A Review of 3d Printing Model of New Blood Vessel Formation For Pharmaceutical Applications

Nidhi Mishra [1*], Priya Vij [1], Akanksha Mishra [1]

Abstract

Cardiovascular diseases (CVDs) are the primary cause of death in older individuals. An established medical approach for treating CVDs involves replacing blocked or restricted arteries. This surgery, known as vascular transplant, is now considered the most effective method and uses the patient's tissue for transplanting. Artificial Blood Vessels (ABVs) are often not utilized for numerous cardiac individuals due to an individual's advanced age, narrow veins, prior medical history, and aberrant conditions. Hence, it is essential to consider the necessity of vascular substitutes, particularly in vascular transplanting involving extremely narrow dimensions and the presence of suitable alternatives. This work aimed to create a new type of synthetic blood vessel by combining polymer-reinforced materials with bioceramic nanomaterials. Research has been conducted on the biomechanical and chemical characteristics of artificial blood arteries for their potential application in bypass surgery of the coronary arteries for atherosclerosis as part of biological development. The work involved the preparation of thermoplastic polyurethane (TPU) by combining nanocrystalline hydroxyapatite (HA) tiny particles utilizing the extrusion process to create the ABVs. The ideal sample was examined using X-ray diffraction (XRD) and Scanned Electron Microscopy (SEM). The ABVs had a significant capability to determine the elasticity modulus, wetting, and permeability of the veins. These characteristics were evaluated using fused lamination modeling and 3D printing. The findings indicate that the constricted arteries, made of TPU composites with nanocrystalline HA small particles, had superior chemical resistance and structural properties.

Keywords: Cardiovascular diseases, pharmaceutical applications, blood vessel formation, 3D printing

Significance | Innovative synthetic blood vessels offer promising solutions for cardiovascular diseases, providing safer, more accessible treatments for aging populations

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1. Introduction

T In recent decades, cardiovascular diseases (CVDs) have emerged as the primary cause of human death and morbidity worldwide Townsend et al. (2022). An established medical technique for CVDs involves substituting the obstructed or constricted segment of the arteries. There are instances where it is necessary to replace the veins in an individual's body due to factors such as age, small vein size, spider veins, and other illnesses. The need for alternate arteries, such as those with modest sizes in vascular grafts, is unavoidable Jamróz et al. (2018). Creativity and an orientation toward management are crucial in any health system. Tissue science aims to create and construct synthetic veins that closely match the characteristics of natural arteries Moore et al. (2022). The study assessed the precision of substituting arteries with artificial replacements using surface oxygenated plasma and acrylamide transplanting. Scientists developed modified nanotechnology to offer a suitable base for producing artificial

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substitutes for vessels that have lost their function and treated their exteriors with oxygen plasma Boucherat et al. (2022). Based on the research, the utilization of fibers and carbohydrates in CVD therapy might potentially result in severe instances of cardiac collapse and fatality Tiemensma et al. (2021). The deposition and accumulation of fatty masses inside the venous walls are the primary factors in the progression of arterial spasms Esmaeili et al. (2019).

Medication use is the primary choice for managing individuals with CVD. In cases when the blockage of the veins is quite severe and can't be resolved with medicinal and angiographic techniques, the course of action is to perform bypass and vascular transplant procedures Jenndahl et al. (2022). It is challenging to avert a heart attack effectively. A heart attack poses a complex challenge for both surgeons and participants, with the latter potentially experiencing protracted postoperative agony Gao et al. (2021).

The objective of this study was to create and analyze a new fabricated bio-nanocomposite collection using Fused Depositing Modeling (FDM) Cailleaux et al. (2021) or Fused Filament Fabrications (FFF) Fico et al. (2022) as a method of additive production for medical purposes. The array consisted of Thermoplastic Polyurethane (TPU) Arifvianto et al. (2021) as the primary material and nanocrystalline Hydroxyapatite (HA) Fiume et al. (2021) as an additional filler, with different amounts utilized for creating multibranch Artificial Blood Vessels (ABVs) Yamada et al. (2023). This was the initial time a method like this was used to manage CVD.

