Reviews on Advanced Materials and Technologies, 2024, vol. 6, no. 4, pp. 164–170
DOI: 10.17586/2687-0568-2024-6-4-164-170

Trends in the Development of Bioresorbable Scaffolds

G.R. Petsukh*, A.V. Podshivalov

Center of Chemical Engineering, ITMO University, Kronverkskiy av., 49, lit. A, St. Petersburg, 197101, Russia

Article history

Received October 14, 2024
Received in revised form
November 09, 2024
Accepted November 11, 2024
Available online December 30, 2024

Abstract

Currently, biomaterials are increasingly in demand in medicine and are fundamental components of tissue engineering. The necessary factors of these materials to ensure their ability to effectively function in the human body are biocompatibility, bioactivity, bioresorption and non-toxicity. An ideal implant should have a number of physical, chemical and biological characteristics to stimulate cell proliferation and promote tissue formation. Bioresorbable polymers have advantages for tissue engineering applications due to a wide range of mechanical properties combined with sufficient chemical inertness and degradation rate. Given the increasing number of studies in the field of biomaterials for medical applications, the purpose of this review is to examine recently developed implantable materials. In this work, emphasis is placed on the development of the composition of polymers that determine the characteristics of future bioresorbable materials, as well as on the choice of optimal parameters and a method for their preparation.

Keywords: Bioresorption; TIPS; BJT; Proliferation; Tissue engineering

1. INTRODUCTION

By 2030, the World Health Organization expects the number of elderly people to increase up to 1.4 billion [1]. From the above forecast, it follows that in the near future, the need for surgical options aimed at solving age-related problems, such as joint wear and tear and decreased calcium levels in the musculoskeletal system, will increase. For example, narrowing or blockage of blood vessels due to plaque accumulation causes a few common diseases, namely atherosclerotic coronary artery disease (CAD) and peripheral arterial disease (PAD), which affect more than 274 million people worldwide [2]. Effective treatment of these diseases is critical to both reducing healthcare costs and improving the quality of life of patients. The use of bioresorbable polymers offers several advantages over traditional implants, such as eliminating the need for re-operation to remove the implant or surgical interventions due to complications associated with it [3]. This is particularly useful in the field of tissue engineering where the material is only needed for a limited healing time [4,5]. Bioresorbable scaffolds act as temporary materials that are expected to be overgrown with a layer of the patient's tissue, while maintaining their shape and satisfying the necessary mechanical loads, and then removed by the body under the action of enzymes [6]. Since the fabricated scaffold must provide structural support for attached cells and create an appropriate environment favorable for their proliferation, such characteristics of biomaterials as rigidity, cytocompatibility, morphology, porosity and reactivity require big attention at the development stage [7,8]. This study pays special attention to the development of the composition of bioresorbable scaffolds that meet the conditions of proliferation, as well as the analysis of methods for their production.

