintaining essential biodegradability and biocompatibility [59, 60].

One important approach involves reinforcing PHAs with bioactive inorganic phases to enhance mechanical and osteogenic properties. Ye et al. showed that adding  $\beta$ -tricalcium phosphate ( $\beta$ -TCP) to PHA matrices increases compressive strength and osteoconductivity, making these composites well-suited for bone tissue engineering scaffolds [61]. Similarly, hydroxyapatite (HA) and related nanocomposites like HAp/CoFe<sub>2</sub>O<sub>4</sub> have been used to promote biomineralization and bone regeneration. Hossain et al. reported that such nanocomposites possess favorable functional group profiles and bandgap properties (3.51–5.47 eV), supporting their use in functionalized bone grafts [62].

The incorporation of conductive components extends PHA functionality to electrically responsive tissues. Combining PHAs with conductive polymers (e.g., polyaniline, polypyrrole) or carbon-based nanomaterials (e.g., graphene oxide, carbon nanotubes) provides adjustable electrical conductivity, enabling applications in neural interfaces, cardiac patches, and biosensing platforms [63].

Advanced manufacturing techniques, including 3D printing and microfluidics, enable the fabrication of complex composite architectures with spatially controlled properties [47, 64]. Combining PHAs with other biodegradable polymers – such as PLA or PCL – allows the design of multimaterial systems with graded mechanical properties and degradation rates that closely match natural tissue heterogeneity [65].

Additionally, encapsulating and controlling the release of bioactive molecules – such as growth factors, antibiotics, or genetic material – from PHA composite microspheres or hydrogels improves their therapeutic function. Guo et al. developed growth factor-loaded PHA microspheres with customized release profiles, supporting long-term bioactivity in regenerative applications [66].

In summary, composite and functionalization strategies significantly broaden the applications of PHAs in biomedical engineering. By combining PHAs with ceramics,

conductive polymers, nanomaterials, and bioactive agents, researchers can create materials with improved mechanical, electrical, antibacterial, and regenerative properties. These advances highlight PHAs as highly adaptable, multifunctional platforms for next-generation medical devices, tissue scaffolds, and drug delivery systems [67, 68].

## **4. Fabrication of PHA scaffolds**

Translating the favorable properties of PHAs into functional tissue engineering constructs critically depends on advanced fabrication technologies. These methods must not only shape PHAs into desired architectures but also preserve their bioactivity and degradation characteristics.

### **4.1 Additive manufacturing techniques**

AM, particularly fused deposition modeling (FDM), has emerged as a highly promising approach for fabricating PHA scaffolds with precise geometric control and complex pore structures. Pryadko et al. emphasized FDM's capability to create customized structures for specific tissue defects, enhancing integration and function [68]. Recent studies have demonstrated the feasibility of 3D printing biosynthetic mcl-PHA produced through fed-batch fermentation using carbon sources such as glycerol and sodium octanoate [69]. These elastomeric scaffolds possess mechanical properties suitable for soft tissue engineering, including tendon regeneration [69, 70]. Furthermore, FDM has been employed to create porous antibacterial PHA scaffolds, such as those based on PAP34HB, which show promise for oral soft tissue regeneration [4].

### **4.2 Thermally induced phase separation**

Thermally induced phase separation (TIPS) represents another effective method for creating highly porous PHA-based scaffolds, often used in combination with other biodegradable polymers. Lopresti et al. fabricated blends of PLLA and PHA, demonstrating that incorporating up to 30 wt% PHA significantly influences morphology, porosity, and mechanical behavior [71]. This technique enables precise control over microstructural features, facilitating the design of scaffolds that mimic the natural extracellular matrix.

### **4.3 Conventional fabrication methods**

Traditional methods such as solvent casting, particulate leaching, and electrospinning remain widely used for PHA scaffold production, particularly in early-stage research and specific biomedical applications. These approaches offer simplicity and cost-effectiveness, enabling the creation of films, fibrous mats, and porous membranes with good biocompatibility [72]. However, they typically lack the architectural precision and reproducibility achievable with advanced AM technologies.

### **4.4 Functionalization and composite strategies**

Recent developments have integrated functionalization steps during or after scaffold fabrication to enhance bioactivity and performance. For instance,

mineral coatings on FDM-printed PHA scaffolds improve osteoconductivity and bone-mimicking properties [73]. Similarly, incorporating antibacterial agents or bioactive molecules through blending, coating, or encapsulation supports applications in infected wound healing and controlled drug delivery [4].

#### **4.5 Emerging approaches and future outlook**

Novel methods such as microfluidic spinning, melt electrowriting, and hybrid manufacturing are expanding opportunities to create high-resolution, multimaterial PHA scaffolds. These technologies enable the replication of hierarchical and heterogeneous tissue structures – such as osteochondral or neurovascular interfaces – with region-specific mechanical and chemical cues.

In summary, PHA scaffold fabrication encompasses a diverse range of techniques, each offering distinct advantages in resolution, scalability, and functional customization. The continued integration of advanced manufacturing, biomaterial science, and biofunctionalization strategies is essential for fully realizing the potential of PHA-based scaffolds in regenerative medicine and personalized healthcare.

### **5. Applications in tissue engineering**

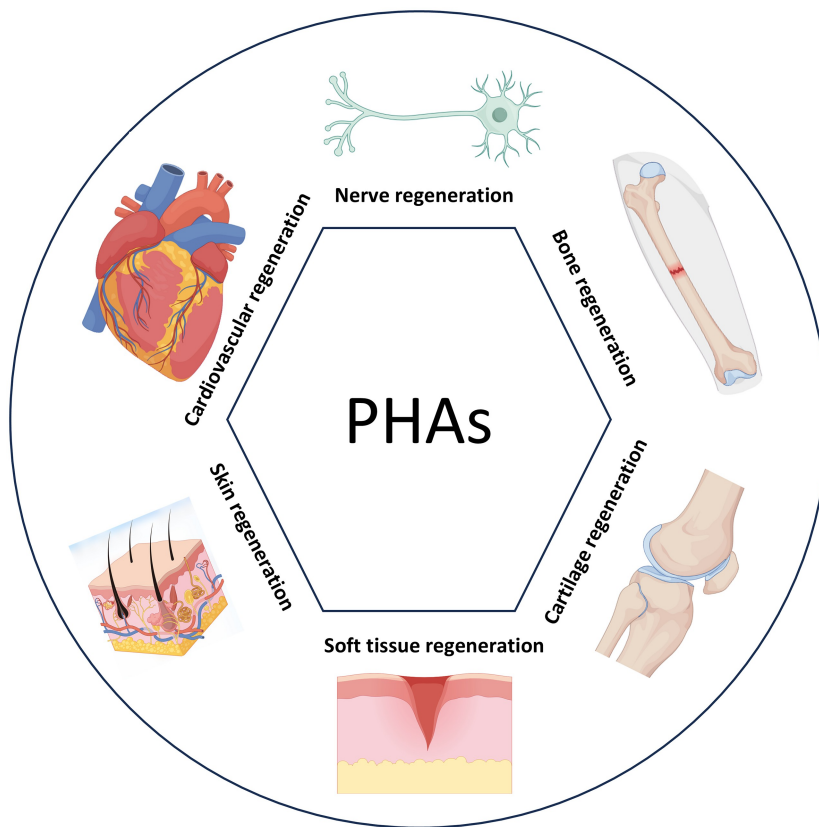
PHAs have emerged as highly promising biomaterials for tissue engineering due to their excellent biocompatibility, adjustable biodegradability, and versatile processability (**Figure 2**). Their applications span a broad spectrum of tissues, including bone, cartilage, neural, and cardiovascular systems, utilizing both inherent material properties and advanced functionalization approaches.

#### **5.1 Bone tissue engineering**

PHA scaffolds have been extensively investigated for bone regeneration, with their mechanical properties and osteoconductivity adjustable through composite design and surface modification. Ye et al. demonstrated that incorporating  $\beta$ -TCP into PHA matrices using FDM significantly enhanced compressive strength and bioactivity, promoting osteogenic differentiation and bone formation [61]. Similarly, the addition of HA or other calcium phosphates improves mineral deposition and scaffold integration in bone defects [74]. The ability to create patient-specific porous structures through 3D printing enables anatomical matching and vascular infiltration, which are crucial for repairing large bone defects.

#### **5.2 Soft tissue regeneration**

mcl-PHAs, such as PHO and PHBHHx, exhibit elastomeric characteristics suitable for soft tissue applications. Panaksri et al. developed biosynthetic mcl-PHA scaffolds with tailored elasticity and degradation behavior, ideal for engineering tendons, ligaments, and blood vessels [69]. Their inherent flexibility and resilience



**Figure 2.**  
*Applications of PHAs in tissue engineering.*

withstand cyclic mechanical loading, mimicking native tissue conditions. Moreover, surface topographic features – such as microgrooves or aligned nanofibers – can guide MSC differentiation and tissue-specific development [75].

### **5.3 Neural tissue engineering**

PHA-based conduits and scaffolds support peripheral nerve regeneration by providing physical guidance and biochemical signals. Combining electrical conductivity – achieved through the incorporation of graphene or polypyrrole – with controlled delivery of neurotrophic factors enhances axonal growth and functional recovery [76]. Microfluidic-generated fibers and 3D-printed channels made from PHAs enable precise architectural control, replicating endoneurial tube structures and promoting Schwann cell alignment [77].

### **5.4 Cartilage tissue engineering**

The viscoelastic and lubricating properties of specific PHA copolymers, such as PHBHHx and P(3HB-co-4HB), make them suitable for cartilage repair. Scaffolds with controlled porosity and surface modifications (e.g., chitosan or HA coatings)

enhance chondrocyte adhesion and glycosaminoglycan production [78]. Researchers have developed bilayered osteochondral scaffolds that combine mineralized PHA for the bone layer and elastomeric PHA for the cartilage zone to address joint interface regeneration.

## **5.5 Cardiovascular applications**

PHA scaffolds find application in vascular graft engineering due to their compliance, suturability, and blood compatibility. Small-diameter tubular scaffolds, fabricated through electrospinning or 3D printing, exhibit antithrombogenic properties when modified with heparin or nitric oxide donors [79]. Additionally, cardiac patches created from conductive PHA composites facilitate cardiomyocyte synchronization and electrical signal propagation in the infarcted heart.

## **5.6 Skin and wound healing**

PHA-based nanofibrous mats and hydrogels accelerate wound healing by maintaining a moist environment, providing antibacterial protection (e.g., via silver nanoparticles), and enabling sustained release of growth factors [76]. Their tunable degradation rate ensures proper tissue integration and reduces the need for frequent dressing changes.

## **5.7 Emerging trends and functional enhancements**

Recent advancements include immunomodulatory PHAs that actively control macrophage polarization and reduce fibrotic responses [78]. Delivering bioactive molecules – such as VEGF for angiogenesis or BMP-2 for bone formation – from PHA microspheres or coatings further enhances regenerative outcomes [61]. Furthermore, four-dimensional (4D) printing of PHAs enables the creation of shape-changing scaffolds that adapt to dynamic physiological conditions.

In summary, PHA scaffolds provide a versatile platform for tissue engineering across various organ systems. Through strategic material design, advanced fabrication, and biofunctionalization, PHAs can be customized to meet specific mechanical, biological, and practical requirements of different clinical applications, opening pathways for next-generation regenerative therapies.

# **6. Drug delivery applications**

Beyond providing structural support in tissue engineering, PHAs have also established themselves as versatile carriers for drug delivery systems. Their inherent biodegradability and biocompatibility, combined with ease of functionalization, as previously discussed, enable the design of controlled-release platforms that can be integrated with scaffold-based therapies.

## **6.1 Versatile carrier systems**

PHAs, particularly medium-chain-length types (mcl-PHAs), exhibit excellent film-forming capability, compatibility with both hydrophobic and hydrophilic

drugs, and adjustable degradation rates – making them suitable for various delivery platforms, including microspheres, nanoparticles, hydrogels, and electrospun fibers [80, 81]. Their production from renewable resources further supports sustainable and scalable biomedical applications [80].

## **6.2 Electrospun fiber-based delivery**

Electrospun PHA fibers, especially those derived from PHBV, offer high surface-area-to-volume ratios and programmable drug release profiles. Kaniuk et al. demonstrated that these fibrous mats enable sustained release of antibiotics or antiinflammatory drugs, supporting applications in wound dressings and postsurgical implants where localized, prolonged drug delivery is essential [52].

## **6.3 Nanoparticulate and microparticulate systems**

PHA-based micro- and nanoparticles serve as promising carriers for encapsulating small molecules, proteins, and nucleic acids. Their surfaces can be modified with targeting ligands (e.g., peptides or antibodies) to achieve tissue- or cell-specific delivery [82, 83]. Reddy et al. emphasized that the tunable thermal and mechanical properties of mcl-PHAs facilitate the design of nanoparticles with enhanced drug-loading capacity and controlled-release behavior [81].

## **6.4 Combinational therapies and regenerative delivery**

PHA scaffolds and particles are increasingly utilized for combination therapy, simultaneously delivering bioactive agents (e.g., growth factors, antibiotics) while supporting tissue regeneration. Pulingam et al. demonstrated that drug-loaded PHA systems significantly reduce microbial infections and accelerate healing in soft tissue models, highlighting their dual role as both degradable scaffolds and therapeutic carriers [83].

## **6.5 Functionalization and hybrid systems**

To improve targeting and release precision, PHAs are often combined with other functional materials. For instance, blending with chitosan or incorporating them into metal-organic frameworks (MOFs) can enhance mucoadhesion, pH-responsive release, and cellular uptake efficiency [82, 84]. Such modifications broaden their applications in gastrointestinal, neurological, and cancer drug delivery.

## **6.6 Future perspectives**

Continuing advances in synthetic biology and material engineering enable the biosynthesis of novel PHA copolymers with customized properties – such as improved hydrophilicity, stimuli-responsive degradation, or innate targeting abilities [85, 86]. Combined with innovations in nanotechnology and precision manufacturing, PHAs are poised to play an expanding role in personalized and programmable drug delivery systems.

The integration of drug delivery functionality into PHA scaffolds represents a convergence of material science and therapeutic design, creating opportunities for

combination systems that support both structural regeneration and localized drug therapy. Looking forward, such multifunctional approaches will be crucial for addressing remaining challenges in scaling up and clinically adopting PHA-based technologies, as discussed in the next section.

## **7. Challenges and future perspectives**

### **7.1 Current challenges in PHA-based tissue engineering**

Despite their significant potential in tissue engineering, several key challenges must be addressed to enable the widespread clinical adoption of PHAs.

**High production costs:** the economic viability of PHA production remains constrained by high fermentation and purification costs. Future efforts should focus on leveraging synthetic biology tools and waste-derived feedstocks to develop more sustainable and cost-effective production methods.

**Limited mechanical performance for specific applications:** although PHAs possess tunable mechanical properties, certain applications – such as load-bearing bone grafts or dynamic tendon repairs – require greater strength, fatigue resistance, and elastic recovery. Advanced composite strategies and copolymer blending are essential to meet these biomechanical demands.

**Degradation rate mismatch:** aligning PHA scaffold degradation rates with tissue regeneration timelines remains challenging. Variations in polymer composition, crystallinity, and in vivo conditions can lead to premature structural failure or delayed resorption, potentially compromising therapeutic outcomes.

**Surface biofunctionalization:** while PHAs are naturally biocompatible, their bioactivity often requires enhancement through surface modification. The development of scalable and reproducible functionalization methods – such as peptide conjugation, plasma treatment, or nanoparticle integration – remains an ongoing area of research.

**Regulatory and standardization hurdles:** the lack of standardized processing protocols and comprehensive long-term safety data impedes regulatory approval. Establishing robust quality control measures and conducting thorough biocompatibility testing are crucial for successful clinical translation.

### **7.2 Future directions and emerging opportunities**

Looking forward, several innovative approaches show significant potential for advancing PHA-based scaffolds toward clinical applications and broader biomedical impact.

**AI-guided material design:** machine learning and computational modeling can accelerate the development of PHA copolymers with customized properties, predicting degradation behavior, mechanical performance, and biological interactions before synthesis.

**4D printing of stimuli-responsive scaffolds:** four-dimensional bioprinting enables the creation of dynamic PHA constructs that change shape or function in response to physiological signals (e.g., pH, temperature, or enzyme activity), facilitating personalized and adaptive tissue regeneration.

Integrated stem cell and immunomodulatory strategies: combining PHA scaffolds with stem cell therapies and immunomodulatory agents (e.g., cytokine-releasing microspheres) can enhance regenerative outcomes while minimizing fibrotic responses.

Harnessing piezoelectric properties: utilizing the inherent piezoelectricity of certain PHAs (e.g., PHB) offers opportunities for electrically stimulated tissue repair, particularly in neural and musculoskeletal applications.

Sustainable production and circular design: aligning PHA production with circular bioeconomy principles – utilizing agricultural waste, CO<sub>2</sub>, or microbial consortia – supports both environmental sustainability and scalable manufacturing.

Clinical translation roadmap: establishing clear regulatory pathways and initiating pilot clinical studies will be essential for transitioning PHA scaffolds from laboratory research to practical medical applications.

## **8. Conclusion**

PHAs represent a frontier in biomaterial science, combining natural origin, tunable properties, and multifunctional characteristics ideal for biomedical engineering. Their exceptional biocompatibility, controllable degradation, and versatile processability support applications ranging from bone and cartilage repair to neural, cardiovascular, and soft tissue regeneration.

The capacity to customize PHA scaffolds through copolymerization, composite formation, and advanced fabrication methods – including electrospinning, 3D/4D printing, and microfluidic patterning – enables the design of structures that closely mimic native tissue environments. Furthermore, integrating drug delivery systems into PHA scaffolds underscores their dual role as both structural supports and therapeutic platforms.

Despite persistent challenges in production economics, mechanical customization, degradation control, and regulatory approval, continuous innovations in material science, biofabrication, and computational design are progressively addressing these limitations. The future of PHAs lies in smart, responsive, and patient-specific scaffolds that not only promote tissue regeneration but also align with sustainable medical practices.

As research continues to elucidate PHA structure-function relationships and manufacturing technologies advance, these biopolymers are positioned to become fundamental materials in next-generation regenerative medicine – bridging ecological sustainability with clinical efficacy in global healthcare.

## **Conflict of interest statement**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Funding information

This work was supported by the Research Project of the Xinjiang Uygur Autonomous Region Health Commission (2025001CXKYXM653126251), the Special Program for Key Research and Development Tasks of the Xinjiang Uygur Autonomous Region (2024B04014, 2024B04014-2), and the Natural Science Foundation of the Xinjiang Uygur Autonomous Region (General Program) (2025D01C106).