The subsequent sections are arranged in the specified fashion: Section 2 provides an overview of the history and literature study on cardiovascular illnesses and the methods used for their detection. Section 3 explores using 3D printing technology to create new blood vessels for pharmacological purposes. Section 4 presents the empirical investigation and its results. Section 5 presents the study's conclusions and findings.

2. Literature Review

This section analyzes the cardiovascular disease detection methods and their impact. This article concisely overviews the presently understood cellular and molecular pathways involved in brain angiography and barrier development (Ben-Zvi, Liebner, 2022). The research offers newly identified communication between cellular and inert components in the growing central nervous system, such as the external matrices. The research discusses current findings about the diversity of barriers and distinct features of the endothelial obstacles in the central nervous system Domínguez et al. (2021). The study examines the circumventricular tissues, the neurological niches in the subventricular region, and the hippocampus.

Angiogenin (ANG), a ribonuclease that promotes the growth of blood vessels, is produced by osteoclasts and plays a crucial role in preventing nearby vascular cells from aging Liu et al. (2021). ANG sustains the growth-promoting function of endothelial tissues via plexin-B2 facilitated synthesis of ribosomal RNA (rRNA). These results demonstrate that the aging of veins in the metaphysis plays a crucial role in how glucocorticoids affect skeletal development.

Elastic fibers are crucial in maintaining the skeletal strength and biomechanical properties of dynamic cells in vertebrates. This study comprehensively examines elastic fibers' development, composition, and role and their progression throughout human life in both standard and pathological conditions Schmelzer, Duca, (2022). The investigation of flexible fibers has been a challenging pursuit in matrix biological processes, primarily due to the remarkable features of elastin.

This study examines how immunotherapy might restore the blood vessels' normal functioning. It also suggests that this approach has promise for enhancing the condition of hypoxia Liu et al. (2021). The limited time frame during which anti-angiogenesis treatment effectively normalizes blood vessels has led to exploring the impact of arterial normalization on immunotherapy. This finding offers a novel approach to combining immunotherapy with radiation Gardin et al. (2020).

The study emphasized the significance of tumor angiogenesis in the processes of tumor development, metastases, and treatment resistance Elebiyo et al. (2022). Vascular normalizing treatment aims to stabilize the blood arteries within tumors to enhance tumor oxygenation and facilitate the administration of drugs, ultimately leading to the eradication of cancer cells. The vascular normalization hypothesis is being investigated in conjunction with immune checkpoint blockers, and current studies suggest a robust interaction between anti-angiogenesis and immunological treatment.

The study presents a bioink that is unique to a particular tissue. This bio-ink is made of alginate, an organic polymer, strengthened by incorporating a matrix of cells obtained from decellularized tissues De Santis et al. (2021). The rheological and gelation characteristics of rECM are advantageous for 3D bioprinting while maintaining physiologically inductive qualities. rECM bio-inks offer a potential and innovative method for creating functional human organs through 3D bioprinting.

This article examines the procedure of synovial angiogenesis in Rheumatoid Arthritis (RA), focusing on the intricate interaction between inflammatory processes, immunological imbalance, low oxygen levels, and synovial thrombosis. The precise method of angiogenesis is also discussed (Wang, Wu, Deng, 2021). The research explores comparable therapeutic approaches for RA, particularly combining targeted vasculature inhibitor treatment and chemotherapy.