* Corresponding author: G.R. Petsukh, e-mail: gosha.jorov@gmail.com

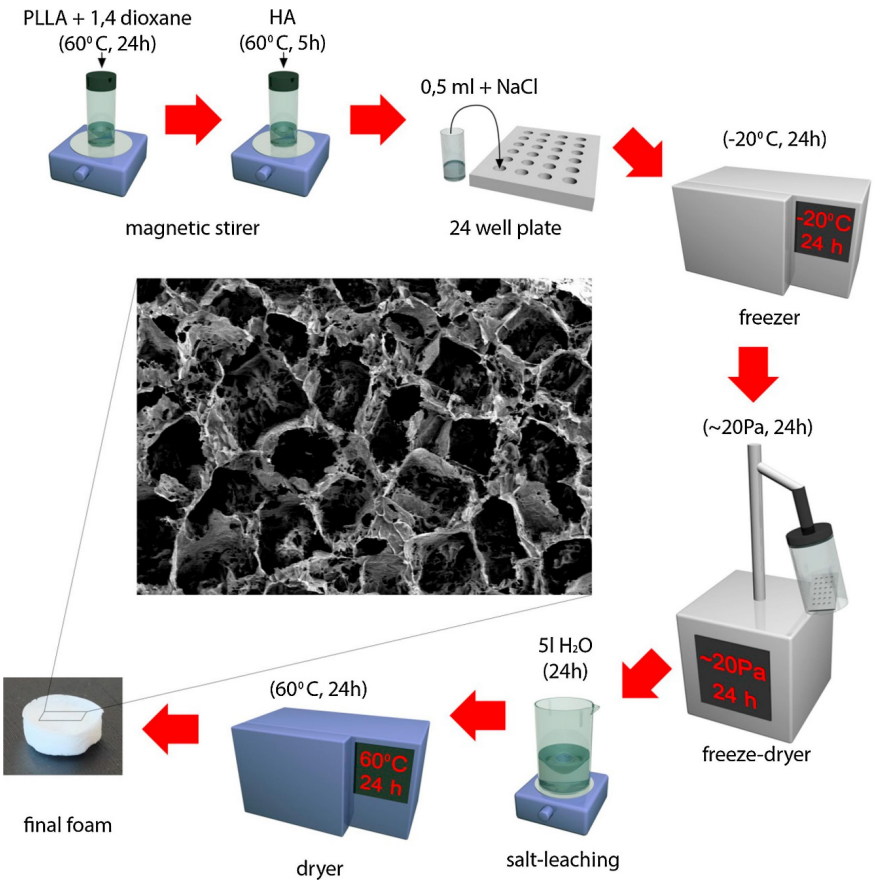

Fig. 1. The scheme for synthesis PLLA/HA scaffolds in TIPS-SL process. Adapted from Ref. [10].

2. SOLVENT METHODS FOR SYNTHESIS OF BIORESORBABLE SCAFFOLDS

Methods based on the treatment of the original polymers with a solvent are widely used in the manufacture of medical devices. The techniques include dissolving the polymer in a suitable organic solvent, mixing it with a filler to form a composite, and finally evaporating the solvent. Solution methods are popular among researchers due to their simplicity and lack of need for expensive equipment. According to the Ref. [9], bioresorbable 3D printing ink composed of citric acid-based biomaterial and poly-L-lactic acid (PLLA) has been developed. A two-phase system was used that enables the in situ formation of semi-crystalline nanofibrous networks of poly-L-lactic acid in a 3D-printed polymer matrix of a citrate-based bioresorbable biomaterial, the first to be used in an absorbable medical device. The resulting composite material achieved an increased Young's modulus of 969.55 MPa in a fully hydrated state, which is 108% better than known pure citrate-based biomaterials. The average ultimate tensile strength (UTS) values for the ink samples were 14.16 MPa, 19.3 MPa and 29.15 MPa, respectively. With the increase of PLLA concentration, the corresponding Young's modulus and UTS increased. The prepolymer concentration has a more dominant effect on the final Young's modulus and UTS because the matrix constitutes the main part of the final scaffold. PLLA acts as a reinforcing agent for the composite. The cytocompatibility of the fabricated substrates was assessed using both leachable extracts and direct contact on 3D printed wafer samples. The samples showed high cell viability (> 95%), comparable to that of the growth medium but much higher than that of the latex extract (~ 68%) with known cytotoxicity. The synthesized framework, printing process and post-processing methods allow the production of materials with 100 μm thick struts that can withstand physiological stress.

Thermally induced phase separation (TIPS) or freeze-drying is another method that allows the synthesis of porous bioscaffolds. The method is based on freezing a solvent/polymer/filler mixture and then reducing the pressure to sublimate the solvent. Unlike other composite manufacturing technologies, the inclusion of filler particles (up to 15 wt.%) in porous scaffolds obtained using TIPS has a minimal effect on the mechanical properties of the scaffold. The article [10] shows that porous matrices based on poly(L-lactide) and synthetic hydroxyapatite (HA) were obtained using TIPS method supported by the salt leaching (SL) process. According to Fig 1, the composites were obtained in 1,4-dioxane with the addition of NaCl.