## Author details

Mamatali Rahman<sup>1,2\*</sup>, Abdusemer Reyimu<sup>1</sup>, Zureguli Tuerxun<sup>1</sup>, Wuerken Jumabayi<sup>1</sup>, Rouzi Kamilijiang<sup>2</sup>, Chuanjiang He<sup>1</sup>, Alimu Keremu<sup>1,2</sup> and Aimin Xu<sup>1</sup>

1 Xinjiang Stem Cells Special Plateau Disease Engineering Technology Research Center, First People's Hospital of Kashgar, Kashgar, The People's Republic of China

2 Orthopedics Center, First People's Hospital of Kashgar, Kashgar, The People's Republic of China

\*Address all correspondence to: [mmtalrh14@tsinghua.org.cn](mailto:mmtalrh14@tsinghua.org.cn)

## IntechOpen

---

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Hanuman S, Pande G, Nune M. Current status and challenges in uterine myometrial tissue engineering. *Bioengineered*. 2023;**14**(1):2251847
- [2] Fu Z, et al. Biological effects, properties and tissue engineering applications of polyhydroxyalkanoates: A review. *International Journal of Biological Macromolecules*. 2025;**293**:139281
- [3] Mai J, et al. Synthesis and physical properties of polyhydroxyalkanoate (PHA)-based block copolymers: A review. *International Journal of Biological Macromolecules*. 2024;**263**:130204
- [4] Chen F, et al. Porous polyhydroxyalkanoates (PHA) scaffolds with antibacterial property for oral soft tissue regeneration. *Chemical Engineering Journal*. 2023;**451**:138899
- [5] Gregory DA, et al. Polyhydroxyalkanoates and their advances for biomedical applications. *Trends in Molecular Medicine* 2022;**28**:331–342
- [6] Wei X, et al. Effect of short-chain thioesterase deficiency on P(3HB-co-LA) biosynthesis in *Escherichia coli*. *Sheng Wu Gong Cheng Xue Bao = Chinese Journal of Biotechnology* 2021;**37**:196–206
- [7] Cai F, et al. Biosynthesis of poly (3-hydroxybutyrate- co -3-hydroxvalerate) from volatile fatty acids by *Cupriavidus necator*. *Journal of Basic Microbiology* 2023;**63**:128–139
- [8] Ai M, Zhu Y, and Jia X. Recent advances in constructing artificial microbial consortia for the production of medium-chain-length polyhydroxyalkanoates. *World Journal of Microbiology and Biotechnology*. 2021;**37**(1):2
- [9] Chen S, et al. Polymorphic crystallization of fractionated microbial medium-chain-length polyhydroxyalkanoates. *Polymer*. 2009;**50**(18):4378–4388
- [10] Grigore ME, et al. Methods of synthesis, properties and biomedical applications of polyhydroxyalkanoates: A review. *Journal of Biomaterials Science, Polymer Edition* 2019;**30**: 695–712
- [11] Nigmatullin R, et al. Medium chain length polyhydroxyalkanoates as potential matrix materials for peripheral nerve regeneration. *Regenerative Biomaterials*. 2023;**10**:rbad063
- [12] Ishak KA, et al. Structure-property interpretation of biological polyhydroxyalkanoates with different monomeric composition: Dielectric spectroscopy investigation. *International Journal of Biological Macromolecules*. 2021;**169**:311–320
- [13] Li Z, Yang J, Loh XJ. Polyhydroxyalkanoates: Opening doors for a sustainable future. *NPG Asia Materials*. 2016;**8**(4):e265–e265
- [14] Aytar Celik P, et al. A novel higher polyhydroxybutyrate producer *Halomonas halmophila* 18H with unique cell factory attributes. *Bioresource Technology*. 2023;**372**:128669
- [15] Musilova J, et al. Genomic and phenotypic comparison of

- polyhydroxyalkanoates producing strains of genus *Caldimonas*/Schlegelella. Computational and Structural Biotechnology Journal. 2023;**21**:21
- [16] Nicolescu CM, et al. Biopolymers Produced by Lactic Acid Bacteria: Characterization and Food Application. *Polymers* 2023;**15**:1539
- [17] Cruz-Romero CL, et al. Biosynthesis of Polyhydroalkanoates Doped with Silver Nanoparticles Using *Pseudomonas putida* and *Pseudomonas aeruginosa* for Antibacterial Polymer Applications. *International Journal Of Molecular Sciences* 2024;**25**:8996
- [18] Mohammadalipour M, et al. Plasma surface modification of electrospun polyhydroxybutyrate (PHB) nanofibers to investigate their performance in bone tissue engineering. *International Journal of Biological Macromolecules*. 2023;**230**:123167
- [19] Rodríguez-Cendal AI, et al. Encapsulation of Transforming Growth Factor- $\beta$ 3 in Poly(hydroxybutyrate-co-hydroxyvalerate) Nanoparticles for Enhanced Cartilage Tissue Engineering. *International Journal Of Molecular Sciences* 2025;**26**:4997
- [20] Faisalina AF, et al. Docetaxel-Loaded Poly(3HB-co-4HB) Biodegradable Nanoparticles: Impact of Copolymer Composition. *Nanomaterials* 2020;**10**:2123
- [21] Wang L, et al. Differentiation of human bone marrow mesenchymal stem cells grown in terpolyesters of 3-hydroxyalkanoates scaffolds into nerve cells. *Biomaterials*. 2010;**31** (7):1691–1698
- [22] Kim HY, et al. Paclitaxel-incorporated nanoparticles using block copolymers composed of poly(ethylene glycol)/poly(3-hydroxyoctanoate). *Nanoscale Research Letters*. 2014;**9** (1):525
- [23] Prakash P, et al. Advances in Polyhydroxyalkanoate Nanocarriers for Effective Drug Delivery: An Overview and Challenges. *Nanomaterials* 2022;**12**:175
- [24] Wei D, and Tan Y. Research progress on medical devices of polyhydroxyalkanoate in orthopedics. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2023;**37**(8):909–917
- [25] Murueva A, et al. Chitosan-modified ceftazidime loaded polyhydroxyalkanoates microparticles: Preparation, characterization and antibacterial evaluation in vitro. *ADMET & DMPK*. 2025;**13** (2):2645
- [26] Yu BY, et al. Effects of the surface characteristics of polyhydroxyalkanoates on the metabolic activities and morphology of human mesenchymal stem cells. *Journal of Biomaterials Science, Polymer Edition* 2010;**21**:17–36
- [27] Hsu Y-C, et al. Improvement of the biocompatibility of polyhydroxyalkanoate by filling with hyaluronic acid. *Journal of Materials Science* 2015;**50**:7790–7799
- [28] Chan RT, et al. Poly (ethylene glycol)-modulated cellular biocompatibility of polyhydroxyalkanoate films. *Polymer International* 2013;**62**:884–892
- [29] Wu C-S, Liao H-T. The mechanical properties, biocompatibility and biodegradability of chestnut shell fibre and polyhydroxyalkanoate composites.

Polymer Degradation and Stability. 2014;**99**:274–282

[30] Aguilar-Rabiela AE, et al. Integration of Mesoporous Bioactive Glass Nanoparticles and Curcumin into PHBV Microspheres as Biocompatible Composite for Drug Delivery Applications. *Molecules* 2021; **26**:3177

[31] Lukasiewicz B, et al. Binary polyhydroxyalkanoate systems for soft tissue engineering. *Acta Biomaterialia*. 2018;**71**:225–234

[32] Wu J, et al. Preparation of functional polyhydroxyalkanoate microspheres and their antibacterial activity and osteogenic effect evaluation. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2023;**37**(8): 929–936

[33] Koller M, Mukherjee A. Polyhydroxyalkanoates—linking properties, applications, and end-of-life options. *Chemical and Biochemical Engineering Quarterly*. 2020;**34**(3): 115–129

[34] Barrett DG, Yousaf MN. Design and applications of biodegradable polyester tissue scaffolds based on endogenous monomers found in human metabolism. *Molecules*. 2009;**14**(10):4022–4050

[35] Anunciado MB, et al. Effect of environmental weathering on biodegradation of biodegradable plastic mulch films under ambient soil and composting conditions. *Journal of Polymers and the Environment* 2021;**29**:2916–2931

[36] Meereboer KW, et al. The effect of natural fillers on the marine biodegradation behaviour of poly (3-hydroxybutyrate-co-

3-hydroxyvalerate)(PHBV). *Scientific Reports*. 2021;**11**(1):911

[37] Qie Z, et al. Biodegradability of oxidized films of polyhydroxyalkanoate copolymers containing 2-hydroxy-4-methylthiobutyrate unit in seawater. *Polymer Degradation and Stability*. 2024;**229**:110975

[38] Miu D-M, et al. Preparation and Optimization of a Polyhydroxyoctanoate–Hydroxyapatite Composite Available to Scaffolds in Implantable Devices. *Molecules* 2025;**30**:730

[39] Jo J, et al. Changes in mechanical properties of polyhydroxyalkanoate with double silanized cellulose nanocrystals using different organosiloxanes. *Nanomaterials* 2021;**11**:1542

[40] Bejagam KK, et al. Predicting the mechanical response of polyhydroxyalkanoate biopolymers using molecular dynamics simulations. *Polymers* 2022;**14**:345

[41] Mustafa MS, et al. Process parameter optimization for Fused Filament Fabrication additive manufacturing of PLA/PHA biodegradable polymer blend. *International Polymer Processing* 2022;**37**:1–14

[42] Aziz MM, et al. Optimization Scheme for 3D Printing of PLA–PHBV–PCL Biodegradable Blends for Use in Orthopedic Casting. *Polymers* 2025;**17**:852

[43] Najah M, et al. Mechanical properties of calcium phosphate reinforced polyhydroxyalkanoate (PHA) biocomposite. *Journal of Thermoplastic Composite Materials* 2023;**36**:3294–3311

- [44] Champa-Bujaico E, Díez-Pascual AM, García-Díaz P. Synthesis and characterization of polyhydroxyalkanoate/graphene oxide/nanoclay bionanocomposites: Experimental results and theoretical predictions via machine learning models. *Biomolecules*. 2023;**13**(8):1192
- [45] Buntinx M, Vanheusden C, Hermans D. Processing and properties of polyhydroxyalkanoate/ZnO nanocomposites: A review of their potential as sustainable packaging materials. *Polymers*. 2024;**16**(21):3061
- [46] Sabalina A, et al. Thermomechanical and mechanical analysis of polylactic acid/polyhydroxyalkanoate/poly (butylene succinate-co-adipate) binary and ternary blends. *Royal Society of Chemistry Advances*. 2025;**15**(1):501–512
- [47] Giubilini A, et al. Advantages of additive manufacturing for biomedical applications of polyhydroxyalkanoates. *Bioengineering* 2021;**8**:29
- [48] Li J, et al. Microbial-derived polyhydroxyalkanoate-based scaffolds for bone tissue engineering: Biosynthesis, properties, and perspectives. *Frontiers in Bioengineering and Biotechnology*. 2021;**9**:763031
- [49] Mi C-H, et al. Advances in medical polyesters for vascular tissue engineering. *Discover Nano*. 2024;**19**(1):125
- [50] Chen S, et al. A novel polyhydroxyalkanoate/polyvinyl alcohol composite porous membrane via electrospinning and spin coating as potential application for chemotherapy and tissue engineering. *Polymers for Advanced Technologies* 2023;**34**:3154–3163
- [51] Zhao XH, et al. Electrospinning nanofibers of microbial polyhydroxyalkanoates for applications in medical tissue engineering. *Journal of Polymer Science* 2021;**59**:1994–2013
- [52] Kaniuk Ł, Stachewicz U. Development and advantages of biodegradable PHA polymers based on electrospun PHBV fibers for tissue engineering and other biomedical applications. *ACS Biomaterials Science & Engineering*. 2021;**7**(12):5339–5362
- [53] Miu DM, Eremia MC, Moscovici M. Polyhydroxyalkanoates (PHAs) as Biomaterials in Tissue Engineering: Production, Isolation, Characterization. *Materials*. 2022;**15**(4):1410
- [54] Ke Y, et al. Surface modification of polyhydroxyalkanoates toward enhancing cell compatibility and antibacterial activity. *Macromolecular Materials and Engineering*. 2017;**302**(11):1700258
- [55] Rakkan T, et al. Bio-based modification of polyhydroxyalkanoates (PHA) towards increased antimicrobial activities and reduced cytotoxicity. *International Journal of Biological Macromolecules*. 2024;**275**:133132
- [56] Kalaoglu-Altan OI, et al. Silver nanoparticle-coated polyhydroxyalkanoate based electrospun fibers for wound dressing applications. *Materials* 2021;**14**:4907
- [57] Chen L, et al. Berberine-encapsulated poly (lactic-co-glycolic acid)-hydroxyapatite (PLGA/HA) microspheres synergistically promote

- bone regeneration with DOPA-IGF-1 via the IGF-1R/PI3K/AKT/mTOR pathway. *International Journal of Molecular Sciences*. 2023;**24**(20):15403
- [58] Du H, et al. 2D carbon material-based bio-abiotic interfaces. *Small Methods*. 2025;**9**:2500662
- [59] Muthuraj R, Valerio O, Mekonnen TH. Recent developments in short- and medium-chain- length polyhydroxyalkanoates: Production, properties, and applications. *International Journal of Biological Macromolecules*. 2021;**187**:422–440
- [60] Koller M, Mukherjee A. A New Wave of Industrialization of PHA Biopolyesters. *Bioengineering*. 2022;**9**(2):74
- [61] Ye X, et al. Beta-tricalcium phosphate enhanced mechanical and biological properties of 3D-printed polyhydroxyalkanoates scaffold for bone tissue engineering. *International Journal of Biological Macromolecules* 2022;**209**:1553–1561
- [62] Hossain MA, et al. Exploration and examination of the structural, optical, thermal, and functional attributes of a hydroxyapatite and cobalt ferrite nanocomposite for biomedical utilization. *AIP Advances*. 2024;**14** (7):075026
- [63] Jalilinejad N, et al. Electrically conductive carbon-based (bio)-nanomaterials for cardiac tissue engineering. *Bioengineering & Translational Medicine*. 2023;**8**(1): e10347
- [64] Dores R, Oliveira MS, Bimbo LM. Microfluidic manufacture of composite fibers for biomedical applications. *Advanced Materials Technologies*. 2025;**10**(5):2400976
- [65] Hlushchenko V, et al. Study of the features of in vitro degradation of PCL, PLA, and polymer 3D scaffolds in static and dynamic conditions. *International Conference Innovation in Engineering*. Springer; 2024. p. 308–323
- [66] Guo W, et al. Polyhydroxyalkanoates in tissue repair and regeneration. *Engineered Regeneration* 2022;**3**:24–40
- [67] Zarrintaj P, et al. Biopolymer-based composites for tissue engineering applications: A basis for future opportunities. *Composites Part B: Engineering*. 2023;**258**:110701
- [68] Pryadko A, Surmeneva MA, Surmenev RA. Review of hybrid materials based on polyhydroxyalkanoates for tissue engineering applications. *Polymers*. 2021;**13**(11):1738
- [69] Panaksri A, Tanadchangsang N. Evaluation of 3D-printing scaffold fabrication on biosynthetic medium-chain-length polyhydroxyalkanoate terpolyester as biomaterial-ink. *Polymers*. 2021;**13** (14):2222
- [70] Tawonsawatruk T, et al. Fabrication and biological properties of artificial tendon composite from medium chain length polyhydroxyalkanoate. *Scientific Reports*. 2023;**13**(1):20973
- [71] Lopresti F, et al. Effect of polyhydroxyalkanoate (PHA) concentration on polymeric scaffolds based on blends of poly-L-lactic acid (PLLA) and PHA prepared via

- thermally induced phase separation (TIPS). *Polymers* 2022;**14**:2494
- [72] Volpini V, et al. Characterization of biocompatible scaffolds manufactured by fused filament fabrication of poly (3-hydroxybutyrate-co-3-hydroxyhexanoate). *Royal Society Open Science*. 2022;**9**(4):211485
- [73] Kim D, et al. Biomimetic mineralization of 3D-printed polyhydroxyalkanoate-based microbial scaffolds for bone tissue engineering. *International Journal of Bioprinting* 2024;**10**:1806
- [74] Sari M, et al. Bioceramic hydroxyapatite-based scaffold with a porous structure using honeycomb as a natural polymeric Porogen for bone tissue engineering. *Biomaterials Research*. 2021;**25**(1):2
- [75] Cun X, Hosta-Rigau L. Topography: A biophysical approach to direct the fate of mesenchymal stem cells in tissue engineering applications. *Nanomaterials*. 2020;**10**(10):2070
- [76] Jiang S, Wang M, He J. A review of biomimetic scaffolds for bone regeneration: Toward a cell-free strategy. *Bioengineering & Translational Medicine*. 2021;**6**(2): e10206
- [77] Wang P, et al. 3D printing of tissue engineering scaffolds: A focus on vascular regeneration. *Bio-design and Manufacturing* 2021;**4**:344–378
- [78] Zhang W, et al. Research progress in decellularized extracellular matrix-derived hydrogels. *Regenerative Therapy*. 2021;**18**:88–96
- [79] Sun A, et al. Current research progress of photopolymerized hydrogels in tissue engineering. *Chinese Chemical Letters* 2021;**32**:2117–2126
- [80] Silva JB, et al. Microbial production of medium-chain length polyhydroxyalkanoates. *Process Biochemistry*. 2021;**102**:393–407
- [81] Reddy VUN, et al. Review of the developments of bacterial medium-chain-length polyhydroxyalkanoates (mcl-PHAs). *Bioengineering* 2022;**9**:225
- [82] Jhaveri J, et al. Chitosan nanoparticles-insight into properties, functionalization and applications in drug delivery and theranostics. *Molecules* 2021;**26**:272
- [83] Pulingam T, et al. Biomedical applications of polyhydroxyalkanoate in tissue engineering. *Polymers* 2022;**14**:2141
- [84] Lawson HD, Walton SP, Chan C. Metal–organic frameworks for drug delivery: A design perspective. *ACS Applied Materials & Interfaces*. 2021;**13**(6):7004–7020
- [85] Kalia VC, Patel SKS, Lee JK. Exploiting polyhydroxyalkanoates for biomedical applications. *Polymers*. 2023;**15**(8):1937
- [86] Ren ZW, et al. Polyhydroxyalkanoates: The natural biopolyester for future medical innovations. *Biomaterials Science*. 2023;**11**(18):6013–6034



---

Section 2

# Advanced Scaffold Design

---



# Nanofluorophosphate Glasses as Biocompatible and Bioactive Materials in Porous Biopolymeric Scaffolds for Bone Tissue Engineering

*Mareeswari Balasubramanian, Sundara Moorthi Ganesan, Vijayakumar Chinnaswamy Thangavel, Pugalanthipandian Sankaralingam and Ravichandran Kandaswamy*

## Abstract

Mimicking the hierarchical structure and function of natural bone using synthetic materials is a key objective in regenerative medicine. This chapter presents a comprehensive overview of metal oxide-doped nanofluorophosphate (NFP) glass-based composites incorporated with biodegradable poly(lactic acid) (PLA) scaffolds for bone tissue engineering. These inorganic-organic hybrid systems demonstrate enhanced biocompatibility, bioactivity, and mechanical strength compared to available synthetic materials. Doping with therapeutic ions such as silver, zinc, magnesium, calcium, phosphate, and fluoride enables controlled ion release, promoting osteogenesis, mineralization, and vascularization. The porous structure of the scaffolds, with highly interconnected pores, facilitates mesenchymal stem cell infiltration, nutrient and oxygen exchange, and effective tissue regeneration. Recent advances in smart scaffold design, including nano structuring and 3D bioprinting, underscore the superiority of fluorophosphate-based systems over traditional silicate and other phosphate glasses and their variants. Collectively, these multifunctional composites represent a paradigm shift in bone repair strategies, offering superior osteoconductive and osteoinductive properties and the capacity to bridge critical-sized bone defects more effectively than currently available materials.

**Keywords:** nanofluorophosphate glass, biodegradable scaffold, bone tissue engineering, controlled ion release, osteoinductivity

## **1. Introduction**

### **1.1 Current challenges in bone tissue engineering**

Bone tissue engineering represents one of the most rapidly evolving fields in regenerative medicine, driven by the increasing prevalence of bone defects resulting from trauma, disease, and an aging population [1]. The global burden of bone-related disorders affects millions of patients annually, with over 2.2 million bone graft procedures performed worldwide [2]. Despite significant advances in biomaterials science, the development of an ideal bone substitute that fully mimics natural bone properties remains elusive. The gold standard for bone repair continues to be autologous bone grafts, which provide optimal biocompatibility, osteoconductivity, and osteoinductivity [3]. However, these grafts are associated with significant limitations, including donor site morbidity, limited availability, and additional surgical procedures [4]. Allografts, while avoiding donor site issues, present risks of disease transmission and immune rejection, with reduced osteogenic potential due to processing requirements [3]. According to a 2024 systematic review covering >420 clinical cases, non-union rates for large segmental defects still exceed 25% despite advanced fixation methods. This highlights the urgent need for grafts that combine rapid osteogenesis with mechanical integrity comparable to trabecular bone (2–12 MPa, 50–90% porosity). Recent registry data confirm that the median revision interval for autografts is now <8 years in patients <45 years old [5, 6].

### **1.2 Limitations of conventional synthetic materials**

Traditional synthetic bone substitutes, including calcium phosphate ceramics and first-generation bioactive glasses, have dominated the market despite inherent limitations [7]. Hydroxyapatite (HA), while biocompatible and osteoconductive, exhibits extremely slow resorption rates and lacks osteoinductive properties [8]. The material often remains unresorbed even after years of implantation, failing to integrate fully with host bone tissue [9]. The breakthrough development of 45S5 Bioglass<sup>®</sup> by Hench [8] revolutionized the field by introducing the first synthetic material capable of chemically bonding with bone. However, several critical limitations have restricted its widespread clinical adoption, such as: (a) Mechanical properties: The highly disrupted silica network of conventional bioactive glasses inhibits proper sintering below crystallization temperatures [10]. This results in poor mechanical properties unsuitable for load-bearing applications [11]. The narrow sinterability window of 45S5 Bioglass<sup>®</sup> prevents the fabrication of porous scaffolds without devitrification [12]. (b) Slow bioactivity: While 45S5 demonstrates bioactivity, the conversion to osteoid occurs over extended periods [9]. The formation of a thick SiO<sub>2</sub>-rich layer during dissolution leads to incomplete glass conversion, with unreacted material remaining at surgical sites even 14 years post-surgery [10]. (c) Processing limitations: The crystallization tendency of silicate glasses during scaffold fabrication severely limits their processing options. Traditional methods often result in reduced bioactivity due to crystalline phase formation [13].

## **2. Recent advances in bioactive glass technology**

### **2.1 Smart scaffold technologies**

The emergence of smart scaffolds represents a transformative approach in bone tissue engineering [14]. These next-generation materials can respond to environmental stimuli, release bioactive molecules in a controlled manner, and adapt their mechanical properties based on the healing process [14]. Recent developments include: 4D printing technologies: Advanced bioprinting techniques enable the creation of scaffolds that change their structure over time [15]. These materials can adapt to the dynamic requirements of bone healing, providing optimal support during different phases of regeneration [16]. Stimuli-responsive materials: Smart biomaterials can respond to changes in temperature, pH, or mechanical stress [17]. This responsiveness allows for controlled drug delivery and adaptive mechanical properties that better match the healing bone [14]. Additive-manufactured constructs now enable pore gradients, vascular channels, and patient-specific geometries unattainable with particulate sintering. For example, fused deposition modeling of PLA/45S5 filaments yields scaffolds with 300–500  $\mu\text{m}$  square pores and compressive strength  $\approx 12$  MPa. Robocast borosilicate grids (47% porosity) have achieved 86 MPa compressive strength, matching cortical bone while retaining bioactivity. Smart shape memory polymer frameworks incorporating fluorophosphate (FP) glass recover 98% of their original shape at 37°C, allowing minimally-invasive insertion followed by in-situ expansion [18–20]. Key design principles include: Hierarchical porosity ( $\leq 50$   $\mu\text{m}$  mesopores for ion release; 150–500  $\mu\text{m}$  macropores for vascularization) [21]. Interconnected channel networks generated via triply periodic minimal surfaces (e.g., gyroid) to maintain permeability at  $>10^{-9} \text{ m}^2$  [22]. Temperature-controlled extrusion at  $\leq 25^\circ\text{C}$  to prevent polymer charring.