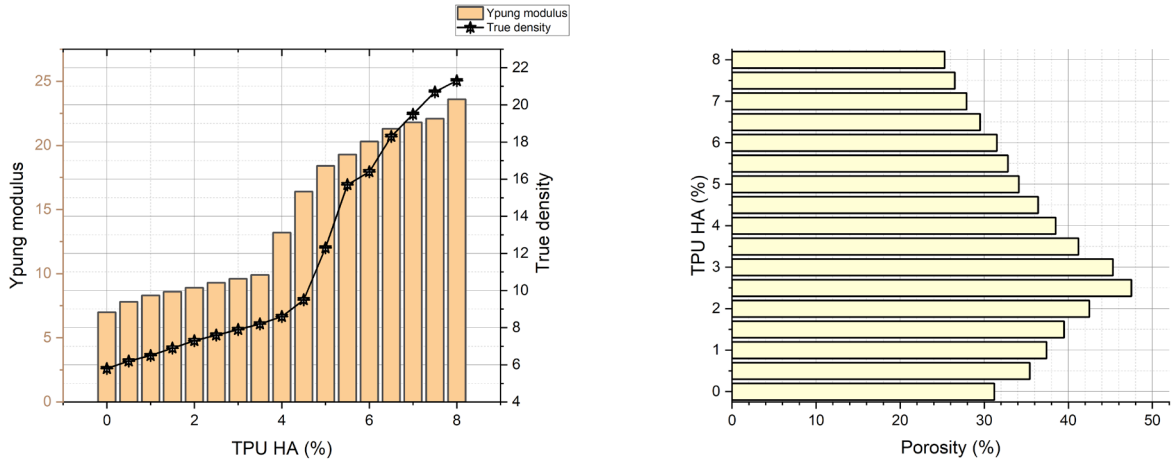

Figure 1. (a) Elastic modulus and (b) Porosity value analysis

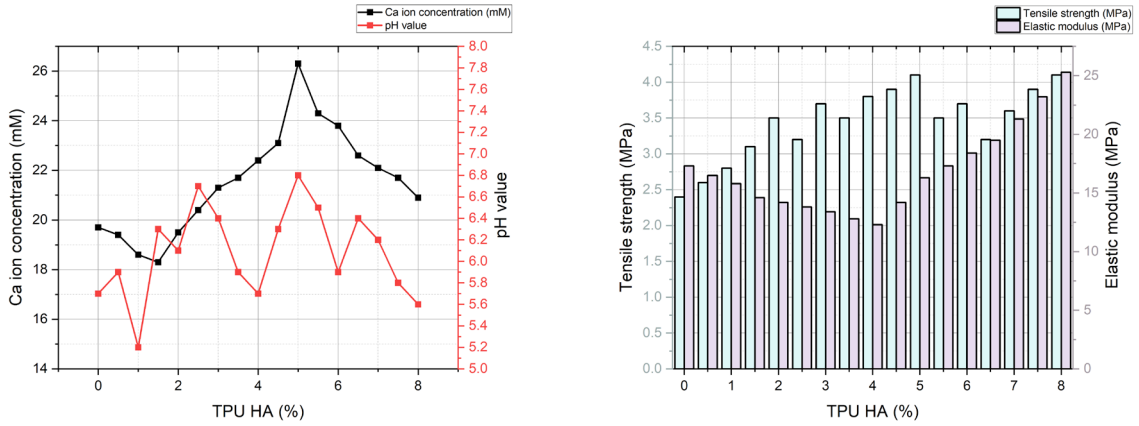

Figure 2. (a) Ca ion concentration and (b) Tensile strength analysis

The literature study examines several strategies that are now accessible and analyzes their advantages and consequences Gu et al. (2020). However, the constraints and difficulties associated with cardiovascular disorders underscore the necessity for novel approaches to detection and analysis Capel et al. (2018).

3. 3D printing based on new blood vessel formation

The utilization of 3D printing technology in the creation of blood vessels for pharmaceutical purposes represents a significant advancement in tissue engineering and regenerative medicine. This section provides a detailed exploration of various aspects related to this innovative approach, including materials, experimental techniques, fabrication processes, and analytical methods. Here, we summarize and discuss the key findings and implications of each subsection.