The Young's modulus values of the scaffolds ranged from 37.0 to 56.2 kPa and increased with higher hydroxyapatite content. A similar trend was observed for compressive stress. Values ranged from 17.4 to over 28 kPa (at 40% strain) and from about 100 kPa to over 280 kPa at 80% strain. The proliferation rate of MC3T3-E1 osteoblast cells was also investigated after 24 and 72 hours. Cell growth values were significantly higher for composites with higher HA content, reaching 307% for the PLLA sample (compared to the same sample after 24 hours) and 1168% for PLLA/HA 25/75. The study showed that the TIPS-SL technique can be used to produce PLLA/HA composites with HA content up to 75 wt.% with a stable porous structure. It was also confirmed that the osteoblast cell proliferation rate was proportional to the HA content in the foam, reaching 3–4 times higher rate for PLLA/HA 25/75 compared to pure PLLA.

The article [11] reports the fabrication of porous poly(L-lactide-co-glycolide) (PLGA) scaffolds by combining TIPS and pore-forming agent leaching. Large pores of about 75–400 μm in diameter in the resulting scaffolds, shown in Fig. 2, were created by sucrose particles, while small pores of less than 20 μm in diameter were formed by phase separation.

Solvent extraction with chloroform and ethanol at low temperatures contributed to the reduction of scaffold cytotoxicity. The addition of beta-tricalcium phosphate (β-TCP) to the samples did not significantly affect the compressive modulus, which was 1.49÷6.64 MPa, but tended to decrease the compressive strength, which reached 0.110÷0.296 MPa. The resulting scaffolds with different pore sizes can potentially be used in bone tissue engineering.

In additive manufacturing, binder jetting (BJT) has shown potential for producing bioresorbable materials. The low-temperature nature of the BJT process is used to create a more temperature-responsive biopolymer. Researchers [12] adapted the concentration of phosphoric acid-based binder solution to 8.75 wt% to improve the cytocompatibility and mechanical strength of calcium phosphate (CaP) CaP/collagen scaffolds. The reduction in viscosity and surface tension, shown in Fig. 3, by physiological heat treatment enabled reliable thermal jet printing of collagen solutions.

The addition of 1–2 wt.% collagen to the binder solution significantly improved the maximum flexural strength and cell viability (150%). To evaluate the bone healing efficacy, the 3D printed scaffolds were implanted into a femoral defect in mice for 9 weeks. The implants were confirmed to be osteoconductive, with a new bone layer comprising bioresorbable materials.

In Ref. [13], a highly printable hydroxyapatite (HAp) composite was developed, which included 60% HAp, 28% carboxymethyl chitosan (CMCT), 2% polyvinylpyrrolidone (PVP) and 10% dextrin. To prepare the samples,

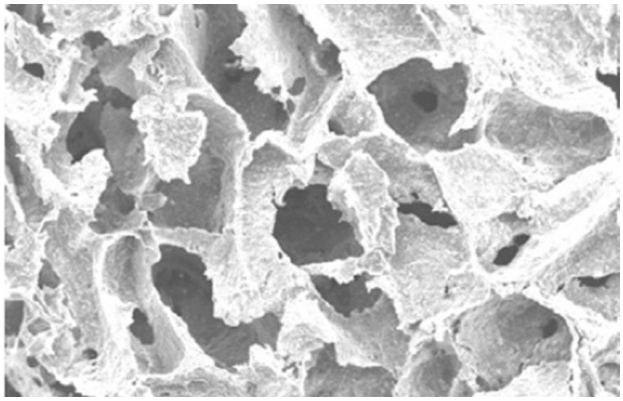

Fig. 2. Micrograph (60x) of PLGA/β-TCP scaffold. Adapted from Ref. [11].