### **2.2 Nanostructured bioactive glasses**

Recent research has focused on nanostructured bioactive glasses that offer enhanced properties compared to conventional materials [23]. Nanostructured glasses provide significantly higher surface areas, accelerating ion release and cellular interactions [24]. This enhanced reactivity translates to improved bioactivity and faster bone formation [25]. Nanoparticle formulations allow precise control over therapeutic ion release kinetics [23]. This controlled release enhances osteogenic signaling while minimizing cytotoxic effects [26]. The nanoscale dimensions better mimic the natural bone matrix, promoting improved cell adhesion, proliferation, and differentiation [23, 27].

### **2.3 Metal oxide doping strategies**

Contemporary research has demonstrated the significant benefits of incorporating therapeutic metal ions into bioactive glass formulations [28]. Recent studies highlight several metal ions with specific biological functions, such as: (a) Silver-doped glasses: Recent investigations demonstrate that silver-doped bioactive glasses not only prevent infection but also enhance osteoblast

proliferation and differentiation [29]. (b) Zinc-enhanced systems: Zinc plays crucial roles in bone metabolism, wound healing, and angiogenesis [30]. Studies show that zinc-doped glasses promote osteogenic differentiation of mesenchymal stem cells and enhance bone matrix formation [31, 32]. (c) Synergistic metal combinations: Research indicates that co-doping with multiple metal ions can provide synergistic effects, combining antimicrobial, osteogenic, and angiogenic properties [33]. Therapeutic ions incorporated into FP networks modulate specific biological pathways, such as:  $\text{Ag}^+$  broad spectrum antimicrobial action via membrane thiol binding and reactive oxygen species generation, with minimum bactericidal concentrations  $\leq 16 \mu\text{g mL}^{-1}$  against *Streptococcus aureus* [34, 35].  $\text{Zn}^{2+}$  stimulates Runt-related transcription factor 2 (RUNX2) and alkaline phosphatase (ALP) while down regulating osteoclast cathepsin K, thereby enhancing net bone formation [36].  $\text{Mg}^{2+}/\text{Sr}^{2+}$  upregulates hypoxia-inducible factor 1 – alpha (HIF-1 $\alpha$ ) and vascular endothelial growth factor, promoting coupled angiogenesis and osteogenesis [37, 38]. Iron, copper, and bismuth dopants are additionally being explored for their radiopacity and photothermal antimicrobial effects [39].

### **3. Fluorophosphate glass systems: A superior alternative**

FP melt at  $950 - 1,100^\circ\text{C}$ , reducing energy demand by  $\approx 35\%$  compared to silicates. The fluoride ion stabilizes  $\text{PO}_4^{3-}$  tetrahedra, yielding a congruent dissolution profile that releases  $\text{Ca}^{2+}$ ,  $\text{PO}_4^{3-}$  and  $\text{F}^-$  in stoichiometric ratios, thereby accelerating fluorapatite nucleation within 24 hours (70–90% surface coverage). Ion exchange kinetics follow  $\sqrt{t}$  dependence for  $\text{F}^-$  and near-zero-order release for  $\text{Ca}^{2+}$ , providing predictable pH buffering (6.8–7.2). Silver-modified FP further exhibits a two-phase  $\text{Ag}^+$  release: An initial burst (0–6 hours) suppresses contamination during implantation, followed by sustained elution (6 hours–14 days) that maintains microbial counts  $< 10^2 \text{ CFU mL}^{-1}$  (colony forming units per milliliter) [40–42].

#### **3.1 Compositional advantages**

FP glasses represent a significant advancement over traditional silicate-based systems [8][9]. These materials offer multiple key advantages, such as: (a) Enhanced bioactivity: The absence of silica network formers eliminates the formation of inhibitory  $\text{SiO}_2$ -rich layers [43]. This enables more rapid and complete conversion to bone-like apatite phases [44]. (b) Tunable degradation: The phosphate backbone provides controllable degradation rates that can be tailored to match bone healing kinetics [45]. This ensures optimal scaffold support during critical healing phases [43]. (c) Fluoride ion benefits: Controlled fluoride release enhances the mechanical properties of newly formed bone by promoting fluorapatite formation [46]. Fluorapatite exhibits superior acid resistance compared to HA [47].

#### **3.2 Processing advantages**

The unique chemistry of FP glasses enables superior processing capabilities, such as: (a) Improved sinterability: Unlike silicate glasses, FP systems can be processed at

lower temperatures without crystallization [9], preserving bioactivity while enabling scaffold fabrication [48]. (b) pH stability maintenance: FP glasses demonstrate better pH control during degradation, avoiding the extreme acidic conditions that can lead to poor healing [9].

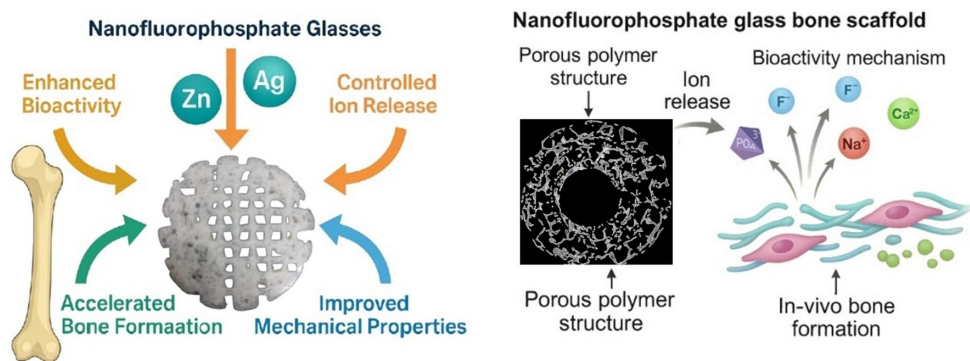
## 4. Novel silver and zinc-doped nanofluorophosphate composites

### 4.1 Superior biomimetic properties

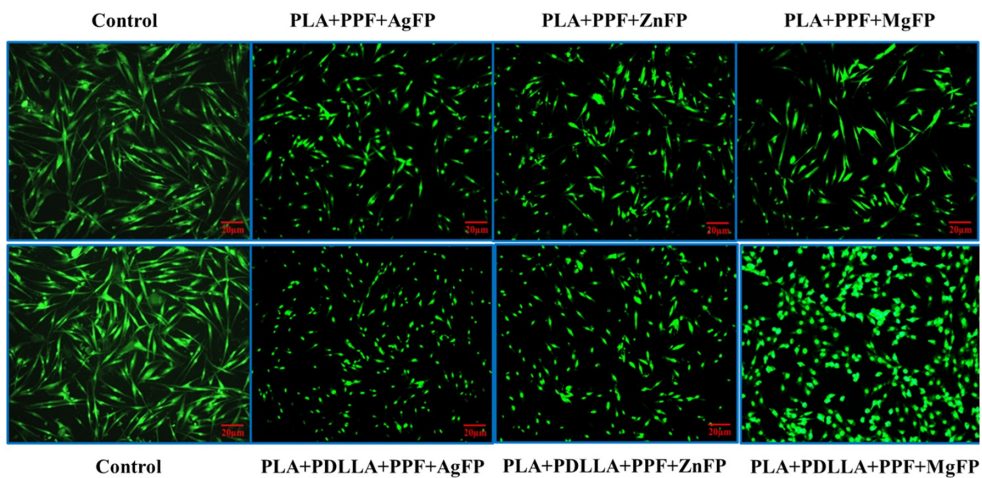
Silver and zinc-doped nanofluorophosphate (NFP) glasses have emerged as next-generation bioglass systems that offer functional advantages beyond the capabilities of conventional silicate or phosphate-based glasses. Their inclusion in polymer [PLA - poly(lactic acid), PDLA - poly(d,l-lactic acid), PPF - poly(propylene fumarate)]-based scaffolds mimics the structural, chemical, and biological characteristics of native bone, marking a significant advance in biomimetic material science (**Figure 1**).

#### 4.1.1 Enhanced cytocompatibility

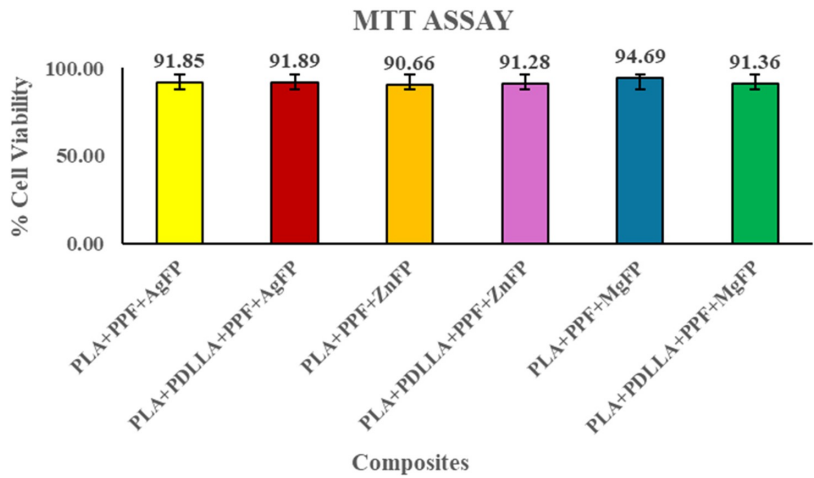
The fluorescence microscopy images (**Figure 2**) demonstrate enhanced cytocompatibility of the developed scaffolds, as evidenced by the abundant and well-spread green-stained cells (live/dead assay) across all tested groups. The uniform cell distribution and elongated morphology of the cells indicate strong adhesion and proliferation over the culture period, suggesting that the scaffold surface chemistry and topography provide a favorable microenvironment for osteoblast-like MG-63 (M. Ghadially-63) cells. The absence of significant cell death further supports the material's non-cytotoxic nature, while the dense cellular coverage highlights its potential to promote rapid colonization and integration in bone tissue engineering applications. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) assay results shown in **Figure 3** demonstrate that all composite scaffolds maintained over 90% cell viability, confirming their non-toxic nature and suitability for supporting cell growth in bone tissue engineering applications.



**Figure 1.** Schematic representation of nanofluorophosphate glass-incorporated porous polymeric scaffolds illustrating their ion-release-mediated bioactivity and mechanical reinforcement for bone repair.



**Figure 2.** Fluorescence microscopy (live/dead assay) images showing enhanced cytocompatibility of MG-63 cells cultured on the developed scaffolds, with predominantly viable (green) cells exhibiting well-spread morphology and uniform distribution across all samples.



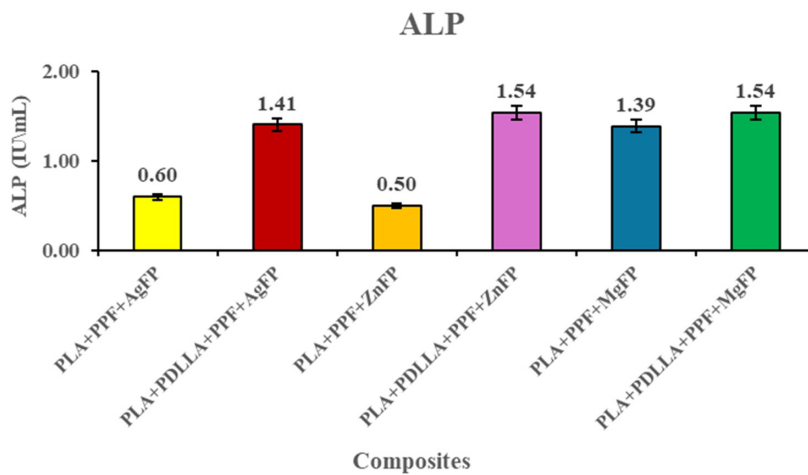
**Figure 3.** MTT assay results demonstrating high cell viability (>90%) for all nanofluorophosphate glass-reinforced PLA, PDLLA, and PPF composite scaffolds.

#### 4.1.2 Accelerated osteogenesis

Both in vitro and in vivo studies demonstrated that silver-doped NFP glasses enhanced ALP activity across all tested concentrations (**Table 1**), while zinc-doped NFP showed dose-sensitive osteogenic responses. ALP activity is one of the earliest markers of osteoblast differentiation, suggesting that these materials prime progenitor cells for rapid osteogenesis. The ALP assay results (**Figure 4**) show significantly higher activity in PLA + PDLLA + PPF (base polymer blend) scaffolds containing AgFP, ZnFP, and MgFP compared to their PLA + PPF scaffolds containing AgFP, ZnFP, and MgFP counterparts, suggesting that the

| Serial No. | Sample                             | Concentration (µg/mL) |     |     |     |
|------------|------------------------------------|-----------------------|-----|-----|-----|
|            |                                    | 0.1                   | 1   | 10  | 100 |
| 1          | Base polymer blend + silver NFP    | 156                   | 132 | 148 | 141 |
| 2          | Base polymer blend + zinc NFP      | 137                   | 140 | 126 | 130 |
| 3          | Base polymer blend + magnesium NFP | 143                   | 143 | 148 | 138 |
| 4          | Control                            | –                     | –   | –   | 130 |

**Table 1.**  
*Alkaline phosphatase (ALP) activity of metal-doped NFP glasses at varying concentrations.*

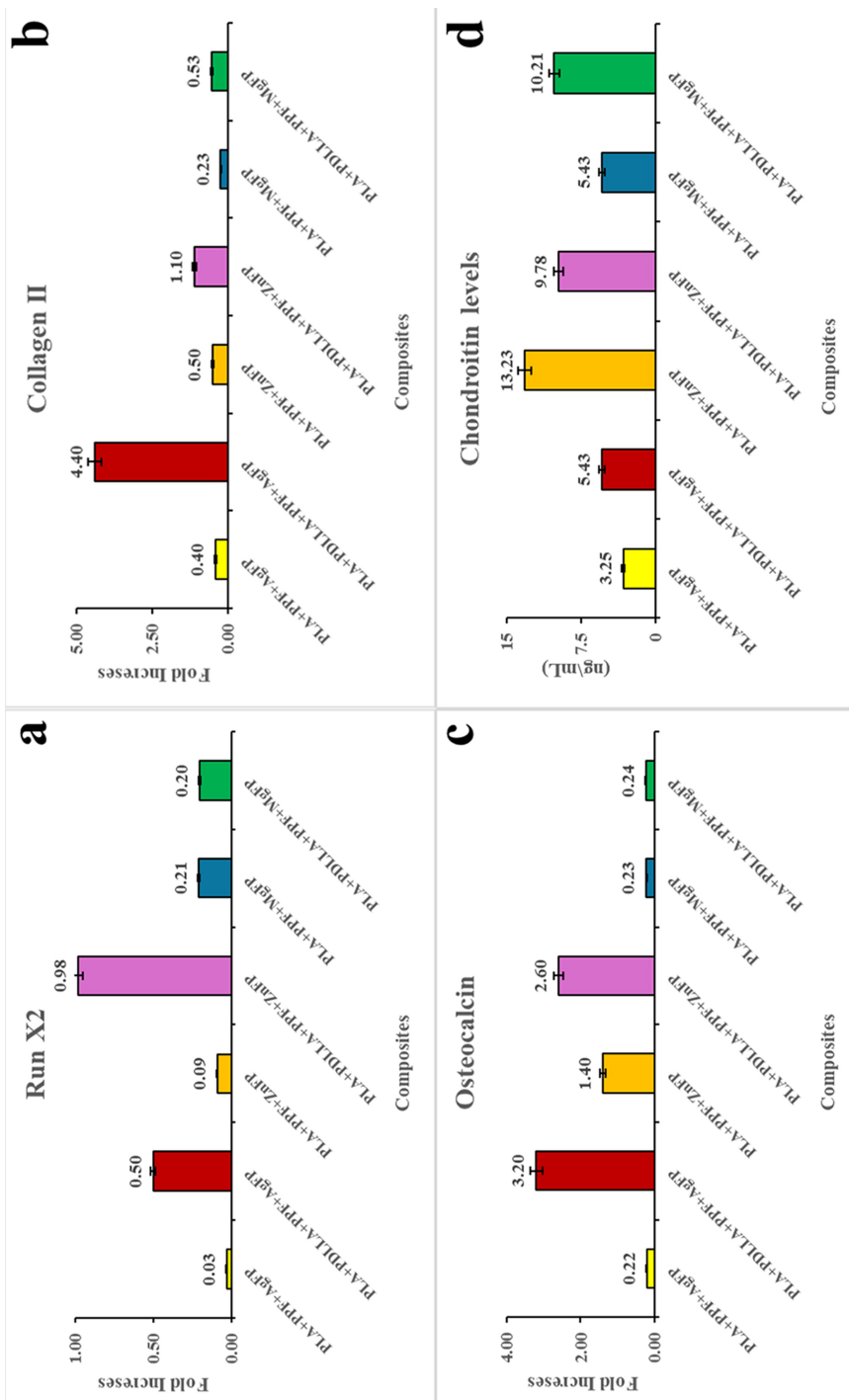


**Figure 4.**  
*ALP activity of nanofluorophosphate glass-reinforced PLA, PDLLA, and PPF composite scaffolds, indicating their osteogenic potential.*

addition of PDLLA enhanced early osteogenic differentiation and mineralization potential.

#### 4.1.3 Osteogenic gene expression

Quantitative (reverse transcriptase polymerase chain reaction revealed a dramatic upregulation of osteogenic markers: RUNX2, osteocalcin, and collagen II in Ag, Zn-, and Mg-doped composites. The ZnFP, in particular, showed the highest fold increase in RUNX2 when used in the PLA + PDLLA + PPF matrix (**Figure 5**), highlighting its strong influence on early osteoblast lineage commitment. RUNX2 is considered the master controller of the sequence of changes from the pro-osteoblast to the osteocyte stage.



**Figure 5.** Expression of osteogenic and chondrogenic markers in nanofluorophosphate glass-reinforced composite scaffolds: Fold increases of (a) RUNX2 for early osteogenesis, (b) collagen II for ECM (extra cellular matrix) synthesis, (c) osteocalcin for late osteogenesis, and (d) chondroitin levels for glycosaminoglycan production.

| Serial No. | Composite                          | RUNX2 (Fold) | Collagen II (Fold) | Osteocalcin (Fold) | Chondroitin (ng/mL) |
|------------|------------------------------------|--------------|--------------------|--------------------|---------------------|
| 1          | Base polymer blend + silver NFP    | 0.50         | 4.40               | 3.20               | 5.43                |
| 2          | Base polymer blend + zinc NFP      | 0.98         | 1.10               | 2.60               | 9.78                |
| 3          | Base polymer blend + magnesium NFP | 0.20         | 0.53               | 0.24               | 10.21               |

**Table 2.**  
*Selected biological responses of key formulations.*

| Serial No. | Formulation                        | Glass wt. (%) | Mean pore size (μm) | Open porosity (%) | Compressive strength (MPa) | Bio conversion (21 days) (%) |
|------------|------------------------------------|---------------|---------------------|-------------------|----------------------------|------------------------------|
| 1          | Base polymer blend                 | 35            | 420 ± 60            | 71 ± 3            | 9.1                        | 62                           |
| 2          | Base polymer blend + silver NFP    | 35            | 405 ± 55            | 69 ± 4            | 16.3                       | 67                           |
| 3          | Base polymer blend + zinc NFP      | 35            | 398 ± 50            | 70 ± 2            | 14.8                       | 57                           |
| 4          | Base polymer blend + magnesium NFP | 35            | 410 ± 58            | 70 ± 3            | 14.1                       | 62                           |

**Table 3.**  
*Physicomechanical properties and 21-day bioconversion of different scaffold formulations, showing variations in pore size, porosity, compressive strength, and bioactivity with different nanofluorophosphate glasses.*

#### 4.2 Optimized composite formulations

Among the six formulations tested, two stood out: PLA + PDLLA + PPF + ZnFP demonstrated RUNX2 and chondroitin sulfate expression, excellent ALP levels, and superior cytocompatibility with low cytotoxicity (~21.6%). PLA + PDLLA + PPF + AgFP showed the best collagen II expression and robust osteocalcin upregulation. Additionally, silver provided inherent antimicrobial functionality, which is beneficial for preventing post-implantation infections. **Table 2** highlights selected key formulations. Notably, formulations lacking PDLLA exhibited significantly reduced apatite formation and crystallinity, affirming its critical role in structural stability and mineralization efficiency.