Materials

The selection of materials is critical for the success of any tissue engineering endeavor. In this study, a variety of substances, including Crude Fucoidan (CF), cell culture media, growth factors, and synthetic filaments, were utilized to facilitate the fabrication and evaluation of artificial blood vessels.

The diverse range of materials chosen underscores the interdisciplinary nature of tissue engineering, where biological, chemical, and mechanical components converge to create functional tissues.

Conditioned Medium Preparation and Collection

The preparation of conditioned media from human adipose-derived stem cells (hASCs) highlights the importance of cellular microenvironments in promoting tissue regeneration. By subjecting the cells to hypoxic conditions, researchers aimed to mimic the physiological environment within the body, enhancing the secretion of trophic factors with therapeutic potential.

Pooling samples from multiple donors mitigates the impact of individual variability, ensuring a more representative analysis of the trophic factors generated by hASCs.

Fucoidan Extract Assay

The assessment of cell expansion, seeding, and viability provides valuable insights into the biological effects of Crude Fucoidan (CF) on endothelial and cancerous cell lines. These experiments elucidate the potential role of CF in promoting cellular proliferation and viability, essential for tissue regeneration.

The use of the MTS test for evaluating metabolic function demonstrates a quantitative approach to assessing cellular health and function in response to experimental treatments.

Theoretical Evaluation

The tube formation assay and quantification of growth hormones offer valuable information on the angiogenic potential of the experimental materials. By examining the formation of vascular structures and the secretion of growth factors, researchers can assess the capacity of artificial blood vessels to support tissue growth and repair.

These experiments provide crucial data for evaluating the therapeutic efficacy of the fabricated blood vessels in promoting neovascularization and tissue regeneration.

Fabrication of the Filament and Design of the Artificial Artery

The fabrication process and design considerations for artificial blood vessels highlight the importance of engineering precision and functionality. By optimizing parameters such as filament composition, extrusion temperature, and structural dimensions, researchers can tailor the properties of the vessels to meet specific physiological requirements.

The use of advanced software and 3D printing techniques enables the precise fabrication of complex vascular structures, demonstrating the potential of additive manufacturing in tissue engineering applications.

Material Characterization, Mechanical Properties, and Biocompatibility

Characterization of the fabricated materials provides essential information on their structural integrity and compatibility with biological systems. Techniques such as X-ray diffraction (XRD) and scanning electron microscopy (SEM) offer insights into the composition and morphology of the materials at the nanoscale.

Evaluation of mechanical properties and biocompatibility is crucial for assessing the safety and performance of artificial blood vessels in vivo. By subjecting the vessels to simulated physiological conditions, researchers can ensure their suitability for clinical applications.

Experimental Techniques

Electrophoresis, Western blot analysis, and cell scratch wound healing assay offer valuable tools for studying cellular behavior and molecular mechanisms underlying tissue regeneration. These techniques provide quantitative data on protein expression, cell migration, and wound healing dynamics, essential for evaluating the therapeutic efficacy of experimental treatments.

Statistical analysis plays a crucial role in interpreting experimental results and determining the significance of observed effects. By employing rigorous statistical methods, researchers can ensure the reliability and reproducibility of their findings, enhancing the validity of the study outcomes.

Overall, a comprehensive overview of the experimental methodologies and techniques employed in the study of 3D-printed blood vessels for pharmaceutical applications has been described. By integrating multidisciplinary approaches and advanced analytical methods, researchers can gain valuable insights into the design, fabrication, and evaluation of tissue-engineered constructs, paving the way for future advancements in regenerative medicine.

4. 3D vessel model analysis

The microstructure assessment of the ABVs involved using theoretical methods. Using high-energy ball milling equipment, the TPU biopolymer was blended with different quantities of HA powder (0 to 8 with a step size of 0.5%). The combined composite particles were introduced into the extrusion device using a predetermined heating speed. Later, the findings acquired from homogenizing TPU and HA filaments were removed and introduced into the 3D printing equipment. The ABV architecture was assessed by evaluating its physical and biological characteristics, and the obtained findings were then compared to the mathematical models.