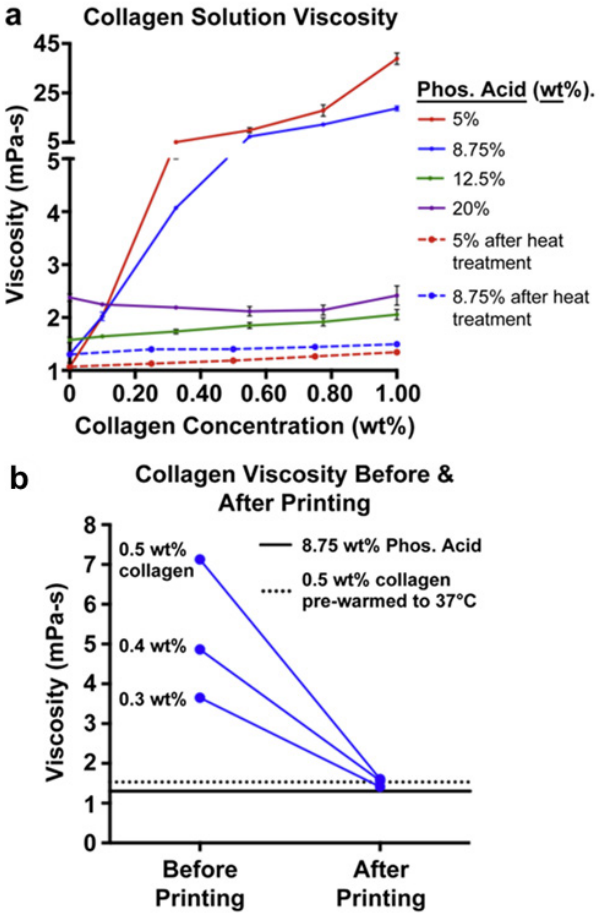

Fig. 3. Viscosity of collagen at 25 °C and a shear rate of 100 s^{-1}: (a) in phosphoric acid solutions; (b) before and after printing. Adapted from Ref. [12].

CMCT was first dissolved in distilled water, and then HAp powder was gradually added to the solution under mechanical stirring for 1 hour at 300 rpm. Then, the resulting suspension was mixed in a vibratory mill for 24 hours at 60 rpm and dried. According to the stress-strain curve, the elasticity modulus and compressive strength of the sample were 10 and 1.3 MPa, respectively, with the increase to 125 and 7.3 MPa after flash dipping. Sintering of printed

parts led to degradation of polymers. The method was developed for a hydroxyapatite composite with a high level of printability, which included 60% HAp, 28% CMCT, 2% PVP, and 10% dextrin. The strength of the printed sample was 1.3 MPa, while an HA-maltodextrin structure was reported with a green strength of 0.7 MPa in the literature. Flash dipping in the low viscosity solution of chitosan led to increasing compressive strength from 1.3 to 7.3 MPa, subsequently decreasing the level of porosity from 42 to 36% (Fig. 4).

According to the Ref. [14], the PCL-TIB system was proposed, obtained by combining 2,3,5-triiodobenzoic acid (TIB) with polycaprolactone (PCL). The created polymer matrix is characterized by increased strength with an elastic modulus of 42÷80 MPa (Fig. 5), as well as the viability of HUVEC cells after 24 hours of more than 88%. Scaffolds implanted in the chest cavity of mice showed long-term visibility in X-rays. Stents with a biodegradable contrast agent retained visibility for up to 20 days, which confirms their suitability for advanced clinical monitoring and use in tissue engineering.

Researchers [15] developed a poly-L-lactide (PLA) composite consisting of 76 wt.% of PLA, 19 wt.% of PCL, and 5 wt.% of microcrystalline cellulose (MCC) and tributyl citrate (TBC) in order to improve the toughness of PLA. The different additions of TBC based on PLA/PCL/MCC (PPM) composite weight were 0, 2, 4, 6, and 8 wt.%. Consequently, the resulting composites were annotated as PPM, PPM/2TBC, PPM/4TBC, PPM/6TBC, PPM/8TBC. Tensile performances of PPM and PPM/TBC composites are presented in Fig. 6.

With the addition of TBC, the strength, elongation at break, and toughness of the PPM/TBC composites were significantly enhanced, indicating an improved interfacial compatibility. MCC emerged as a more effective reinforcing agent, thus exhibiting superior performance without compromising of strength and stiffness of PPM.

In Ref. [16] composites of poly(butylene succinate) (PBS) and PLA were successfully fabricated. For the composite with 30 wt.% of PLA fibers, the Young's modulus increased to 749 MPa, which was 94% higher than that of pure PBS. This indicates that the PBS matrix was significantly strengthened by the addition of PLA fibers. The PBS/PLA fiber composites obtained by the simple melt blending method demonstrated a combination of increased strength and elastic modulus while maintaining the biodegradability of the PBS matrix.