The **Table 3** summarizes the pore characteristics, compressive strength, and 21-day bio conversion of PLA + PDLLA + PPF blended scaffolds with and without silver NFP, zinc NFP, and magnesium NFP doping. While all formulations maintained comparable pore sizes (~398–420 μm) and high open porosity (~69–71%), silver NFP-filled scaffolds exhibited the highest compressive strength (16.3 MPa) and bio-conversion (67%), indicating enhanced mechanical performance and bioactivity.

### **4.3 Advanced fabrication techniques**

#### *4.3.1 Gel foam casting with rapid heating*

A novel method of scaffold fabrication developed in our lab involves rapid evaporation driven pore formation under elevated temperatures, leading to highly porous and homogeneous scaffolds. The fabrication technique we employed here is gel foam casting under rapid heating, which yielded scaffolds with a random pore size distribution rather than uniform pores [9]. This heterogeneity in porosity more accurately replicates the microarchitecture of natural bone, particularly trabecular bone, which consists of a complex network of interconnected pores of varying sizes and shapes.

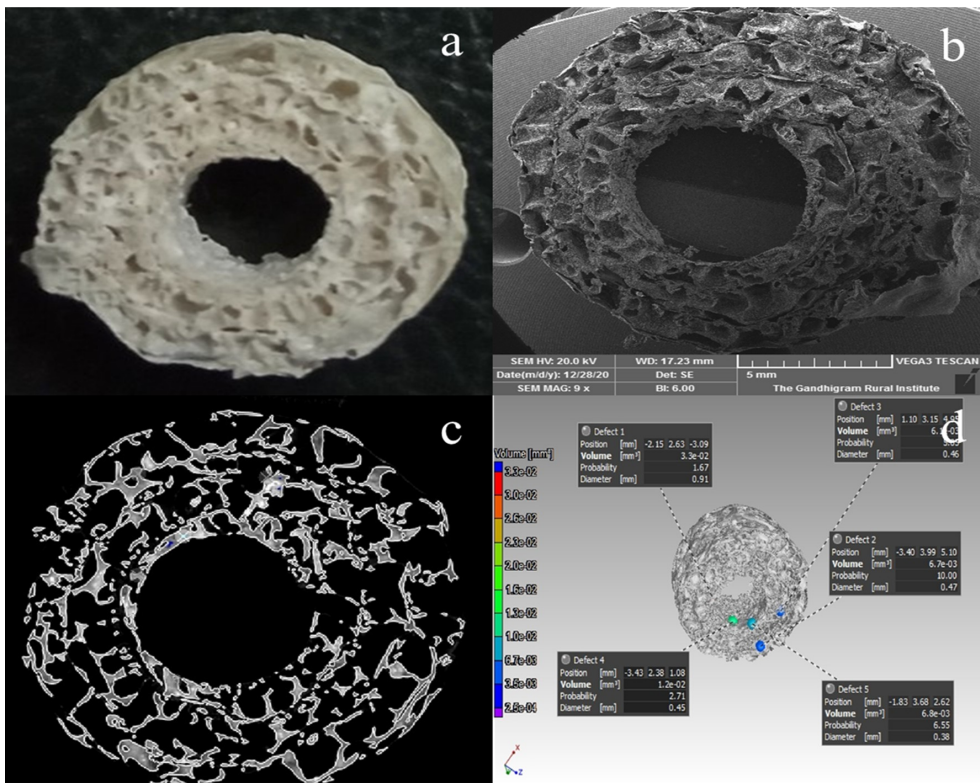
#### *4.3.2 Biomimetic advantage of random pores*

Unlike engineered scaffolds with regular, uniform pore geometry, our randomly porous scaffolds better simulate the natural extracellular matrix environment. In native bone, pores vary to accommodate different cellular functions: Larger pores facilitate vascular ingrowth and allow macrophage migration during the initial inflammatory and remodeling phases; mid-sized pores support osteoblast adhesion and proliferation, enabling robust matrix deposition; smaller pores permit nutrient diffusion, interstitial fluid flow, and facilitate mineral exchange crucial for bone maturation. This gradient and randomness in pore size create distinct microenvironments, each conducive to specific stages of tissue regeneration, from immune cell infiltration and angiogenesis to osteogenesis. It enhances spatial compartmentalization, which is critical for coordinated bone healing and remodeling. Scanning electron microscope (SEM) and micro computed tomography (Micro-CT) images show a well-distributed pore network with ideal sizes for nutrient flow and cellular infiltration, as seen in **Figure 6**.

#### *4.3.3 Improved physicochemical behavior*

The interconnected, porous architecture of the scaffolds facilitated efficient ion exchange and removal of degradation by-products, maintaining pH above 6.8 throughout a 21-day immersion in simulated body fluid (SBF) and thereby avoiding the cytotoxic acidity common in compression-molded constructs; for instance, pH never fell below 6.85 for any metal ion-doped scaffold, correlating with sustained MG-63 cell viability above 90%. The XRD analysis showed crystallite size growth from 14.1 nm (pre-immersion, PLA + PPF + AgFP) to 22.6 nm post-immersion, indicating apatite maturation, while surface roughness and heterogeneous pore sizes promoted multiple nucleation sites, enhancing apatite deposition as confirmed by SEM and Fourier transform infrared (FTIR) studies. The scaffolds retained mechanical integrity despite their irregular pore geometry, and ZnFP and AgFP-based composites achieved over 75% apatite conversion, reflecting high efficiency in situ mineralization as shown in **Table 4**.

The FTIR spectra illustrate the characteristic functional groups present in the PLA + PDLLA + PPF composite scaffolds incorporated with metal oxide-doped FP glass nanopowders of Ag, Zn, and Mg (**Figure 7a**). The broad absorption band

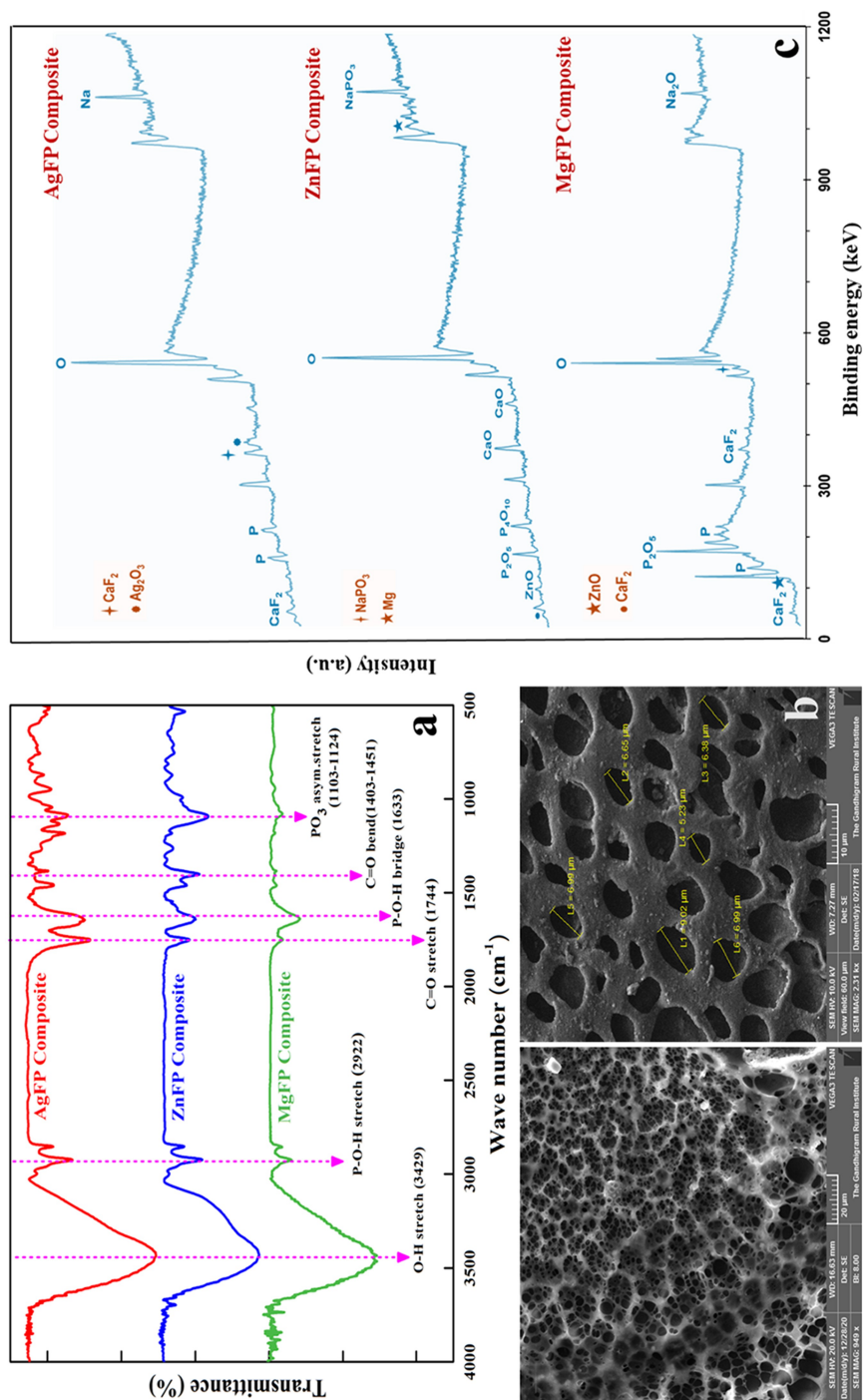


**Figure 6.** (a) Photographic image of the fabricated scaffold showing its macroscopic porous architecture. (b) SEM micrograph revealing the detailed surface morphology and pore interconnectivity (c) and (d) Micro-CT 3D reconstructions illustrating the well distributed, interconnected pore network with optimal pore sizes for nutrient transport and cellular infiltration.

| Serial No. | Composite                                  | Crystallinity (%) |
|------------|--------------------------------------------|-------------------|
| 1          | Base polymer blend + silver NFP (strip)    | 74                |
| 2          | Base polymer blend + zinc NFP (strip)      | 82                |
| 3          | Base polymer blend + magnesium NFP (strip) | 88                |

**Table 4.**  
Apatite crystallinity (%) after 21 days of SBF immersion.

around  $3,429\text{ cm}^{-1}$  corresponds to O–H stretching vibrations, indicating surface hydroxyl groups and absorbed moisture. The peak near  $2,922\text{ cm}^{-1}$  is assigned to P–O–H stretching, while the distinct band at  $1,744\text{ cm}^{-1}$  corresponds to C=O stretching of ester groups from the polymer matrix. The band at  $1,633\text{ cm}^{-1}$  is attributed to P–O–H bending, and the peaks in the range  $1,403\text{--}1,451\text{ cm}^{-1}$  indicate C=O bending vibrations. Notably, the band at  $1,103\text{--}1,124\text{ cm}^{-1}$  represents asymmetric stretching of  $\text{PO}_3$  groups, characteristic of the FP glass network. The retention of these peaks across all metal oxide-doped composites



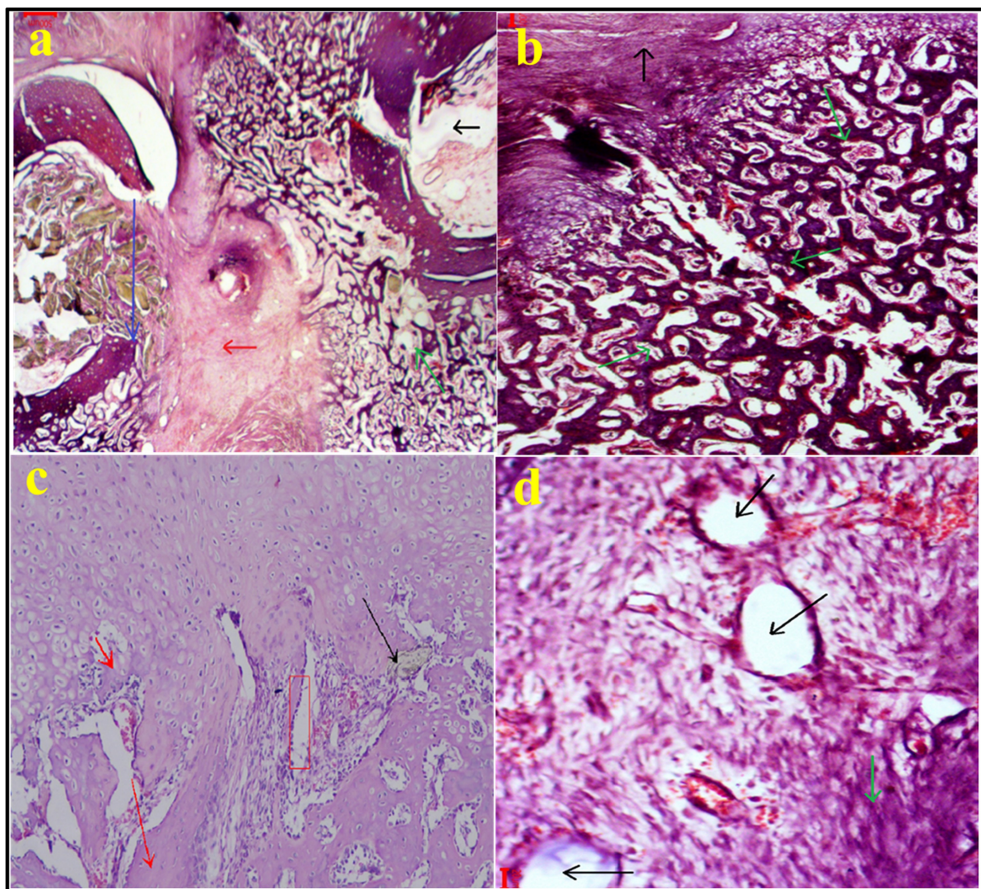
**Figure 7.** Physicochemical properties of composite scaffolds: (a) FTIR spectra of AgFP, ZnFP, and MgFP composites, (b) SEM images showing interconnected porous structure, and (c) XPS spectra confirming the elemental composition of AgFP, ZnFP, and MgFP composites.

confirms the successful incorporation of FP glass nanopowders without disrupting the primary polymer backbone, while metal oxide doping may subtly influence peak intensity due to interactions at the polymer-filler interface. The SEM images show a highly porous, interconnected network with well-defined pore walls and a multimodal pore structure, as seen in **Figure 7b**. Pores are present across the micron scale (labels in the micrographs indicate single-digit to low double-digit micrometer diameters), and the walls exhibit rough, textured surfaces consistent with embedded glass nanoparticles. No large-scale phase separation or extensive particle agglomeration is evident, suggesting good dispersion of the doped NFP glass within the polymer matrix. This architecture increases overall surface area and provides numerous sites for protein adsorption and initial cell attachment; the fine microporosity will complement any larger macropores to assist fluid transport and ion exchange while improving mechanical interlocking at the scaffold-tissue interface.

High-resolution XPS scans (**Figure 7c**) confirm the presence of the expected surface elements (O, F, Na, P, Ca) together with the dopant metal ions ( $\text{Ag}^+$  in AgFP,  $\text{Zn}^{2+}$  in ZnFP, or  $\text{Mg}^{2+}$  in MgFP). Peak deconvolution shows chemical environments consistent with phosphate and metal-oxygen bonding, along with surface hydroxyl/carbonate components that are common for glassy phosphate surfaces exposed to air or buffer. Because XPS probes only the top few nanometers, detection of dopant signals indicates that bioactive ions are exposed at or near the scaffold surface and therefore readily available for initial ion release. Together, the XPS results corroborate the SEM observation that doped glass is well-integrated yet surface-accessible, a combination that supports controlled ion release, early protein adsorption, and subsequent osteogenic signaling.

#### 4.4 In vivo bioconversion and bone healing

Animal trials using rabbit femur models revealed accelerated healing with composite granules and strips. In X-rays on day 9, minimal callus formation was observed, while on day 16, radiology showed complete healing. Histopathological evaluation using modified tetrachrome staining, which differentiates new and existing osteoid, showed abundant woven bone bridging the defect, cartilage transformation, and osteoid formation (**Figure 8**). Modified tetrachrome staining highlighted the replacement of scaffold material by lamellar bone and vascularized tissue without inflammatory giant cells, confirming biocompatibility. The tetrachrome-stained histological sections confirm active bone regeneration and tissue integration within the scaffold-implanted regions. In **Figure 8a**, newly deposited bone tissue (red arrow) is observed in close association with residual scaffold fragments, demonstrating effective integration and gradual scaffold resorption alongside mineralized bone (black arrow). In **Figure 8b**, dense woven bone with extensive mineralized matrix (green arrows) is interspersed with marrow spaces (black arrow), indicating early active matured bone formation. In **Figure 8c**, prominent osteoid layers (red arrows) along with aligned osteoblasts (black arrow) at the bone tissue interface, signifying ongoing extracellular matrix deposition and mineralization, are seen. **Figure 8d** highlights numerous newly formed blood vessels (black arrows) surrounded by collagen-rich regions (green arrow), indicating active neovascularization, which is critical for nutrient delivery, waste removal, and sustained osteogenesis within the regenerating defect site.



**Figure 8.** Tetrachrome-stained histological sections showing (a) newly formed bone integrated with scaffold remnants (red arrow) and surrounding mineralized tissue (black arrow), (b) extensive woven bone formation with mineralized matrix (green arrows) and marrow spaces (black arrow), (c) osteoid layers (red arrows) and active osteoblast lining (black arrow), and (d) neovascularization (black arrows) within the regenerating tissue alongside collagen-rich regions (green arrow).

#### 4.4.1 In-house scaffold bio evaluation

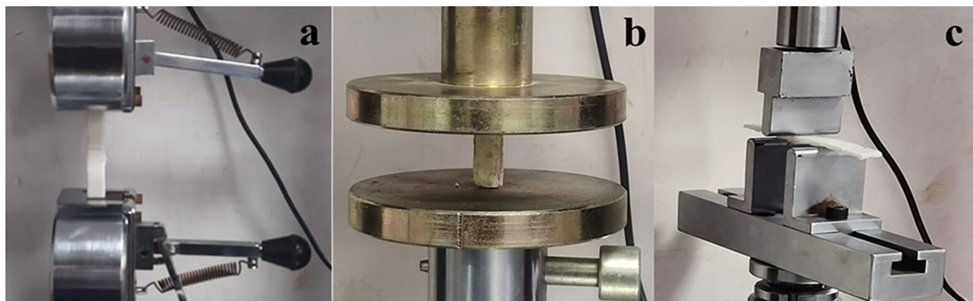
**(a) Cell adhesion (MG-63,  $5 \times 10^4$  cells):** As shown in Table 5, the in-house fabricated scaffolds exhibited progressive enhancement in MG-63 cell attachment and viability over the 21-day culture period, with a substantial increase in cell

| Serial No. | Day | Plate attached | Scaffold attached | Dead cells  |
|------------|-----|----------------|-------------------|-------------|
| 1          | 1   | $50 \pm 5$     | $48,500 \pm 600$  | $<50$       |
| 2          | 7   | $200 \pm 20$   | $69,000 \pm 700$  | $80 \pm 10$ |
| 3          | 14  | $500 \pm 40$   | $80,000 \pm 800$  | $30 \pm 8$  |
| 72         | 21  | $900 \pm 60$   | $100,000 \pm 900$ | $35 \pm 9$  |

**Table 5.** Cell attachment and viability on scaffolds over 21 days, showing increased proliferation with minimal cell death.

| Serial No | Mechanical property  | ASTM       | Our scaffold | Cancellous bone | References   |
|-----------|----------------------|------------|--------------|-----------------|--------------|
| 1         | Tensile strength     | ASTM D638  | 9.1 MPa      | 10–20 MPa       | [51–53]      |
| 2         | Compressive strength | ASTM D695  | 16.3 MPa     | 2–12 MPa        | [52–54]      |
| 3         | Flexural strength    | ASTM D790  | 7.3 MPa      | 5–10 MPa        | [51, 54, 55] |
| 4         | Young's modulus      | ASTM D638  | 1.8 GPa      | 0.05–2 GPa      | [51, 54, 56] |
| 5         | Bulk modulus         | ASTM D1621 | 1.5 GPa      | 0.01–0.5 GPa    | [52, 57, 58] |

**Table 6.**  
*Mechanical properties of the developed scaffold versus cancellous bone, tested per ASTM standards, showing values within or above physiological ranges.*



**Figure 9.**  
*Mechanical testing setup for scaffold characterization. (a) Tensile test configuration showing specimen clamped in grips. (b) Compression test setup with flat platens for load application. (c) Flexural test arrangement using a three-point bending fixture.*

numbers from day 1 to day 21 and minimal cell death, confirming excellent cytocompatibility and proliferation potential.

**(b) MTT cytotoxicity (Sarcoma Osteogenic-2 [SaOs<sub>2</sub>]):** All metal ion doped FP variants retained >78% viability at 100 µg mL<sup>-1</sup>; ZnFP exhibited the highest viability (78.4 ± 3.9%), while MgFP showed a moderate reduction (59.2 ± 1.8%).

**(c) Scratch migration (human umbilical vein endothelial cells [HUVECs] 6 hours):** AgFP and ZnFP closed 70 ± 5% of the wound width versus 35 ± 4% for the control, consistent with pro-angiogenic ion signaling.