The strength values obtained from the materials with different quantities of HA powder are depicted and evaluated in Figs 1(a) and 1(b). The Young's modulus of the specimen rose from 12 to 25 MPa when the HA flour was added to TPU. The composite's enhanced elasticity is attributed to the elevated Young's modulus of HA compared to TPU. The measured hardness parameter rose from 0.4 to 0.83 (N) as the percentage of HA powder in the TPU polymer increased. While the permeability measurements showed an increase in permeability from 32% to 48%, the permeability stayed consistent in the specimens having 2.8 and 5 wt% of HA.

The Ca ion density of a sample soaked in simulated body fluid for 20 days at a heat of 37°C in an incubated state is depicted in Figs 2(a) and 2(b). Based on the acquired findings, the concentration of Ca2+ ions was reduced after 20 days. According to Fig. 3(a), the pH of the specimen did not change after 20 days of culture in SBF saltwater. Changes in the amount of calcium ions and the PO4 category of HA were found after the initial and second week in the specimens containing 2.4 and 6 wt% of HA, respectively.

The anti-angiogenic effect of the selected fucoidan was also tested in vivo in a CAM experiment. To assess this, the number of veins descending into the specific area of interest was measured on day 15, which marked the study's conclusion. This was seven days following the CF injections. The CAM grew gradually, as anticipated, but no definitive distinctions were identified among the CTR and CF (0.8 mg mL−1) situations. Therefore, the CAM was collected, and photographs of the developing embryo were taken on day 8. It was seen that the fucoidan situation resulted in a less filled CAM in the area surrounding the area of injection, as shown by the ring. This discovery was validated by measuring the blood vessels of all images: the control state showed 24.8 ± 4.3 vessels, while the fucoidan group exhibited roughly 23 ± 5.3 veins.

5. Conclusion

Cardiovascular diseases are well recognized as a significant contributor to global mortality. Revascularization, which involves replacing or widening obstructed arteries, is a frequently performed medical intervention for managing CVDs. It is now considered the most effective method for autograft transplanting in vascular grafting. Artificial veins are typically regarded as preferred options for vascular substitution. The need for alternative synthetic vessels, particularly tiny ones, must be acknowledged.

Tissue engineers want to create artificial vasculature that closely mimics the compliance of actual veins. Artificial reproductive systems should provide biological compatibility, non-toxicity, and immunity to diseases while preserving their mechanical qualities and coagulation of the blood. TPU and HA are nanomaterials with significant potential for delivering these advantages, yet enhancements are required to address certain biochemical and mechanical limitations. Although there have been attempts to create TPU with satisfactory qualities and improve its properties by chemical alterations at the surface or mass stages, there is potential for additional development in this area. By implementing necessary adjustments to enhance the characteristics of artificial blood vessels made from TPU, these substances can be utilized to produce functional blood vessels.

Alterations in shear stress experienced by microorganisms result in changes to the penetrating and mass accumulation inside these microbes, mainly owing to harm caused to the endothelium layer. This component can significantly contribute to the development of fat cells, ultimately leading to heart disorders. The current study investigates the parameters that influence the shear stress on the microwave device barrier, modulus of elasticity, and permeability of ABVs due to the issue's significance. The findings suggest that a mixture of empirical assessments can imitate the micromechanical actions of arterial vessels. The permeability of blood arteries significantly impacts the shear tension and modulus of elasticity of the veins. The findings demonstrated that the rheological properties of blood have a substantial effect on the fluctuations in shear stress. The study's findings revealed the impact of the blockage rate, pore setting, and vein reinforcing level on the elastic elasticity and permeability of the tube. The specimens' metabolism suggested that including bioceramics might improve the veins' flexible modulus responsiveness.

Author contribution

N.M., P.V., A.M. wrote, reviewed and edited the article. All authors read and approved for publication.

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Competing financial interests

The authors have no conflict of interest.

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