The data [17] indicate the receipt of scaffolds chitosan (CH), collagen (Col) and nano-hydroxyapatite (nHA) loaded with crocin (Cro). The CH/Col/nHA scaffolds demonstrated interconnected porous structures with the mean porosity of 58÷90%. The cell study results indicated that the Cro loaded in scaffolds cause reduction in the Cro-

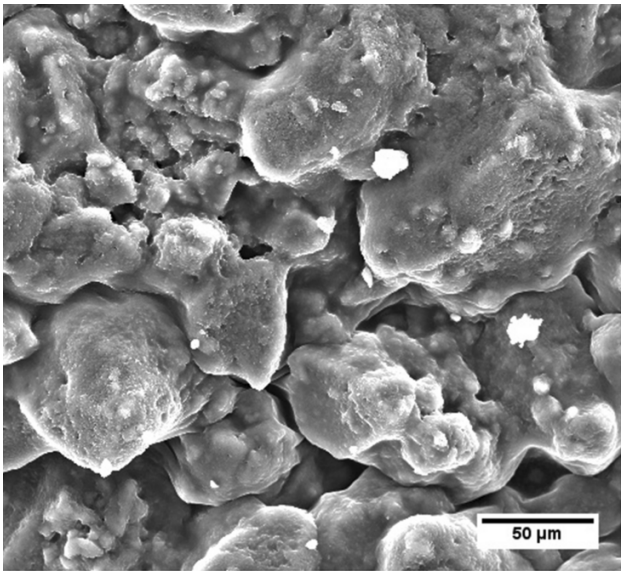

Fig. 4. SEM image of HAp/CMCT composite. Adapted from Ref. [13].

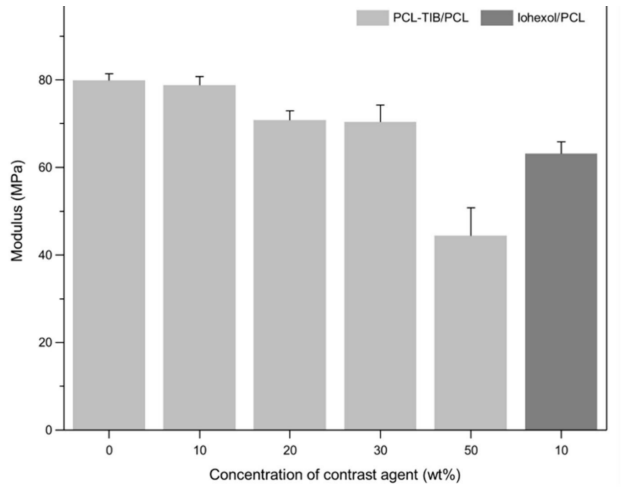

Fig. 5. Elastic modulus of the PCL-TIB scaffolds. Adapted from Ref. [14].

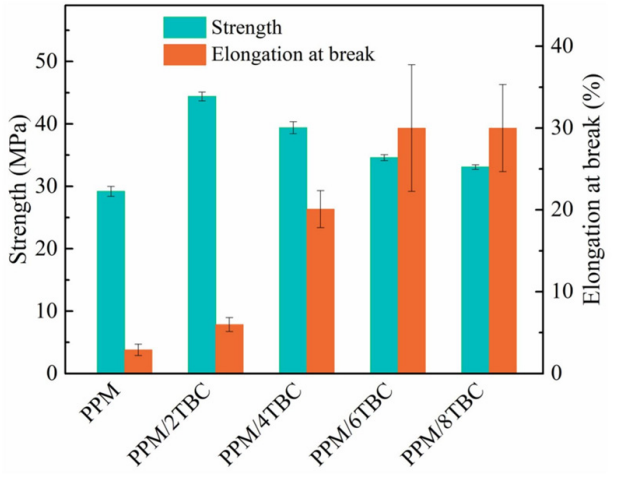

Fig. 6. Tensile strength and elongation at break of PPM scaffolds. Adapted from Ref. [15].