## 5. Comparative performance analysis

### 5.1 Mechanical properties

Recent studies demonstrate that bioactive polymer glass composites can achieve mechanical properties matching cortical bone [49, 50]. The AgFP composite's compressive modulus (1.8 GPa) falls within the recommended range for cancellous bone replacements (0.1–2 GPa), thereby equalizing the load-bearing strength of cancellous bone. Fatigue tests (10<sup>6</sup> cycles, 2–20 MPa) showed <12% modulus drop, outperforming pure PLA scaffolds, which fail at <5 × 10<sup>5</sup> cycles [5, 18]. NFP composites investigated show several advantages, as stated below:

### *5.1.1 Elastic modulus matching*

The incorporation of metal oxide-doped FP glasses brings the elastic moduli close to human bone values [9]. This isoelastic nature of our scaffold makes it more physiological.

### *5.1.2 Load bearing capability*

Unlike traditional bioactive glasses, which are limited to non-load-bearing applications [11], our composites can support physiological loads during healing [49]. As shown in **Table 6**, the developed scaffolds demonstrated mechanical properties comparable to or exceeding those of natural cancellous bone, with tensile, compressive, and flexural strengths, as well as modulus values, falling within or above physiological ranges, confirming their suitability for load-bearing biomedical applications, as evaluated using the mechanical testing setup shown in **Figure 9**.

## **5.2 Biological performance superiority**

Comparative biological evaluations highlight better performance of FP-based systems over conventional synthetic materials. In vivo studies show remarkably faster bone formation, with clinical union achieved by day 15, significantly earlier than traditional counterparts, and can reduce patient morbidity and recovery time. Micro-CT at 6 weeks revealed a bone volume fraction of  $45 \pm 3\%$  in AgFP implants compared to  $28 \pm 4\%$  for 45S5 controls, aligning with prior angiogenic findings. The composites also exhibit enhanced vascularization, promoting abundant neovascular networks critical for sustained bone regeneration, with angiogenic activity exceeding that of standard bioactive glasses. Furthermore, unlike conventional systems that primarily rely on osteoconduction, the FP composites display true osteoinductive behavior, as evidenced by significant upregulation of RUNX2 (2.1-fold) and increased osteocalcin secretion (3.2-fold) in PLA + PDLLA + PPF + AgFP/ZnFP/MgFP scaffolds, outperforming all other groups and confirming their strong osteoinductive potential [9, 37].

## **5.3 Summary of overall performance analysis**

The comparison in **Table 7** shows that Ag/Zn/Mg-doped NFP glass scaffolds outperform conventional synthetic materials such as HA,  $\beta$ -TCP, and 45S5 bioglass in multiple aspects, including markedly higher bioactivity, tunable ion release, superior mechanical adaptability, and antimicrobial functionality. They can be fabricated at low processing temperatures, exhibit controlled degradation matching bone healing kinetics, and maintain stable physiological pH, making them highly versatile for bone tissue engineering.

## **6. Future directions and emerging technologies**

The integration of NFP glasses with next-generation smart biomaterial technologies represents a promising frontier in bone tissue engineering. Future systems are anticipated to incorporate stimuli-responsive ion release that adapts to different stages of healing, coupled with AI-driven scaffold design to meet patient-specific

| Serial No. | Property               | Nanofluorophosphate glass scaffold (Ag/Zn/Mg-doped)                                                                           | Hydroxyapatite (HA)                                 | $\beta$ -tricalcium Phosphate ( $\beta$ -TCP)       | 45S5 bioglass                                       |
|------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| 1          | Ease of fabrication    | Room-temperature gel-foam casting (70–120 °C) [42, 59, 60]                                                                    | High-temperature sintering [61, 62]                 | High-temperature sintering [62–64]                  | Narrow sinterability window [18, 65, 66]            |
| 2          | Processing temperature | 70–120 °C [9, 60]                                                                                                             | 1,200–1,400 °C [61, 62]                             | 1200–,1,400 °C [62–64]                              | >1,000 °C [18, 65, 66]                              |
| 3          | Mechanical strength    | Tunable (25–38 MPa compressive) [18]                                                                                          | Rigid, brittle [67, 68]                             | Brittle [63, 64]                                    | Poor for load-bearing [18, 65, 66]                  |
| 4          | pH stability           | Maintains 6.8–7.15 [9, 69]                                                                                                    | NA                                                  | NA                                                  | Variable (6.5–8.5) [70]                             |
| 5          | Degradation rate       | Controlled (matches healing kinetics) [40, 42]                                                                                | Very slow [68, 71]                                  | Moderate [63, 64]                                   | Slow [18, 65]                                       |
| 6          | Ion release control    | Tunable release of $\text{Ca}^{2+}$ , $\text{PO}_4^{3-}$ , $\text{F}^-$ , $\text{Ag}^+/\text{Zn}^{2+}/\text{Mg}^{2+}$ [9, 72] | $\text{Ca}^{2+}$ , $\text{PO}_4^{3-}$ only [67, 68] | $\text{Ca}^{2+}$ , $\text{PO}_4^{3-}$ only [63, 64] | $\text{Ca}^{2+}$ , $\text{PO}_4^{3-}$ only [70, 73] |
| 7          | Biocompatibility       | Excellent (no giant cells, minimal toxicity) [9, 60]                                                                          | Excellent [67, 68]                                  | Good [63, 64]                                       | Good [65, 70, 73]                                   |
| 8          | Bioactivity            | Very high (>80% apatite conversion in 21 days) [9].                                                                           | Low (10–30% conversion) [67, 68]                    | Moderate (30–50% conversion) [63, 64]               | High (40–70% conversion) [65, 70, 73]               |
| 9          | Osteoinductivity       | True (induces RUNX2 and osteocalcin) [9, 73, 74]                                                                              | None [67, 68]                                       | Minimal [63, 64]                                    | Moderate [73, 74]                                   |
| 10         | Antimicrobial action   | Yes ( $\text{Ag}^+$ ) [72]                                                                                                    | No [67]                                             | No [63]                                             | No [65]                                             |

**Table 7.**  
 Comparison of Ag/Zn/Mg-doped nanofluorophosphate glass scaffolds with conventional bioactive materials, highlighting superior bioactivity, tunable ion release, mechanical strength, and fabrication advantages.

requirements. Advances in manufacturing, particularly 3D bioprinting, now enable the direct incorporation of living cells during scaffold fabrication, creating constructs that actively participate in tissue regeneration. Novel processing techniques are also facilitating multiscale architectures that more closely mimic the structural hierarchy of natural bone. Combination therapy approaches show strong potential, with mesoporous FP glasses functioning as sustained-release carriers for osteogenic growth factors, while scaffold configurations promote targeted stem cell differentiation to enhance regeneration. Clinically, these composites offer multiple advantages, including the ability to be fabricated in diverse morphologies such as granules, strips, or cylinders, giving surgeons flexibility in surgical applications. They are more cost-effective than expensive growth factors or demineralized bone matrices, can be mass-produced efficiently, and retain their functional properties after ethylene oxide sterilization, ensuring seamless integration into existing clinical workflows [9].

## **7. Challenges and solutions**

Despite their superior performance, NFP composites face several challenges that must be addressed for successful clinical translation. Current data, largely derived from small animal models, necessitate validation through large animal studies, alongside extended in vivo investigations to evaluate long-term biocompatibility, integration, and durability. Regulatory pathways for these novel composites also need to be clearly defined to streamline approval processes. Furthermore, scaling up production from laboratory to industrial levels will require meticulous process optimization to ensure consistent quality, the implementation of standardized testing protocols for comprehensive material characterization, and leveraging economies of scale to achieve competitive cost reduction.

## **8. Conclusion**

NFP glass-based composites, particularly silver and zinc ion-doped formulations, demonstrate exceptional potential in bone tissue engineering by combining enhanced bioactivity, superior mechanical strength for load-bearing applications, and excellent biocompatibility. Their proven ability to accelerate bone formation, as evidenced by significant volumetric bioconversion in preclinical models, alongside histological confirmation of healthy bone integration, underscores their clinical relevance. The versatility in fabrication allows for diverse morphological designs, meeting varied surgical needs, while cost-effective mass production ensures scalability over expensive biological alternatives. With optimized ion release kinetics and compatibility with advanced manufacturing techniques, these materials align well with the future of personalized medicine, offering a robust, adaptable, and economically viable platform for next-generation bone regeneration therapies. NFP glass scaffolds doped with  $\text{Ag}^+$ ,  $\text{Zn}^{2+}$  and  $\text{Mg}^{2+}$  ions, fabricated via low-temperature 3D extrusion, fulfill ISO 23,317 criteria for bioactivity while delivering mechanical and biological performance that surpasses legacy silicate glasses. Integration of our rheology-stabilized paste printing protocol ensures homogeneous glass dispersion, high pore interconnectivity, and reproducible layer fusion – key factors for commercial scalability and regulatory approval.

## **Author contributions**

1. Mareeswari Balasubramanian: Original draft preparation, formal analysis, investigation, review, and editing.
2. Sundara Moorthi Ganesan: Data acquisition, software, writing, review, and editing.
3. Vijayakumar Chinnaswamy Thangavel: Methodology, supervision, review, and editing.

4. Pugalanthipandian Sankaralingam: Conceptualization, synthesis, project administration, and funding acquisition.
5. Ravichandran Kandaswamy: Supervision and validation.

## **Conflict of interest**

The authors declare no conflicts of interest.

## **Data availability statement**

Data will be made available upon request.

## **Funding**

The research was fully funded by Bone Substitutes, Madurai-625014, India.

## **Acknowledgment**

The authors are deeply grateful to Bone Substitutes, Madurai, for preparing all the composites and designing the scaffolds.

## **Author details**

Mareeswari Balasubramanian<sup>1</sup>, Sundara Moorthi Ganesan<sup>1</sup>, Vijayakumar Chinnaswamy Thangavel<sup>2\*</sup>, Pugalanthipandian Sankaralingam<sup>2</sup> and Ravichandran Kandaswamy<sup>1</sup>

1 Department of Rubber and Plastics Technology, Madras Institute of Technology Campus, Anna University, Chromepet, Chennai, India

2 Bone Substitutes, Madurai, Tamil Nadu, India

\*Address all correspondence to: [ctvijay22@yahoo.com](mailto:ctvijay22@yahoo.com)

## **IntechOpen**

---

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Bose S, Roy M, Bandyopadhyay A. Recent advances in bone tissue engineering scaffolds. *Trends in Biotechnology*. 2012;**30**(10):546–554
- [2] Percival KM, Paul V, Hussein GA. Recent advancements in bone tissue engineering: Integrating smart scaffold technologies and bio-responsive systems for enhanced regeneration. *International Journal of Molecular Sciences*. 2024;**25**(11):6012
- [3] Sohn HS, Oh JK. Review of bone graft and bone substitutes with an emphasis on fracture surgeries. *Biomaterials Research*. 2019;**23**:9
- [4] Sohn H-S, Oh J-K. Review of bone graft and bone substitutes with an emphasis on fracture surgeries. *Biomaterials Research*. 2019;**23**(1):9
- [5] Farjaminejad S, et al. Advances and challenges in polymer-based scaffolds for bone tissue engineering: A path towards personalized regenerative medicine. *Polymers* 2024;**16**:3303
- [6] Ghassemi T, et al. Current concepts in scaffolding for bone tissue engineering. *The Archives of Bone and Joint Surgery* 2018;**6**:90
- [7] Jones JR. Reprint of: Review of bioactive glass: From Hench to hybrids. *Acta Biomaterialia*. 2015;**23**:S53–S82
- [8] Hench LL, Jones JR. Bioactive glasses: Frontiers and challenges. *Frontiers in Bioengineering and Biotechnology*. 2015;**3**:194
- [9] Sankaralingam PugalanthiPandian, Sakthivel Poornimadevi, Chinnaswamy Thangavel, Vijayakumar. Novel composites for bone tissue engineering. In: Haidar ZS, editor. *Biomimetics - Bridging the Gap*. Rijeka: IntechOpen; 2022. p. 73–94. DOI: 10.5772/intechopen.106255
- [10] Hulsen DJ, et al. 4 - S53P4 bioactive glass. In: Arts JJC, Geurts J, editors. *Management of Periprosthetic Joint Infections (Pjis)*. Woodhead Publishing; 2017. p. 69–80. Available from: <https://www.sciencedirect.com/book/9780081002056/management-of-periprosthetic-joint-infections-pjis>
- [11] Essien E, Nwude D, Adams L. Bioactive SiO<sub>2</sub>-K<sub>2</sub>O-CaO-P<sub>2</sub>O<sub>5</sub> Glass-ceramic Scaffold Prepared Using Polyurethane Foam Template. Vol. **69**. *Cerâmica*; 2023. p. 30–38. Available from: <https://www.scielo.br/j/ce/a/qbnHbjhv4rvFpmSx3xnVLYw/?format=html&lang=en>. The Publisher is “SciELO Brazil”
- [12] Bairo F, Hamzehlou S, Kargozar S. Bioactive glasses: Where are we and where are we going?. *Journal of Functional Biomaterials*. 2018;**9**(1):25
- [13] Zhu Y, et al. Bioactive glass in tissue regeneration: Unveiling recent advances in regenerative strategies and applications. *Advanced Materials*. 2025;**37**(2):2312964
- [14] Yuan X, et al. Recent advances in 3D printing of smart scaffolds for bone tissue engineering and regeneration. *Advanced Materials* 2024;**36**:e2403641
- [15] Sun J, et al. Advances in 3D-printed scaffold technologies for bone defect repair: Materials, biomechanics, and clinical prospects. *BioMedical Engineering OnLine* 2025;**24**:51

- [16] Alonzo M, et al. Bone tissue engineering techniques, advances and scaffolds for treatment of bone defects. *Current Opinion in Biomedical Engineering*. 2021;17:100248
- [17] Farazin A, Darghiasi SF. Advanced polymeric scaffolds for bone tissue regeneration. *Exploration of BioMat-X*. 2025;2:101340
- [18] Liu X, et al. Mechanical properties of bioactive glass (13-93) scaffolds fabricated by robotic deposition for structural bone repair. *Acta Biomaterialia* 2013; 9:7025–7034
- [19] Distler T, et al. Polymer-bioactive glass composite filaments for 3D scaffold manufacturing by fused deposition modeling: Fabrication and characterization. *Frontiers in Bioengineering and Biotechnology*. 2020;8:552
- [20] Pfau MR, Grunlan MA. Smart scaffolds: Shape memory polymers (SMPs) in tissue engineering. *Journal of Materials Chemistry B*. 2021;9 (21):4287–4297
- [21] Fu Q, et al. Bioactive glass scaffolds for bone tissue engineering: State of the art and future perspectives. *Materials Science and Engineering: C*. 2011;31:1245–1256
- [22] Kolan KCR, et al. 3D-printed biomimetic bioactive glass scaffolds for bone regeneration in rat calvarial defects. *International Journal of Bioprinting*. 2020;6(2):274
- [23] Lyons JG, et al. Nanostructured biomaterials for bone regeneration. *Frontiers in Bioengineering and Biotechnology*. 2020;8:922
- [24] Lei B, et al. Versatile fabrication of nanoscale sol–gel bioactive glass particles for efficient bone tissue regeneration. *Journal of Materials Chemistry*. 2012;22:16906–16913
- [25] Lei B, et al. Surface nanoscale patterning of bioactive glass to support cellular growth and differentiation. *Journal of Biomedical Materials Research, Part A*. 2010;94:1091–1099
- [26] Pajares-Chamorro N, Chatzistavrou X. Bioactive glass nanoparticles for tissue regeneration. *ACS Omega*. 2020;5(22):12716–12726
- [27] Zaczek-Moczydlowska MA, et al. Biomimetic natural biomaterial nanocomposite scaffolds: A rising prospect for bone replacement. *International Journal of Molecular Sciences*. 2024;25(24):13467
- [28] Hoppe A, Mouriño V, Boccaccini AR. Therapeutic inorganic ions in bioactive glasses to enhance bone formation and beyond. *Biomaterials Science*. 2013;1(3):254–256
- [29] Mostafa AA, et al. Bioactive glass doped with noble metal nanoparticles for bone regeneration: In vitro kinetics and proliferative impact on human bone cell line. *RSC Advances*. 2021;11:25628–25638
- [30] Zamani D, Moztaaradeh F, Bizari D. Alginate-bioactive glass containing Zn and Mg composite scaffolds for bone tissue engineering. *International Journal of Biological Macromolecules*. 2019;137:1256–1267
- [31] Naruphontjirakul P, Li M, Boccaccini AR. Strontium and zinc co-doped mesoporous bioactive glass nanoparticles for potential use in bone

tissue engineering applications. *Nanomaterials*. 2024;**14**(7):575

[32] Jalilvand M, et al. Fabrication and characterization of nanocomposite scaffold containing zinc-doped mesoporous bioglass: Evaluation of the antioxidant properties, hemocompatibility and proliferation of apical papilla stem cells. *BioImpacts: BI*. 2025;**15**:30300

[33] Dittler ML, et al. Bioactive glass (45S5)-based 3D scaffolds coated with magnesium and zinc-loaded hydroxyapatite nanoparticles for tissue engineering applications. *Colloids and Surfaces B: Biointerfaces*. 2019;**182**:110346

[34] Raja FNS, et al. Synergistic antimicrobial metal oxide-doped phosphate glasses; a potential strategy to reduce antimicrobial resistance and host cell toxicity. *ACS Biomaterials Science & Engineering*. 2022;**8**:1193–1199

[35] Rodriguez O, et al. Rapidly-dissolving silver-containing bioactive glasses for cariostatic applications. *Journal of Functional Biomaterials*. 2018;**9**:28

[36] Nagasaki R, et al. Synthesis and characterization of bioactive glass and zinc oxide nanoparticles with enamel remineralization and antimicrobial capabilities. *Materials* 2023;**16**:6878

[37] Dai Q, et al. 3D printing of Cu-doped bioactive glass composite scaffolds promotes bone regeneration through activating the HIF-1 $\alpha$  and TNF- $\alpha$  pathway of hUVECs. *Biomaterials Science*. 2021;**9**:5519–5532

[38] Dhivya V, et al. Effects of strontium-containing fluorophosphate glasses for enhancing bioactivity and enamel remineralization. *Materials Characterization*. 2021;**181**:111496

[39] Saha R, Chakraborty J. Multifaceted Biomedical Applications of Bismuth Oxide-Doped Bioactive Glass: Synthesis Challenges, Characterization and Potential Clinical Implications. Vol. 50. Elsevier; 2024. DOI: 10.1016/j.ceramint.2024.09.036

[40] Dhivya V, et al. Impact of silver on fluorophosphate glasses to improve in vitro bioactivity and antibacterial efficacy. *Ceramics International*. 2022;**48**:25346–25354

[41] Akhtach S, et al. Structural characterization, in vitro bioactivity, and antibacterial evaluation of low silver-doped bioactive glasses. *Ceramics International*. 2021;**47**:29036–29046

[42] Ganesan SM, et al. Impact of aging on metal oxide-doped fluorophosphate nanopowder. *New Journal of Chemistry*. 2024;**48**:17120–17134

[43] Shaharyar Y, et al. Structure-solubility relationships in fluoride-containing phosphate based bioactive glasses. *Journal of Materials Chemistry B*. 2015;**3**:9360–9373

[44] Rajkumar G, et al. Influence of fluoride for enhancing bioactivity onto phosphate based glasses. *Journal of Non-Crystalline Solids*. 2018;**493**:108–118

[45] Sharmin N, Rudd CD. Structure, thermal properties, dissolution behaviour and biomedical applications of phosphate glasses and fibres: A review. *Journal of Materials Science*. 2017;**52**(15):8733–8760

- [46] Ali S, Farooq I, Iqbal K. A review of the effect of various ions on the properties and the clinical applications of novel bioactive glasses in medicine and dentistry. *The Saudi Dental Journal*. 2014;**26**(1):1–5
- [47] Chen X, et al. Halide-containing bioactive glasses enhance osteogenesis in vitro and in vivo. *Biomaterials Advances*. 2022;**143**:213173
- [48] Contreras Jaimes AT, et al. Phosphate/Silicate Ratio Allows for Fine-Tuning of Bioactive Glass Crystallisation and Glass-Ceramic Microstructure. Vol. 2, *Glass: Europe*; 2024:1–26
- [49] Koleganova VA, et al. Bioactive glass/polymer composite materials with mechanical properties matching those of cortical bone. *Journal of Biomedical Materials Research, Part A*. 2006;**77**: 572–579
- [50] Xiao W, et al. Tough and strong porous bioactive glass-PLA composites for structural bone repair. *Journal of Materials Science*. 2017;**52**:9039–9054
- [51] Ma C, et al. Biomechanics and mechanobiology of the bone matrix. *Bone Research*. 2022;**10**:59
- [52] Goldstein SA. The mechanical properties of trabecular bone: Dependence on anatomic location and function. *Journal of Biomechanics*. 1987;**20**(11):1055–1061
- [53] Røhl L, et al. Tensile and compressive properties of cancellous bone. *Journal of Biomechanics*. 1991;**24**:1143–1149
- [54] Teoh SH, Chui CK. Bone material properties and fracture analysis: Needle insertion for spinal surgery. *Journal of the Mechanical Behavior of Biomedical Materials*. 2008;**1**(2):115–139
- [55] Feng Z. [Fracture toughness of cortical bone in tension, shear, and tear—a comparison of longitudinal and transverse fracture]. Sheng Wu Yi Xue Gong Cheng Xue Za Zhi = *Journal of Biomedical Engineering* = Shengwu Yixue Gongchengxue Zazhi. 1997;**14** (3):199–204
- [56] Currey JD, Pitchford JW, Baxter PD. Variability of the mechanical properties of bone, and its evolutionary consequences. *Journal of the Royal Society Interface*. 2007;**4**(12):127–135
- [57] Bittner-Frank M, et al. Cortical and trabecular mechanical properties in the femoral neck vary differently with changes in bone mineral density. *JBMR Plus*. 2024;**8**(6):ziae049
- [58] Morgan EF, Unnikrisnan GU, Hussein AI. Bone mechanical properties in healthy and diseased states. *Annual Review of Biomedical Engineering*. 2018;**20**:119–143
- [59] Shirgill S, et al. Silver-doped bioactive glass fibres as a potential treatment for wound-associated bacterial biofilms. *Biofilm*. 2023;**5**:100115
- [60] Chen L, et al. Zinc doped synthetic polymer composites for bone regeneration: A promising strategy to repair bone defects. *International Journal of Nanomedicine*. 2025;**20**:8567–8586
- [61] Metsger DS, Rieger MR, Foreman DW. Mechanical properties of sintered hydroxyapatite and tricalcium phosphate ceramic. *Journal of Materials*

- Science Materials in Medicine. 1999;**10**(1):9–17
- [62] Indurkar A, et al. Advances in sintering techniques for calcium phosphates ceramics. *Materials (Basel)*. 2021;**14**(20):6133.
- [63] Bang L, et al. Effect of temperature on the characteristics of beta-tricalcium phosphate for use as bone substitute material. *Journal of Engineering Science and Technology*. 2022;**17**:1577–1588
- [64] Tanimoto Y, Nishiyama N. Preparation and physical properties of tricalcium phosphate laminates for bone-tissue engineering. *Journal of Biomedical Materials Research, Part A*. 2008;**85**(2):427–433
- [65] Plewinski M, et al. The effect of crystallization of bioactive bioglass 45S5 on apatite formation and degradation. *Dental Materials*. 2013;**29**:1256–1264
- [66] Rahaman MN, et al. Bioactive glass in tissue engineering. *Acta Biomaterialia*. 2011;**7**:2355–2373
- [67] Tonino AJ, et al. Bone remodeling and hydroxyapatite resorption in coated primary hip prostheses. *Clinical Orthopaedics and Related Research*. 2009;**467**:478–484
- [68] Jang SJ, et al. Bone regeneration of hydroxyapatite with granular form or porous scaffold in canine alveolar sockets. *Vivo* 2017;**31**:335–341
- [69] Hyunh NB, et al. Surface modification of bioresorbable phosphate glasses for controlled protein adsorption. *ACS Biomaterials Science & Engineering* 2021;**7**:4483–4493
- [70] Manafi S, Mirjalili F, Reshadi R. Synthesis and evaluation of the bioactivity of fluorapatite-45S5 bioactive glass nanocomposite. *Progress in Biomaterials*. 2019;**8**(2):77–89
- [71] Klimek L, et al. An evaluation of the mechanical properties of a hybrid composite containing hydroxyapatite. *Materials (Basel)*. 2023;**16**:4548
- [72] Valappil SP, et al. Effect of silver content on the structure and antibacterial activity of silver-doped phosphate-based glasses. *Antimicrobial Agents and Chemotherapy*. 2007;**51**:4453–4461
- [73] Varanasi VG, et al. The ionic products of bioactive glass particle dissolution enhance periodontal ligament fibroblast osteocalcin expression and enhance early mineralized tissue development. *Journal of Biomedical Materials Research, Part A*. 2011;**98**:177–184
- [74] Schmitz SI, et al. Superior biocompatibility and comparable osteoinductive properties: Sodium-reduced fluoride-containing bioactive glass belonging to the CaO-MgO-SiO<sub>2</sub> system as a promising alternative to 45S5 bioactive glass. *Bioactive Materials*. 2020;**5**:55–65

# Three-Dimensional Printed Biomimetic Polymer Scaffolds for Wound Healing

*Ankush Kumar, Navjeet Singh, Dimple Sethi Chopra,  
Dhandeep Singh and Nirmal Singh*

## Abstract

Skin tissue engineering and regeneration have been successful in designing constructs that resemble biological tissues. Three-dimensional (3D) bioprinting has transformed conventional approaches by enabling the development of personalized architectures that mimic natural systems through computer-aided design. Compared to traditional skin regeneration methods, 3D bioprinted dermal replacements offer superior automation and standardization for clinical use. They provide the required precision for incorporating living cells, growth factors, and other biomolecules. The fabrication of 3D matrices for wound healing requires bio printable materials known as bioinks. Natural and synthetic biopolymers such as collagen, alginate, chitosan, and hyaluronic acid have been widely used as bioinks. These bioinks should possess good printability, mechanical strength, stability, biocompatibility, biodegradability, non-toxicity, high availability, and strong shape fidelity after the printing process.

**Keywords:** biomimetic, scaffolds, wound healing, regeneration, extracellular matrix (ECM), biodegradability hydrogel, 3D printing, cell adhesion, cell proliferation, skin regeneration, biomedical engineering

## 1. Introduction

Engineering in biomedicine (BME) is a relatively new area of biology and medicine research aimed at enhancing disease management and healthcare. For biomedical research, including diagnostic and therapeutic applications, it offers design concepts and values [1]. Biomedical engineering (BME) integrates biology, medicine, behavior, and health with physical, chemical, mathematical, and computational sciences, as well as engineering principles. It advances fundamental concepts, generates knowledge at both the molecular and organ system levels, and develops unique biologics, materials, processes, implants, devices, and informatics approaches for disease prevention, diagnosis, treatment, rehabilitation, and overall health improvement [2].

Through the integration of engineering and medical sciences, BME combines fields like tissue engineering, genetics, neural engineering, stem cell engineering, chemical engineering, and clinical engineering to enhance healthcare for people [1]. It serves as a bridge between engineering and medicine by combining problem-solving and design skills with medical and biological knowledge, leading to advances in diagnosis, monitoring, and therapy. Over the years, BME has evolved from different engineering disciplines into a distinct field of study. Like other interdisciplinary specializations that eventually grow into independent fields, BME is a clear example of this progression [3].

Polymeric scaffolds are three-dimensional (3D) structures that support tissue regeneration. These scaffolds may be cell-free, allowing the body's own cells to populate the structure after implantation, or preloaded with cells or therapeutic agents to promote healing. Cell- or drug-loaded scaffolds can deliver stem cells or biologically active substances directly to the injury site. Common stem cell sources include bone marrow-derived stem cells, adipose tissue-derived stem cells, embryonic stem cells, induced pluripotent stem cells (iPSCs), and genetically modified cells – all of which play important roles in tissue repair and regeneration [4].

The human body is an incredibly advanced autonomous system, built from billions of molecular nanomachines encoded by the DNA of a single zygote. These nanomachines are responsible for renewing specific cell types in a tightly regulated manner and repairing damaged tissues. Despite this remarkable capacity, the body's ability to self-heal is limited – varying with cell type and influenced by factors such as aging, degenerative diseases, and traumatic injury. In fact, some tissues have little to no regenerative ability. To address these limitations, polymeric scaffolds play a crucial role in creating functional constructs that stimulate tissue and organ regeneration, restore or improve lost function, and provide alternatives to autografts, allografts, or even full-organ transplantation. Engineered tissues like skin, cartilage, blood vessels, brain tissue, gastrointestinal tissues, and corneas highlight the growing applications of this approach [5].

Regenerative medicine and BME aim to restore the structure and functionality of damaged or deteriorating tissues by using cells, biomaterials, and bioactive compounds. By stimulating spontaneous healing or developing functional tissue replacements, these methods present effective alternatives to conventional organ transplantation [6]. Recent advances in biodegradable and bioactive polymeric scaffolds have significantly improved the efficacy of regenerative therapies by mimicking the extracellular matrix (ECM) and facilitating controlled tissue growth. Biomimetic scaffolds are specifically designed as biomaterial architectures that promote native tissue regeneration [7].

With regard to regenerative medicine and tissue engineering, 3D scaffolds have gained significant attention as a promising strategy. For example, a bone graft or scaffold should not only mimic the structure and mechanical properties of the natural bone ECM but also carry out key functions like those performed by the ECM in other tissues, such as skin. Regenerative medicine and tissue engineering are rapidly developing fields that aim to preserve, repair, or enhance the function of damaged tissues and organs. The creation of scaffolds, 3D biomaterial constructs that promote cellular activity and aid in the development of functional tissues, is a crucial component of these strategies. However, the

body's self-healing potential remains restricted by the type of cells that make up the tissue, as well as by multiple factors influencing self-repair, including degenerative diseases, trauma, and aging.

## **2. Polymer used in scaffolds**

Polymers have been classified in various ways in the current literature. One of the most common approaches is to categorize them into two groups: natural and synthetic. Natural polymers include polysaccharides such as alginate and chitosan, as well as protein-based materials like collagen, gelatin, elastin, keratin, and silk. Synthetic polymers, on the other hand, comprise materials such as polycaprolactone (PCL), polylactic acid (PLA), and polyvinyl alcohol (PVA) [8].

### **2.1 Synthetic polymer**

The superior biodegradability of synthetic polymers like PCL, PLA, and PGA makes them popular for use in tissue engineering and medication delivery, offering little toxicity and the capacity to create permeable scaffolds. PLA is FDA-approved, highly processable, and well-suited for bone tissue applications, particularly when combined with bioactive materials such as gelatin or hydroxyapatite. Because of its higher tensile strength as well as faster rate of degradation, PGA is frequently combined with PLA to customize its characteristics. Their copolymer, PLGA, provides tunable degradation profiles and high biocompatibility, making it highly suitable for biomedical applications. However, materials like pure PCL exhibit limited cell adhesion, necessitating surface modifications or blending strategies to improve cellular interactions [9].

#### *2.1.1 Polycaprolactone*

PCL is an FDA-approved aliphatic and hydrophobic polyester with significant potential in biomedical applications due to its biocompatibility, processability, and versatility. It can be used as a thermo-responsive bioink for 3D printing and can also be blended with other polymers to tailor its properties. PCL is particularly useful for drug delivery systems (DDS), as it can encapsulate a wide range of active compounds. PCL scaffolds have been explored as DDS for cancer therapy, showing considerable promise in osteosarcoma treatment. In addition, PCL-based materials can simulate the consistency of biological tissues, providing support in surgical procedures. One of its key advantages is its slow degradation rate, which allows for sustained drug release and prolonged structural support, making it especially suitable for long-term implantable devices. Furthermore, its mechanical strength and flexibility enhance its suitability for tissue engineering applications that require load-bearing capacity [8].

#### *2.1.2 Poly (lactic acid)*

A biocompatible and biodegradable polymer, PLA, has several uses in the biomedical field. It is FDA-approved and has been employed in scaffolds, cell carriers, DDS, sutures, and various other medical devices. PLA-based scaffolds have been investigated as DDS

for the controlled release of diverse therapeutic agents, including vascular endothelial growth factor (VEGF) for tissue regeneration; prednisolone and dexamethasone for anti-inflammatory effects; paclitaxel (PTX) for accelerating endothelialization and preventing lumen stenosis; polyhexamethylene biguanide (PHMB) and chlorhexidine (CHX) for antibacterial activity; and doxorubicin for tumor treatment [10–13].

### *2.1.3 Poly (glycolic acid)*

Polyglycolic acid (PGA) was the first biodegradable material to be used in clinical applications and is more hydrophilic than both PCL and PLA. PGA fibrous scaffolds are particularly important in wound healing for diabetic patients, where they have been employed to deliver monocyte chemoattractant protein-1 (MCP-1) for drug delivery [14]. In addition, PGA has been widely applied in bone and tissue engineering. It is often blended with polymers such as PLA and PLLA to enhance its mechanical properties, biodegradability, and biocompatibility [15].

### *2.1.4 Polyvinyl alcohol*

PVA is hydrophilic in nature, a semi-crystalline polymer recognized for its mechanical strength and biocompatibility. These characteristics make it a promising material for various biomedical applications, including surgical repairs, wound dressings, membranes, artificial skin, and scaffold materials [8]. Hybrid PVA/PEG scaffolds have further demonstrated effective ciprofloxacin release, enabling strong antimicrobial activity [16].

## **2.2 Natural polymer**

Natural polymers such as collagen, gelatin, chitosan, alginate, and plant-derived polysaccharides exhibit excellent biocompatibility and effectively simulate the ECM environment [17].

### *2.2.1 Collagen*

A group consisting of at least 29 distinct polymeric proteins, known as collagen, makes up a significant portion of the ECM's protein content, accounting for between 20% and 30% of mammals' total protein weight. Collagen can be obtained directly from animal tissues and purified, or produced as recombinant proteins. Various forms of collagen scaffolds are fabricated through processes such as polymerization, fibrillogenesis, and fiber formation. As a natural substrate for cellular attachment, proliferation, and differentiation, collagen also contributes to the mechanical strength and elasticity of tissues [4].

Collagen exposure at the site of damage triggers the clotting cascade, resulting in the creation of a fibrin clot that stops bleeding during the inflammatory phase of wound healing, which includes hemostasis and inflammation. Additionally, by acting as strong neutrophil chemoattractants, boosting phagocytosis and immune responses, and altering gene expression, collagen type I and IV fragments function as mediators of inflammation [18, 19].

### *2.2.2 Chitosan*

Chitosan, a polymer with significant potential for biomedical applications, is derived from the deacetylation of chitin, which is obtained from the exoskeletons of crustaceans such as crabs and lobsters [20]. Bio-orthogonalized chitosan scaffolds with esterase-activated release have been investigated for peripheral nerve regeneration and repair. Preclinical studies indicate that such scaffolds hold high potential as peripheral nerve conduits, as they can stimulate Schwann cell proliferation [21]. To support diverse descending inputs into the brain, chitosan scaffolds combined with neurotrophin-3 have been used to promote the formation of relay neural circuits. This approach has shown promise in facilitating functional recovery following spinal cord injury and paraplegia by recruiting endogenous neural stem cells to the lesion site, where they differentiate into mature neurons [21].

The cationic nature of chitosan is particularly important in wound healing, as it contributes to its antimicrobial and hemostatic properties. Chitosan promotes blood clotting through interactions with anionic red blood cells. Its antimicrobial action is attributed to the inhibition of bacterial cell wall biosynthesis, resulting from electrostatic interactions with anionic components of bacterial cell walls. Consequently, chitosan exhibits broad-spectrum antibacterial activity, while its functionalized forms have been shown to enhance cell proliferation, mineralization, and osteoblast differentiation, further supporting its value in regenerative medicine [22–24].

### *2.2.3 Alginate*

Alginate, an anionic polymer derived from brown seaweed, is a cornerstone biomaterial due to its safety, affordability, and simple gelation with calcium ions [25]. The structural similarity of alginate hydrogels to the ECM makes them highly versatile. Key applications include advanced wound care, where they create a moist healing environment and reduce infection [26], as well as drug delivery. Furthermore, alginate gels are a promising platform for cell transplantation in tissue engineering, with the goal of replacing lost or damaged organs and tissues [27].

## **3. Polymeric scaffolds requirement**

In tissue engineering, scaffolds derived from various biomaterials and fabrication methods are essential for regenerating different tissues. However, when determining a scaffold's suitability for biomedical use, a common set of critical factors must always be considered, regardless of the intended tissue application.

### **3.1 Biocompatibility**

In the context of tissue engineering, a polymeric scaffold's primary and most critical property is its biocompatibility. Cells must be able to adhere, migrate, and proliferate on the scaffold before depositing a new ECM. Following implantation, the scaffold or tissue-engineered construct should elicit only a minimal immune response to avoid severe inflammation that could impair healing or lead to rejection [28].

### **3.2 Biodegradability**

The ultimate goal of tissue engineering is for the body's own cells to gradually replace the implanted scaffold or tissue-engineered construct. Scaffolds are not intended to serve as permanent implants; instead, they must degrade naturally to allow cells to synthesize their own ECM [28]. The degradation byproducts should be biocompatible and safely eliminated from the body without causing harm to other organs. To ensure that scaffold degradation occurs in parallel with new tissue formation, a controlled immune response and the regulated recruitment of cells, such as macrophages, are required. With the increasing application of tissue engineering techniques in clinical practice, immunological considerations have become an essential focus of research [29, 30].

### **3.3 Mechanical property**

It is essential that a scaffold is mechanically compatible with the tissue it is meant to repair, providing structural stability during implantation [28]. When repairing load-bearing structures like bone, the scaffold must have sufficient initial integrity to endure the full duration of tissue remodeling. Critically, this strength must be balanced with porosity, as an overly dense structure can impede vital vascularization and cell migration into the scaffold [31].

### **3.4 Scaffold architecture**

Scaffold architecture plays a critical role in tissue engineering applications. High porosity and an interconnected pore network are essential scaffold properties that enable cell infiltration and proper nutrient diffusion throughout the construct and to the newly formed ECM. In addition, waste products must be able to diffuse outward through this porous structure, and scaffold degradation byproducts should be safely eliminated from the body without adversely affecting surrounding tissues or organs. One of the major challenges in tissue engineering is core degradation, which occurs due to insufficient vascularization and inadequate waste removal from the center of tissue-engineered constructs [32, 33].

### **3.5 Manufacturing technology**

A key step toward making a polymer-scaffold-based construct viable for both medical and market success is the shift from lab-scale, single-sample production to cost-effective, small-batch manufacturing. The successful clinical translation of tissue engineering technologies is contingent upon establishing scalable manufacturing processes that comply with good manufacturing practice (GMP) guidelines [33].

## **4. 3D printing**

Three-dimensional printing is a method of additive manufacturing characterized by its process of building objects one layer at a time under ambient temperature conditions. The process starts when a machine distributes a fine layer

of powder onto a build platform. Following this, a binder solution is selectively applied to fuse the powder particles together. The platform then lowers, and a subsequent layer is added and bound. This cycle repeats until the final structure is complete, at which point any unbound powder is removed in a post-processing step. Scaffolds can be created directly with this method or produced indirectly using a 3D-printed mold [34, 35].

A significant advantage of 3D printing for biomedical purposes is its operation at room temperature, which allows for the safe integration of heat-sensitive biomolecules. This makes it possible to embed a wide array of therapeutic agents – from proteins and peptides to living cells – directly into the scaffold. Such “biofunctionalized” scaffolds have immense potential in supporting bone regeneration by boosting cellular activity and encouraging new bone growth [36, 37].

The bioprinting process for skin tissue engineering comprises four key phases: pre-processing, bioprinting, post-processing, and *in vivo* application (see **Figure 1**). The initial “pre-processing” stage involves creating a hydrogel bioink by combining components such as cross-linked polymers, cells (including stem and immune cells), and growth factors. This bioink provides the hydrated, biocompatible microenvironment necessary to keep the cells alive.

During the “bioprinting” stage, a 3D bioprinter nozzle precisely dispenses the bioink in droplets to fabricate a customized 3D scaffold that mimics native skin architecture. Next, the “post-processing” stage involves maturing the printed construct into a stable scaffold. Once applied to a wound, this scaffold integrates with the host tissue, supports cellular growth, promotes the formation of new blood vessels (angiogenesis), and facilitates the deposition of the ECM.

Finally, in the “*in vivo* application” stage, the scaffold accelerates healing by promoting tissue regeneration. It is designed to gradually degrade and be replaced by new tissue, ultimately restoring the skin’s function [38].

#### 4.1 Inkjet bioprinting

The earliest attempts to print living cells were carried out using modified commercial inkjet printers [39]. One of the first challenges of inkjet bioprinting was that printed cells dried out rapidly on the substrate, leading to cell death. Researchers overcame this limitation by embedding cells in water-rich polymer environments, giving rise to cell-loaded hydrogels that protected cell viability and supported tissue development [40]. Over the past few decades, advancements in inkjet printing have led to the development of several droplet generation and delivery methods. Among these, drop-on-demand (DOD), electrohydrodynamic (EHD), and continuous inkjet (CIJ) printing are the most widely recognized. While DOD and EHD techniques have already been successfully adapted for 3D bioprinting, CIJ printing has not yet been employed in this context. The following section focuses on the principles, advantages, and applications of DOD and EHD printing in 3D bioprinting [41–43].