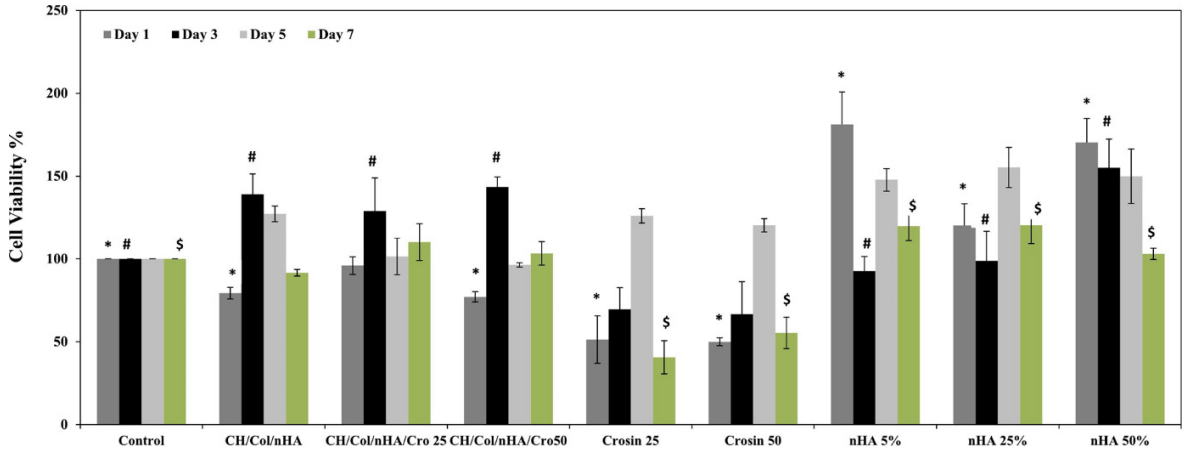

Fig. 7. Cell viability of CH/Col/nHA/Cro scaffolds. Adapted from Ref. [17].

Table 1. Key properties and the composition of the materials considered in this work.

System composition	Characteristics	Bioeffects	Reference
Poly-l-lactic acid (PLLA) (0.5÷4 wt.%), methacrylated poly (dodecanediol citrate) (mPDC) (10 wt.%)	Young's modulus (YM) is 969.55 MPa; the tensile strength (TS) reached 29.15 MPa	HUVEC cell viability after 24 h > 95%	[9]
PLA, hydroxyapatite (HAp)	Porosity 88.1÷98.2%, pore sizes: from 50 to 400 μm; YM was from 37.0 to 56.2 kPa, compressive stress at 40% deformation: 17.4÷280 kPa	The proliferation rate of MC3T3-E1 on scaffolds after 72 hours ranged from 307 to 1168%	[10]
PLGA, β-tricalcium phosphate (β-TCP)	Porosity 89.5÷91.4%, pore size from 75 to 400 μm; YM: from 1.49 ± 0.43 to 6.64 ± 1.03 MPa; TS: from 0.110 ± 0.058 to 0.296 ± 0.056 MPa	No data	[11]
CaP/Collagen	Viscosity from 1.01 ± 0.03 to 1.72 ± 0.04 mPa·s; Bending strength: 60 ÷ 80 kPa	C3H/10T1/2 cell viability was 150% after 72 hours	[12]
Hydroxyapatite, carboxymethylchitosan, polyvinylpyrrolidone, dextrin	YM: 125 MPa; TS: 7.3 MPa	No data	[13]
Polycaprolactone (PCL); 2,3,5-triiodobenzoic acid (TIB)	YM: 42÷80 MPa	HUVEC cell viability after 24 h is 88%	[14]
PLA, polycaprolactone (PCL), microcrystalline cellulose (MCC) and tributyl citrate (TBC)	TS: up to 45 MPa	No data	[15]
Poly(L-lactide) (PLA), poly(butylene succinate) (PBS)	For composites: YM up to 749 MPa, yield strength up to 39.7 MPa, elongation at break up to 344%	No data	[16]
Chitosan (CH), collagen (Col) and nano-hydroxyapatite (nHA) loaded with crocin (Cro)	TS: 0.468÷0.641 MPa	The burst drug release occurred after 5 h of incubation (ca. 46%); 110.2 ± 11.25 % of fibroblast (L929) cell viability after 7 days	[17]

toxicity. The cell viability of fibroblast (L929) for all components in composite structures of 3D printing and fabricated scaffolds are demonstrated in Fig. 7.