DOD bioprinting can be actuated using thermal, piezoelectric, or acoustic mechanisms, each producing picoliter droplets with precise spatial control. In thermal DOD, vapor bubbles are generated to expel droplets, although transient heat exposure may affect cell viability. Piezoelectric DOD employs crystal deformation to generate pressure pulses with minimal thermal stress, while acoustic DOD uses pressure waves for gentle droplet ejection, albeit with trade-offs in printing speed

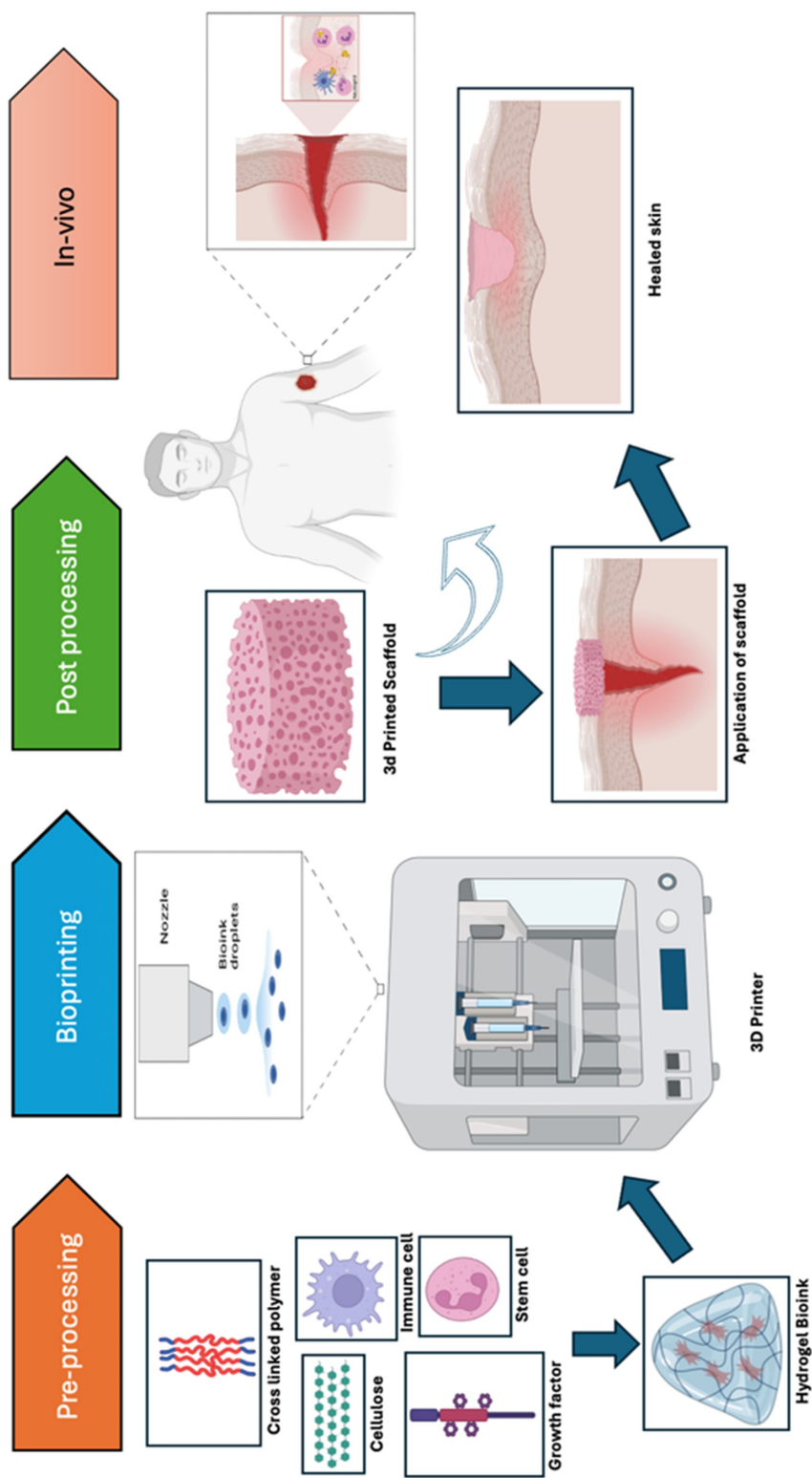


Figure 1. “Workflow diagram showing pre-processing, bioprinting, post-processing, and in vivo application steps in 3D bioprinting for wound healing.” .

and hardware complexity [44–47]. For stable jetting, bioinks typically require low viscosities ( $\approx 1\text{--}10\text{ mPa s}$  for DOD) and appropriate surface tension, with printability often assessed using the Z number ( $1/\text{Oh}$ ), which falls within a well-defined practical window [48].

EHD bioprinting, by contrast, uses high electric fields to draw ultrafine jets, achieving sub-nozzle or even sub-micron resolution. This enables the precise patterning of skin cell micro-architectures but necessitates careful optimization to mitigate jet instability and field-induced stress on cells [49, 50]. Across both modalities, high cell viability depends on factors such as waveform tuning, nozzle design, humidity regulation, anti-clogging strategies, and bioink rheology optimization [51, 52].

In wound healing applications, DOD and EHD printing have been applied to deposit keratinocytes and fibroblasts within GelMA, alginate, hyaluronic acid (HA), and collagen-based hydrogels. These constructs are often co-loaded with growth factors or antimicrobials to enhance re-epithelialization, angiogenesis, and matrix organization in excision wound models [53–55].

## **4.2 Laser base bioprinting**

Several droplet generation strategies have emerged from decades of inkjet printing advancements. The most recognized are DOD, EHD, and CIJ. To date, only DOD and EHD have been successfully integrated into 3D bioprinting. The working principles and applications of these two methods are highlighted below [41–43].

In DOD bioprinting, droplet ejection is achieved through thermal, piezoelectric, or acoustic actuation, each producing picoliter-scale droplets with precise spatial control. Thermal DOD relies on the rapid formation of vapor bubbles to expel droplets, piezoelectric DOD employs crystal deformation to generate pressure pulses, and acoustic DOD utilizes pressure waves for gentle droplet release. Each method offers distinct advantages and trade-offs in terms of cell viability, printing speed, and hardware complexity.

## **4.3 Laser-assisted bioprinting**

Originally used for metal deposition, laser-assisted printing was later adapted into what is now known as laser-assisted bioprinting (LAB) [48]. This technique involves a laser pulse, a donor slide (or ribbon), and a receiver slide. The donor ribbon is specifically constructed with a transparent glass base, a thin metallic coating, and a layer of bioink on top. When struck by the laser pulse, the metal layer instantly vaporizes, creating the energy needed to propel the bioink onto the receiving slide.

This scaffold-free approach provides exceptionally high cell viability [49] and achieves spatial resolutions between  $10\text{--}50\text{ }\mu\text{m}$  [39]. LAB also allows precise positioning of different cell types, with some studies reporting the ability to deposit even single cells per droplet. However, despite its remarkable accuracy, the technique is still costly and faces limitations in terms of long-term stability and large-scale application. Even so, LAB continues to show great promise, especially when integrated with other biofabrication methods [50–53].

#### **4.4 Extrusion-based bioprinting**

Driven by pneumatic or mechanical pressure [46, 55], extrusion bioprinting is a method where bioink is dispensed through a nozzle to form predefined structures. Its main strength lies in fabricating constructs with very high cell densities [54]. To ensure a successful outcome, it's critical to assess process parameters like viscosity, nozzle diameter, and the consequent shear stress before printing begins [56].

Highly viscous hydrogels, which often do not require chemical additives for curing, are frequently employed in extrusion-based bioprinting [57]. Because hydrogels behave as non-Newtonian fluids, their viscosity changes with shear rate. High viscosity increases shear stress, which can accelerate cell death. In contrast, shear-thinning behavior is particularly advantageous as it enhances flow control, improves printing accuracy, and reduces viscosity under applied force. However, excessively low viscosities compromise structural integrity and print fidelity, even though they may facilitate improved cellular infiltration [58].

### **5. Other techniques: Freeze-drying, electrospinning, solvent casting and particulate leaching, sol-gel method**

The goal of creating functional tissues and organs, which form the body's 3D architecture, requires the use of scaffolds. These are fabricated using techniques that ensure proper cell distribution and guide 3D growth [59]. Primarily, tissue engineering scaffolds encourage cells to attach and provide a framework for 3D tissue development [60]. To be effective, the scaffold's microscale environment must be conducive to cell survival and function, while its macroscale structure must allow for nutrient transport and the coordination of multicellular processes [59].

#### **5.1 Freeze-drying**

The technique of freeze-drying operates on the principle of sublimation. It begins when polymers and ceramics are dissolved in an appropriate solvent (like water or an organic one) and then emulsified with an aqueous phase. This solution is then cooled below its freezing point. Afterward, heat is applied to trigger sublimation, where the frozen solvent transitions directly from a solid into a gas, leaving behind a solid scaffold that is then dried [36, 61]. This process produces porous structures by removing the solvent and concentrating solutes within the ice phase. Freeze-drying is particularly advantageous because it enables the rapid fabrication of highly porous scaffolds without exposing biological components to high temperatures that could damage their activity [62–65]. For instance, Wu et al. [66] developed a porous gelatin scaffold using a unidirectional freeze-drying technique, which was shown to be non-toxic to cartilage cells and to promote extensive cell growth and spreading.

#### **5.2 Electrospinning**

As a powerful and flexible technique, electrospinning is used to produce 3D networks of nanofibers [67]. The process operates on the principle of a high-voltage electric field ejecting continuous, ultra-thin fibers when electrostatic forces

overpower the polymer solution's surface tension [68]. The process requires a syringe pump with a spinneret, a metal collector, and a high-voltage power supply. As the charged jet of polymer solution is ejected, the solvent evaporates during its trajectory, leaving behind a solid nonwoven fibrous membrane. Electrospinning setups can be classified as horizontal or vertical, depending on the orientation of the syringe and electric field relative to the ground.

In a study, Tan et al. [69] developed biodegradable nanofiber scaffolds made from cellulose acetate butyrate and PEG using electrospinning. The resulting fibers demonstrated improved tensile strength, strong cell adhesion, and excellent biocompatibility with human dermal fibroblasts, while remaining non-toxic. These findings highlight the potential of such nanofibers as promising scaffolds for tissue engineering applications [69].

### **5.3 Solvent casting and particulate leaching**

Particulate leaching combined with solvent casting is a widely used technique for producing highly porous scaffolds with controllable pore sizes. Its main advantages are simplicity and the absence of a need for specialized equipment [70–72]. The process begins by creating a polymer solution, which is then blended with salt particles of a predefined size. Next, the solvent is evaporated, trapping the salt particles within the polymer. The resulting composite is then placed in distilled water to dissolve the salt, leaving behind a highly porous structure. The final scaffold has a pore size that directly corresponds to the size of the salt particles used.

### **5.4 Sol-gel methods**

The sol-gel method is widely used for the inorganic polymerization of metal alkoxides. In this approach, a surfactant is added to form a colloidal solution (sol), which then undergoes condensation to produce a gel. Using a hybrid sol-gel process, Chen et al. [73] developed bioactive glass (BG) ceramics containing sodium oxide. These materials exhibited improved mechanical stiffness while retaining biodegradability. Importantly, the properties of the resulting scaffold are highly dependent on the procedure, as well as on the specific additives and processing parameters applied [72].

## **6. Biomedical application of polymeric scaffolds**

The remarkable biocompatibility of polymeric scaffolds, combined with their ability to facilitate controlled drug delivery, makes them invaluable for applications like tissue engineering, cartilage repair, and nerve regeneration [74].

### **6.1 Bone tissue engineering**

Bone's structure is a natural composite, divided into organic and inorganic phases [75]. The organic phase is dominated by type I collagen, while the inorganic phase consists largely of calcium phosphates (~70%), which exist predominantly in the crystalline structure of hydroxyapatite ( $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$ ) [76]. To effectively design scaffolds for bone tissue engineering (BTE), it's crucial to have a foundational knowledge of the bone regeneration process. This natural healing mechanism is

initiated in response to events like injury, trauma, or the surgical implantation of a BTE scaffold [75]. Bone formation, or osteogenesis, proceeds through two distinct pathways: endochondral ossification and intramembranous ossification [77].

## **6.2 Cartilage regeneration**

The ECM of cartilage tissue relies on key components like glycosaminoglycans (GAGs) and proteoglycans (PGs) [78]. This specialized matrix serves two main functions: it provides a low-friction surface for joint articulation, and it absorbs mechanical shocks, protecting the underlying bone [79, 80]. The goal of cartilage tissue engineering (CTE) is to improve the body's natural repair processes. This is often done by seeding scaffolds with cells like chondrocytes or mesenchymal stem cells (MSCs) and adding growth factors to promote cell adhesion, growth, and specialization [81–83]. A wide variety of biomaterials, from synthetic polymers like PEG, PLGA, and PCL to natural ones such as collagen, alginate, and hyaluronan, have been investigated. Furthermore, modern 3D bioprinting techniques now allow for the creation of patient-specific, anisotropic scaffolds, which can integrate more effectively with native cartilage tissue [78].

## **6.3 Skin and wound healing**

Tissue engineering employs natural, synthetic, or semi-synthetic materials to mimic the ECM, thereby regulating collagen deposition, cytokine expression, signaling pathways, and tissue morphology. In doing so, it promotes angiogenesis, reduces inflammation, influences cell proliferation, and guides ECM remodeling [84–86]. Polymeric scaffolds, although non-pharmacological in nature, play a pivotal role in restoring, enhancing, or replacing the functions of damaged tissues and organs. In wound healing, they serve two primary functions. These biomaterials have a dual role: in one capacity, they provide a physical framework for endogenous cells to adhere, proliferate, and move, thereby enhancing tissue repair and wound closure; in another capacity, they act as a temporary protective barrier over the wound, creating an optimal environment to accelerate the body's innate healing mechanisms [87].

## **6.4 Nerve regeneration**

Bioengineered solutions are increasingly being explored for addressing clinical challenges such as the repair of peripheral nerve gaps. An effective nerve conduit must provide a microenvironment that supports cellular interactions and promotes axonal regeneration across the injured site [88]. For very small nerve injuries – where the gap is only a few millimeters – the recommended medical approach is tension-free end-to-end suturing, in which the severed nerve ends are stitched together without stretching or undue tension [89]. However, for larger gaps, scaffolds based on natural and synthetic polymers are being investigated to facilitate nerve tissue regeneration. To be effective, a scaffold should closely mimic the nanofibrous architecture of the native ECM, thereby stimulating the activity of surrounding cells and supporting functional nerve repair [90, 91]. Among the available fabrication methods, electrospinning has emerged as a particularly promising technique due to its ability to produce nanofibrous

structures that closely replicate the ECM in both fiber size and spatial organization [92].

## **6.5 Cardiac and vascular application**

Cardiovascular disease (CVD) is an umbrella term for a range of conditions affecting the heart and blood vessels. Of these disorders, coronary heart disease (CHD) is responsible for the majority of deaths [93, 94]. CHD occurs due to atherosclerosis, a process where fatty plaques build up inside the arteries, narrowing them and restricting blood supply to the heart, which can ultimately lead to ischemia. As an interventional strategy, stents are commonly deployed at lesion sites to restore perfusion in patients with 50%–70% stenosis [95]. However, earlier FDA-approved bioresorbable stents exhibited complications arising from their relatively high strut thickness, while permanent metallic stents are associated with long-term risks, such as the late catch-up phenomenon [93].

Polymer-based bioresorbable scaffolds (BRS) present a promising alternative to permanent implants, but their use is limited by lower mechanical strength compared to metallic scaffolds such as cobalt–chromium alloys or stainless steel. For example, poly(L-lactic acid) (PLLA)-based BRS have a tensile modulus nearly 100 times lower than that of metal stents. The mechanical behavior and crystallinity of PLA are largely influenced by the methyl side group present on its polymer backbone. PLA occurs in two main forms: poly(D,L-lactic acid) (PDLLA), which is amorphous, and PLLA, which is semi-crystalline with crystallinity levels reaching up to 70%. The higher crystallinity of PLLA contributes to its superior structural integrity and mechanical stability. In contrast, PGA, which lacks a methyl side group, allows tighter chain packing, resulting in a higher melting point, improved mechanical strength, and increased crystallinity. However, the absence of steric hindrance also makes PGA more susceptible to hydrolytic degradation [93, 96].

## **6.6 Drug delivery systems**

A DDS refers to any platform designed to improve the safety and efficacy of therapeutics by enabling localized loading and controlled release of active compounds. Polymeric scaffolds are particularly attractive in this context, as they allow drugs to be encapsulated and released in a sustained manner at the target site. Controlled release minimizes adverse effects associated with fluctuating drug levels and repeated administrations of immediate-release formulations – an issue that becomes increasingly important as drug loading increases. Owing to their site-specific implantation, scaffolds provide a spatiotemporally regulated release profile that is superior to conventional delivery approaches [97, 98].

Beyond drug release, the physicochemical interactions between polymeric scaffolds and biological components promote tissue regeneration by facilitating cellular adhesion, proliferation, and integration with host tissue [99]. Importantly, scaffolds also act as reservoirs for growth factors, enabling the delivery of key signaling proteins from the transforming growth factor beta (TGF- $\beta$ ) superfamily, including differentiation, osteogenic, and angiogenic factors. Targeted delivery of these biomolecules accelerates regenerative processes and enhances functional tissue repair.

## **7. Conclusion(s)**

In BME, especially in tissue engineering and regenerative medicine, polymeric scaffolds are key tools. Their ability to sustain cellular functions, duplicate the ECM, and aid the delivery of pharmaceutical medicine makes the healing and regeneration of damaged tissues a possibility. The blending of natural and synthetic polymers in hybrid scaffolds enhances their biological functionality even more. The last few years have witnessed advances in manufacturing techniques such as 3D printing, electrospinning, and freeze-drying, which have significantly improved the function and structure of scaffolds.

Smart scaffolds and nanotechnology are two examples of ongoing technologies that provide promising solutions, despite challenges such as immunological response, poor vascularization, and finding a balance between mechanical strength and biodegradability. Comprehensive clinical testing and translational studies are needed to maximize the use of polymeric scaffolds.

## **Acknowledgments**

The author acknowledge Punjabi University, Patiala, for providing academic support during manuscript preparation.

## **Conflict of Interest**

The authors declare no conflict of interest.

## **Author details**

Ankush Kumar, Navjeet Singh, Dimple Sethi Chopra\*, Dhandeep Singh and Nirmal Singh

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India

\*Address all correspondence to: [dimplechopra1973@gmail.com](mailto:dimplechopra1973@gmail.com)

## **IntechOpen**

---

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Zhang XY. Biomedical engineering for health research and development. *European Review for Medical & Pharmacological Sciences*. 2015;**19**(2):220–224
- [2] Rubenstein V, Yin W, Frame MD. Biofluid mechanics: An introduction to fluid mechanics, macrocirculation, and microcirculation. In: *Nature Biotechnology*. Amsterdam, Netherlands: Academic Press; 2011. DOI: 10.1016/B978-0-12-381383-1.00001-1
- [3] Pereira AM, Silva TH, Reis RL. Biomedical engineering. In *Biomedical Engineering Tools for Management for Patients with COVID-19*. Shastri VP, editor. 1st ed. Amsterdam, Netherlands: Academic Press; 2022. p. 131–147. DOI: 10.1016/B978-0-12-820718-5.00009-X
- [4] Rico-Llanos GA, Borrego-González S, Moncayo-Donoso M, Becerra J, Visser R. Collagen type I biomaterials as scaffolds for bone tissue engineering. *Polymers*. 2021;**13**(4):599
- [5] Echeverria Molina MI, Malollari KG, Komvopoulos K. Design challenges in polymeric scaffolds for tissue engineering. *Frontiers in Bioengineering and Biotechnology*. 2021;**9**:617141
- [6] Mao AS, Mooney DJ. 2015. Regenerative medicine: Current therapies and future directions. *Proceedings of the National Academy of Sciences of the United States of America*. **112**(47): 14452–14459. DOI: 10.1073/pnas.1508520112
- [7] Uklejewski R, Winiecki M. 2024. *Advances in Biomimetic Scaffolds for Hard Tissue Surgery*. Biomimetics (Basel). **9**(5):279. DOI: 10.3390/biomimetics9050279
- [8] Calori IR, Braga G, de Jesus PD, Bi H, Tedesco AC. Polymer scaffolds as drug delivery systems. *European Polymer Journal*. 2020;**129**:109621
- [9] Cho SJ, Jung SM, Kang M, Shin HS, Youk JH. Preparation of hydrophilic PCL nanofiber scaffolds via electrospinning of PCL/PVP-b-PCL block copolymers for enhanced cell biocompatibility. *Polymer*. 2015; **69**:95–102
- [10] Farto-Vaamonde X, Auriemma G, Aquino RP, Concheiro A, Alvarez-Lorenzo C. Post-manufacture loading of filaments and 3D printed PLA scaffolds with prednisolone and dexamethasone for tissue regeneration applications. *European Journal of Pharmaceutics and Biopharmaceutics*. 2019;**141**:100–110
- [11] Zhang Y, Wang J, Xiao J, Fang T, Hu N, Li M, Deng L, Cheng Y, Zhu Y, Cui W. An electrospun fiber-covered stent with programmable dual drug release for endothelialization acceleration and lumen stenosis prevention. *Acta Biomaterialia*. 2019;**94**:295–305
- [12] Llorens E, Calderon S, Del Valle LJ, Puiggali J. Polybiguanide (PHMB) loaded in PLA scaffolds displaying high hydrophobic, biocompatibility and antibacterial properties. *Materials Science and Engineering: C*. 2015;**50**:74–84
- [13] Dai J, Jin J, Yang S, Li G. Doxorubicin-loaded PLA/pearl electrospun nanofibrous scaffold for drug delivery and tumor cell treatment. *Materials Research Express*. 2017; **47**:075403

- [14] Yin H, Ding G, Shi X, Guo W, Ni Z, Fu H, Fu Z. A bioengineered drug-Eluting scaffold accelerated cutaneous wound healing In diabetic mice. *Colloids and Surfaces B: Biointerfaces*. 2016;**145**:226–231
- [15] Liu Y, Nelson T, Cromeens B, Rager T, Lannutti J, Johnson J, Besner GE. HB-EGF embedded in PGA/ PLLA scaffolds via subcritical CO<sub>2</sub> augments the production of tissue engineered intestine. *Biomaterials*. 2016;**103**:150–159
- [16] Zhou XH, Wei DX, Ye HM, Zhang X, Meng X, Zhou Q. Development of poly (vinyl alcohol) porous scaffold with high strength and well ciprofloxacin release efficiency. *Materials Science and Engineering: C*. 2016;**67**:326–335
- [17] Dutta SD, Patel DK, Lim KT. Functional cellulose-based hydrogels as extracellular matrices for tissue engineering. *Journal of Biological Engineering*. 2019;**13**(1):55
- [18] Ricard-Blum S. The collagen family. *Cold Spring Harbor Perspectives in Biology*. 2011;**3**(1):a004978. DOI: 10.1101/cshperspect.a004978
- [19] Koivisto L, Heino J, Häkkinen L, Larjava H. Integrins in wound healing. *Advanced Wound Care (New Rochelle)*. 2014;**3**(11):762–783
- [20] Gholap AD, Rojekar S, Kapare HS, Vishwakarma N, Raikwar S, Garkal A, Mehta TA, Jadhav H, Prajapati MK, Annapure U. Chitosan scaffolds: Expanding horizons in biomedical applications. *Carbohydrate Polymers*. 2024;**323**:121394
- [21] Wang Z, Duan H, Hao F, Hao P, Zhao W, Gao Y, Gu Y, Song J, Li X, Yang Z. Circuit reconstruction of newborn neurons after spinal cord injury in adult rats via an NT3-chitosan scaffold. *Progress in Neurobiology*. 2023;**220**:102375
- [22] Affes S, Aranaz I, Acosta N, Heras A, Arbiol J, Rinaudo M, et al. Physicochemical and biological properties of chitosan derivatives with varying molecular weight produced by chemical depolymerization. *Biomass Conversion and Biorefinery*. 2024;**14**:4111–4121
- [23] Rahman L, Goswami J. Recent development on physical and biological properties of chitosan-based composite films with natural extracts: A review. *Journal of Bioactive and Compatible Polymers*. 2021;**36**(3): 225–236
- [24] Zhao D, Yu S, Sun B, Gao S, Guo S, Zhao K. 2018. Biomedical Applications of Chitosan and Its Derivative Nanoparticles. *Polymers (Basel)*. **10** (4):462. DOI: 10.3390/polym10040462
- [25] Gombotz WR, Wee SF. Protein release from alginate matrices. *Advanced Drug Delivery Reviews*. 1998;**31**:267–285
- [26] Lee KY, Mooney DJ. Alginate: Properties and biomedical applications. *Progress in Polymer Science*. 2012;**37** (1):106–126
- [27] Langer R, Vacanti JP. Tissue engineering. *Science*. 1993;**260**:920–926
- [28] O'brien FJ. Biomaterials & scaffolds for tissue engineering. *Materials Today*. 2011;**14**(3):88–95
- [29] Brown BN, Valentin JE, Stewart-Akers AM, McCabe GP, Badylak SF. Macrophage phenotype and remodeling

outcomes in response to biologic scaffolds with and without a cellular component. *Biomaterials*. 2009;**30**(8):1482–1491

[30] Lyons FG, Al-Munajjed AA, Kieran SM, Toner ME, Murphy CM, Duffy GP, O'Brien FJ. The healing of bony defects by cell-free collagen-based scaffolds compared to stem cell-seeded tissue engineered constructs. *Biomaterials*. 2010;**31**(35):9232–9243

[31] Hutmacher DW. 2000. Scaffolds in tissue engineering bone and cartilage. *Biomaterials*. **21**(24):2529–2543. DOI: 10.1016/s0142-9612(00)00121-6

[32] Ko HC, Milthorpe BK, McFarland CD. Engineering thick tissues - the vascularisation problem. *European Cells and Materials*. 2007;**14**:1–19

[33] Hollister SJ. Scaffold engineering: A bridge to where? *Biofabrication*. 2009;**11**:012001

[34] Wu BM, Borland SW, Giordano RA, Cima LG, Sachs EM, Cima MJ. Solid free-form fabrication of drug delivery devices. *Journal of Controlled Release*. 1996;**40**(1-2):77–87

[35] Cima MJ, Sachs E, Cima LG, Yoo J, Khanuja S, Borland SW, Wu B, Giordano RA. Computer-derived microstructures by 3D printing: Sio-and structural materials. *Journal of Materials Research*. 1991;**6**(5):697–711

[36] Roseti L, Parisi V, Petretta M, Cavallo C, Desando G, Bartolotti I, Grigolo B. Scaffolds for bone tissue engineering: State of the art and new perspectives. *Materials Science and Engineering: C*. 2017;**78**:1246–1262

[37] Tarafder S, Bose S. Polycaprolactone-coated 3D printed tricalcium phosphate scaffolds for bone tissue engineering: In vitro alendronate release behavior and local delivery effect on in vivo osteogenesis. *ACS Applied Materials & Interfaces*. 2014;**6**(13):9955–9965

[38] Weng T, Zhang W, Xia Y, Wu P, Yang M, Jin R, Xia S, Wang J, You C, Han C, Wang X. 3D bioprinting for skin tissue engineering: Current status and perspectives. *Journal of Tissue Engineering*. 2021;**12**:20417314211028574

[39] Murphy SV, Atala A. 3D bioprinting of tissues and organs. *Nature Biotechnology*. 2014;**32**(8):773–785

[40] Iwanaga S, Arai K, Nakamura M. Inkjet bioprinting. In *Essentials of 3D Biofabrication and Translation*. Academic Press: Elsevier Inc; 2015. p. 61–79

[41] Wijshoff H. The dynamics of the piezo inkjet printhead operation. *Physics Reports*. 2010;**491**(4-5):77–177

[42] Gudapati H, Dey M, Ozbolat I. A comprehensive review on droplet-based bioprinting: Past, present and future. *Biomaterials*. 2016;**102**:20–42

[43] Shah MA, DG L, BY L, Hur S. Classifications and applications of inkjet printing technology: A review. *IEEE Access*. 2021;**9**:140079–140102

[44] Raman R, Bhaduri B, Mir M, Shkumatov A, Lee MK, Popescu G, Kong H, Bashir R. High-resolution projection microstereolithography for patterning of neovasculature. *Advanced Healthcare Materials*. 2016;**5**(5):610–619

- [45] Yue K, Trujillo-de Santiago G, Alvarez MM, Tamayol A, Annabi N, Khademhosseini A. Synthesis, properties, and biomedical applications of gelatin methacryloyl (GelMA) hydrogels. *Biomaterials*. 2015;**73**: 254–271
- [46] Kačarević ŽP, Rider PM, Alkildani S, Retnasingh S, Smeets R, Jung O, Ivanišević Z, Barbeck M. An introduction to 3D bioprinting: Possibilities, challenges and future aspects. *Materials*. 2018;**11**(11):2199
- [47] Yang H, KH Y, Narayan RJ, Ma S. Laser-based bioprinting for multilayer cell patterning in tissue engineering and cancer research. *Essays in Biochemistry*. 2021;**65**(3):409–416
- [48] Bohandy J, Kim BF, Adrian FJ. Metal deposition from a supported metal film using an excimer laser. *Journal of Applied Physics*. 1986;**60** (4):1538–1539
- [49] Mandrycky C, Wang Z, Kim K, Kim DH. 3D bioprinting for engineering complex tissues. *Biotechnology Advances*. 2016;**34**(4):422–434
- [50] Kawecki F, Clafshenkel WP, Auger FA, Bourget JM, Fradette J, Devillard R. Self-assembled human osseous cell sheets as living biopapers for the laser-assisted bioprinting of human endothelial cells. *Biofabrication*. 2018;**10**3:035006
- [51] Odde DJ, Renn MJ. Laser-guided direct writing of living cells. *Biotechnology and Bioengineering*. 2000;**67**(3):312–318
- [52] Barron JA, Wu P, Ladouceur HD, Ringeisen BR. Biological laser printing: A novel technique for creating heterogeneous 3-dimensional cell patterns. *Biomedical Microdevices*. 2004;**6**(2):139–147
- [53] Catros S, Guillemot F, Nandakumar A, Ziane S, Moroni L, Habibovic P, van Blitterswijk C, Rousseau B, Chassande O, Amédée J, Fricain JC. Layer-by-layer tissue microfabrication supports cell proliferation in vitro and in vivo. *Tissue Engineering Part C: Methods*. 2012;**18** (1):62–70
- [54] Bishop ES, Mostafa S, Pakvasa M, Luu HH, Lee MJ, Wolf JM, Ameer GA, He TC, Reid RR. 3-D bioprinting technologies in tissue engineering and regenerative medicine: Current and future trends. *Genes & Diseases*. 2017;**4** (4):185–195
- [55] Xia Z, Jin S, Ye K. Tissue and organ 3D bioprinting. *SLAS TECHNOLOGY: Translating Life Sciences Innovation*. 2018;**23**(4):301–314
- [56] Nair K, Gandhi M, Khalil S, Yan KC, Marcolongo M, Barbee K, Sun W. Characterization of cell viability during bioprinting processes. *Biotechnology Journal: Healthcare Nutrition Technology*. 2009;**4**(8): 1168–1177
- [57] Wüst S, Müller R, Hofmann S. Controlled positioning of cells in biomaterials—approaches towards 3D tissue printing. *Journal of Functional Biomaterials*. 2011;**2**(3):119–154
- [58] Kraut G, Yenchesky L, Prieto F, Tovar GE, Southan A. Influence of shear thinning and material flow on robotic dispensing of poly (ethylene glycol) diacrylate/poloxamer 407 hydrogels. *Journal of Applied Polymer Science*. 2017;**134**29:45083

- [59] Subia B, Kundu J, Kundu SC. Biomaterial scaffold fabrication techniques for potential tissue engineering applications. *Tissue Engineering*. 2010;**141**(13-18):13–18
- [60] Ikada Y. Challenges in tissue engineering. *Journal of the Royal Society Interface*. 2006;**3**(10):589–601
- [61] George M, Abraham TE. Polyionic hydrocolloids for the intestinal delivery of protein drugs: Alginate and chitosan —A review. *Journal of Controlled Release*. 2006;**114**(1):1–4
- [62] Khan MU, Al-Thebaiti MA, Hashmi MU, Aftab S, Abd Razak SI, Abu Hassan S, Abdul Kadir MR, Amin R. Synthesis of silver-coated bioactive nanocomposite scaffolds based on grafted beta-glucan/hydroxyapatite via freeze-drying method: Anti-microbial and biocompatibility evaluation for bone tissue engineering. *Materials*. 2020;**13**(4):971
- [63] Govindan R, Gu FL, Karthi S, Girija EK. Effect of phosphate glass reinforcement on the mechanical and biological properties of freeze-dried gelatin composite scaffolds for bone tissue engineering applications. *Materials Today Communications*. 2020;**22**:100765
- [64] Samourides A, Browning L, Hearnden V, Chen B. The effect of porous structure on the cell proliferation, tissue ingrowth and angiogenic properties of poly (glycerol sebacate urethane) scaffolds. *Materials Science and Engineering: C*. 2020;**108**:110384
- [65] Preethi GU, Sreekutty J, Unnikrishnan BS, Archana MG, Syama HP, Deepa M, Shiji R, Anusree KS, Sreelekha TT. Doxorubicin eluting microporous polysaccharide scaffolds: An implantable device to expunge tumour. *Materials Science and Engineering: C*. 2020;**107**:110332
- [66] Wu X, Liu Y, Li X, Wen P, Zhang Y, Long Y, Wang X, Guo Y, Xing F, Gao J. Preparation of aligned porous gelatin scaffolds by unidirectional freeze-drying method. *Acta Biomaterialia*. 2010;**6**(3):1167–1177
- [67] Sarkar K, Gomez C, Zambrano S, Ramirez M, De Hoyos E, Vasquez H, Lozano K. Electrospinning to forcespinning™. *Materials Today*. 2010;**13**(11):12–14
- [68] Jia W, Li M, Kang L, Gu G, Guo Z, Chen Z. Fabrication and comprehensive characterization of biomimetic extracellular matrix electrospun scaffold for vascular tissue engineering applications. *Journal of Materials Science*. 2019;**54**(15):10871–10883
- [69] Tan HL, Kai D, Pasbakhsh P, Teow SY, Lim YY, Pushpamalar J. Electrospun cellulose acetate butyrate/ polyethylene glycol (CAB/PEG) composite nanofibers: A potential scaffold for tissue engineering. *Colloids and Surfaces B: Biointerfaces*. 2020;**188**:110713
- [70] Thavornnyutikarn B, Chantarapanich N, Sittisriseripratip K, Thouas GA, Chen Q. Bone tissue engineering scaffolding: Computer-aided scaffolding techniques. *Progress in Biomaterials*. 2014;**3**(2):61–102
- [71] Bajaj P, Schweller RM, Khademhosseini A, West JL, Bashir R. 3D biofabrication strategies for tissue engineering and regenerative medicine. *Annual Review of Biomedical Engineering*. 2014;**16**(1):247–276

- [72] Abdelaziz AG, Nageh H, Abdo SM, Abdalla MS, Amer AA, Abdal-Hay A, Barhoum A. A review of 3D polymeric scaffolds for bone tissue engineering: Principles, fabrication techniques, immunomodulatory roles, and challenges. *Bioengineering*. 2023;**10**(2):204
- [73] Chen QZ, Li Y, Jin LY, Quinn JM, Komesaroff PA. A new sol-gel process for producing Na<sub>2</sub>O-containing bioactive glass ceramics. *Acta Biomaterialia*. 2010;**6**(10):4143–4153
- [74] Jagur-Grodzinski J. Biomedical application of functional polymers. *Reactive and Functional Polymers*. 1999;**39**(2):99–138
- [75] Liu Y, Luo D, Wang T. Hierarchical structures of bone and bioinspired bone tissue engineering. *Small*. 2016;**12**(34):4611–4632
- [76] Kačarević Ž P, Rider P, Alkildani S, Retnasingh S, Pejakić M, Schnettler R, Gosau M, Smeets R, Jung O, Barbeck M. An introduction to bone tissue engineering. *The International Journal of Artificial Organs*. 2020;**43**(2):69–86
- [77] Wubneh A, Tsekoura E, Ayranci C, et al. Current state of fabrication technologies and materials for bone tissue engineering. *Acta Biomaterialia*. 2018;**80**:1–30
- [78] Jelodari S, Ebrahimi Sadrabadi A, Zarei F, Jahangir S, Azami M, Sheykhhasan M, Hosseini S. New insights into cartilage tissue engineering: Improvement of tissue-scaffold integration to enhance cartilage regeneration. *BioMed Research International*. 2022;**2022**:7638245
- [79] Luo Y, Sinkeviciute D, He Y, et al. The minor collagens in articular cartilage. *Protein & Cell* 2017;**8**:560–572
- [80] Sutherland AJ, Converse GL, Hopkins RA, Detamore SM. The bioactivity of cartilage extracellular matrix in articular cartilage regeneration. *Advanced Healthcare Materials*. 2015;**4**(1):29–39
- [81] Francis SL, Di Bella C, Wallace GG, Choong MPF. Cartilage tissue engineering using stem cells and bioprinting technology-barriers to clinical translation. *Frontiers in Surgery*. 2018;**5**:70
- [82] Mamidi MK, Das AK, Zakaria Z, Bhonde R. Mesenchymal stromal cells for cartilage repair in osteoarthritis. *Osteoarthritis and Cartilage*. 2016;**24**(8):1307–1316
- [83] Nukavarapu SP, Dorcenus LD. Osteochondral tissue engineering: Current strategies and challenges. *Biotechnology Advances*. 2013;**31**(5):706–721
- [84] Sun G, Shen YI, Harmon JW. Engineering Pro-Regenerative Hydrogels for Scarless Wound Healing. *Advanced Healthcare Materials*. 2018;**7**(14):e1800016. DOI: 10.1002/adhm.201800016
- [85] Tottoli EM, Dorati R, Genta I, Chiesa E, Pisani S, Conti B. 2020. Skin Wound Healing Process and New Emerging Technologies for Skin Wound Care and Regeneration. *Pharmaceutics*. **12**(8):735. DOI: 10.3390/pharmaceutics12080735
- [86] Hosseini M, Shafiee A. Engineering Bioactive Scaffolds for Skin Regeneration. *Small*. 2021;**17**(41):e2101384. DOI: 10.1002/smll.202101384
- [87] Rakhorst G, Ploeg R. Biomaterials in Modern Medicine: The Gronigen Perspective. Singapore: World Scientific; 2008

- [88] Mobasser A, Faroni A, Minogue BM, Downes S, Terenghi G, Reid AJ. Polymer scaffolds with preferential parallel grooves enhance nerve regeneration. *Tissue Engineering Part A*. 2015;**21**(5-6):1152–62
- [89] Zhang H, Guo J, Wang Y, Shang L, Chai R, Zhao Y. Natural polymer-derived bioscaffolds for peripheral nerve regeneration. *Advanced Functional Materials*. 2022;**32**41:2203829
- [90] Gu X, Ding F, Yang Y, Liu J. Construction of tissue engineered nerve grafts and their application in peripheral nerve regeneration. *Progress in Neurobiology*. 2011;**93**:204–230
- [91] Davoudi P, Assadpour S, Derakhshan MA, Ai J, Solouk A, Ghanbari H. Biomimetic modification of polyurethane-based nanofibrous vascular grafts: A promising approach towards stable endothelial lining. *Materials Science and Engineering: C Materials for Biological Applications*. 2017;**80**:213–221
- [92] Tunali-Akbay T, Kahraman MV, Oktay B, İpekci H, Kayaman-Apohan N. Bioactivated poly (vinyl alcohol) /poly (acrylic acid) based nanofiber for high-performance membrane techniques. *Letters in Applied NanoBioScience*. 2020;**9**(1):819–823
- [93] Toong DWY, Toh HW, Jck N, Wong PEH, Leo HL, Venkatraman S, Tan LP, Ang HY, Huang Y. 2020. Bioresorbable Polymeric Scaffold in Cardiovascular Applications. *International Journal of Molecular Sciences*. **21**(10):3444. DOI: 10.3390/ijms21103444
- [94] Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. 2016. Epidemiology of coronary heart disease and acute coronary syndrome. *Annals of Translational Medicine*. **4**(13):256. DOI: 10.21037/atm.2016.06.33
- [95] Karabulut A, Cakmak M. 2015. Treatment strategies in the left main coronary artery disease associated with acute coronary syndromes. *Journal of the Saudi Heart Association*. **27**(4):272–276. DOI: 10.1016/j.jsha.2015.03.002
- [96] Berglund J, Guo Y, Wilcox JN. 2009. Challenges related to development of bioabsorbable vascular stents. *EuroIntervention*. **5**(Suppl F): F72–9. DOI: 10.4244/EIJV51FA12
- [97] Baumann B, Jungst T, Stichler S, Feineis S, Wiltshcka O, Kuhlmann M, Lindén M, Groll J. Control of nanoparticle release kinetics from 3D printed hydrogel scaffolds. *Angewandte Chemie International Edition*. 2017;**56**(16):4623–4628
- [98] Ardeshtirzadeh B, Anaraki NA, Irani M, Rad LR, Shamshiri S. Controlled release of doxorubicin from electrospun PEO/chitosan/graphene oxide nanocomposite nanofibrous scaffolds. *Materials Science and Engineering: C*. 2015;**48**:384–390
- [99] Shi W, Sun M, Hu X, Ren B, Cheng J, Li C, Duan X, Fu X, Zhang J, Chen H, Ao Y. Structurally and functionally optimized silk-fibroin–gelatin scaffold using 3D printing to repair cartilage injury in vitro and in vivo. *Advanced Materials*. 2017;**29**29:1701089

*Edited by Adnan Haider,  
Sajjad Haider and Sumra Wajid Abbasi*

The success of tissue engineering relies on more than cells and growth factors; it depends on the scaffolds that support, guide, and regulate tissue regeneration. *Polymeric Scaffolds - The Backbone of Modern Tissue Engineering* offers a comprehensive exploration of the materials that underpin modern regenerative medicine. This book examines the design, fabrication, and biological performance of polymer-based scaffolds, highlighting how their physicochemical properties influence cell behaviour and tissue development. The text presents both established concepts and cutting-edge innovations shaping the field today. Bridging fundamental science with translational research, this book also addresses clinical challenges and future directions in scaffold-based therapies. Written by experts and tailored for students, researchers, and professionals, this book serves as both an essential reference and an inspiring guide for those working at the forefront of biomaterials and tissue engineering.

*Robert Koprowski, Biomedical Engineering Series Editor*

Published in London, UK

© 2026 IntechOpen  
© blackdovfx / iStock

**IntechOpen**

ISSN 2631-5343

ISBN 978-1-83635-938-8