The toxicity of cells was not observed in fabricated scaffolds. The drug release profile showed that the burst release of the drug occurred after 5 h (ca. 46%) of incubation for both structures and then, it progressively leveled off to reach ca. 38% of total drug after 48 h of incubation. By loading 25 and 50 μl of crocin, the Young's modulus improved by 71% and 74%, respectively, compared to the free drug scaffold.

The main parameters, as well as the composition of the products considered in this work, are briefly summarized in Table 1 for the convenience of readers.

3. CONCLUSIONS

Thus, tissue engineering focuses on the regeneration of damaged tissues by creating bioresorbable materials. However, creating an ideal scaffold that meets the requirements for biocompatibility, mechanical strength, ease of fabrication, and cost-effectiveness remains a challenging and urgent task. Combining biopolymers to create composites with improved functionality has the potential to overcome the limitations of raw materials. Therefore, the discovery of new polymers and the study of existing systems will continue to be the focus of future research in the field of tissue engineering. Hybrid scaffolds that integrate bioresorbable polymers with various fillers will provide the desired mechanical strength while accelerating the healing process.

To summarize, the future of tissue engineering using bioresorbable polymers is very promising, given targeted advances in material development, fabrication technologies, and personalized medicine. New methods such as TIPS and BJT are expected to enable the creation of patient-specific scaffolds with precise pore architecture that can improve tissue integration and vascularization.

REFERENCES

[1] *Ageing and health. World Health Organization report for 2022*, Electronic resource, URL: https://www.who.int/ru/news-room/fact-sheets/detail/ageing-and-health (accessed 12.10.2024).

[2] R. Bauersachs, U. Zeymer, J.B. Brière, C. Marre, K. Bowrin, M. Huelsebeck, Burden of coronary artery disease and peripheral artery disease: a literature review, *Cardiovasc. Ther.*, 2019, art. no. 8295054.

[3] B. Gareb, N.B. Van Bakelen, A. Vissink, R.R.M. Bos, B. Van Minnen, Titanium or biodegradable osteosynthesis in maxillofacial Surgery? In vitro and in vivo performances, *Polymers*, 2022, vol. 14, №. 14, art. no. 2782.

[4] C. Li, C. Guo, V. Fitzpatrick, A. Ibrahim, M.J. Zwierstra, P. Hanna, A. Lechtig, A. Nazarian, S.J. Lin, D.L. Kaplan, Design of biodegradable, implantable devices towards clinical translation, *Nat. Rev. Mater.*, 2020, vol. 5, no. 1, pp. 61–81.

[5] M. Maintz, C. Tourbier, M. de Wild, P.C. Cattin, M. Beyer, D. Seiler, P. Honigmann, N. Sharma, F.M. Thieringer, Patient-specific implants made of 3D printed bioresorbable polymers at the point-of-care: material, technology, and scope of surgical application, *3D Print. Med.*, 2024, vol. 10, no. 1, art. no. 13.

[6] M. Dobrzyńska-Mizera, J.M. Dodda, X. Liu, M. Knitter, R.N. Oosterbeek, P. Salinas, E. Pozo, A.M. Ferreira, E.R. Sadiku, Engineering of Bioresorbable Polymers for Tissue Engineering and Drug Delivery Applications, *Adv. Healthcare Mater.*, 2024, art. no. 2401674.

[7] M.M. Farag, Recent trends on biomaterials for tissue regeneration applications, *J. Mater. Sci.*, 2023, vol. 58, no. 2, pp. 527–558.

[8] S. Vach Agocsova, M. Culenova, I. Birova, L. Omanikova, B. Moncmanova, L. Danisovic, S. Ziaran, D. Bakos, P. Alexy, Resorbable Biomaterials Used for 3D Scaffolds in Tissue Engineering: A Review, *Materials*, 2023, vol. 16, no. 12, art. no. 4267.

[9] H.O.T. Ware, T.Y. Ding, C. Collins, B. Akar, N. Akbari, H. Wang, C. Duan, G. Ameer, C. Sun, In situ formation of micro/nano phase composite for 3D printing clinically relevant bioresorbable stents, *Mater. Today Chem.*, 2022, vol. 26, art. no. 101231.

[10] K. Szustakiewicz, M. Gazińska, B. Kryszak, M. Grzymajło, J. Pigłowski, R.J. Wiglusz, M. Okamoto, The influence of hydroxyapatite content on properties of poly (L-lactide)/hydroxyapatite porous scaffolds obtained using thermal induced phase separation technique, *Eur. Polym. J.*, 2019, vol. 113, pp. 313–320.

[11] Y. Yang, J. Zhao, Y. Zhao, L. Wen, X. Yuan, Y. Fan, Formation of porous PLGA scaffolds by a combining method of thermally induced phase separation and porogen leaching, *J. Appl. Polym. Sci.*, 2008, vol. 109, no. 2, pp. 1232–1241.

[12] J.A. Inzana, D. Olvera, S.M. Fuller, J.P. Kelly, O.A. Graeve, E.M. Schwarz, S.L. Kates, H.A. Awad, 3D printing of composite calcium phosphate and collagen scaffolds for bone regeneration, *Biomaterials*, 2014, vol. 35, no. 13, pp. 4026–4034.

[13] F. Dini, S.A. Ghaffari, J. Javadpour, H.R. Rezaie, Binder jetting of hydroxyapatite/carboxymethyl chitosan/polyvinylpyrrolidone/dextrin composite: the role of polymeric adhesive and particle size distribution on printability of powders, *J. Mater. Eng. Perform.*, 2022, vol. 31, no. 7, pp. 5801–5811.

[14] Y.J. Jeong, B. Choi, S. Kim, J. Jo, A. Shanmugasundaram, S. Kang, H. Kim, E. Choi, D.W. Lee, Fully bioresorbable, all-polymer-based, 3D-printed scaffolds with prolonged radiopacity and enhanced durability, *J. Chem. Eng.*, 2024, vol. 494, art. no. 152851.

[15] G. Ye, X. Zhang, H. Bi, Construction of high-performance and sustainable polylactic acid composites for 3D printing applications with plasticizer, *Int. J. Biol. Macromol.*, 2024, vol. 269, art. no. 132162.

[16] J. Li, X. Wang, Y. Li, H. Hu, X. Liang, Rheological, thermal, and mechanical properties of poly (butylene succinate) (PBS)/poly (L-lactide) (PLA) fiber biodegradable green composites, *Colloid Polym. Sci.*, 2024, vol. 302, no. 7, pp. 1053–1066.

[17] N. Jirofti, M. Hashemi, A. Moradi, F. Kalalinia, Fabrication and characterization of 3D printing biocompatible crocin-loaded chitosan/collagen/hydroxyapatite-based scaffolds for bone tissue engineering applications, *Int. J. Biol. Macromol.*, 2023, vol. 252, art. no. 126279.

УДК 617.58–77

Тренды в разработке биорезорбируемых каркасов

Г.Р. Пецух, А.В. Подшивалов

Центр химической инженерии Университета ИТМО, Санкт-Петербург, 197101, Россия

Аннотация. В настоящее время биоматериалы получают всё больший спрос в медицине и являются основополагающими компонентами тканевой инженерии. Необходимыми факторами данных материалов, позволяющими обеспечить их способность эффективно функционировать в организме человека, являются биосовместимость, биоактивность, биорезорбция и нетоксичность. Идеальный имплантат должен иметь ряд физических, химических и биологических характеристик, чтобы стимулировать пролиферацию клеток, а также способствовать формированию тканей. Биорезорбируемые полимеры обладают преимуществами для применения в тканевой инженерии благодаря широкому спектру механических свойств в сочетании с достаточной химической инертностью и скоростью деградации. Учитывая увеличение числа исследований в области биоматериалов медицинского применения, целью данного обзора является изучение недавно разработанных имплантируемых материалов. В данной работе основное внимание уделено разработке состава полимеров, определяющих характеристики будущих биорезорбируемых материалов, а также выбору оптимальных параметров и способа их получения.

Ключевые слова: биорезорбция; TIPS; BJT; пролиферация; тканевая инженерия