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3D Printed Porous Scaffold Polymers Based on Polymerization-Induced Phase Separation and Their Applications in Biomedical Fields

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Abstract. The integration of polymerization-induced phase separation (PIPS) with three-dimensional (3D) printing provides a transformative strategy for fabricating porous scaffolds in biomedical applications. Unlike traditional 3D printing, which faces challenges in pore control and material diversity, PIPS enables in situ formation of interconnected networks without sacrificial templates, allowing tunable pore size, distribution, and connectivity across multiple scales. This review introduces the principles of PIPS and its coupling with advanced platforms such as digital light processing (DLP), emphasizing parameters that govern phase separation behavior. It further highlights functional polymer systems, including photosensitive, degradable, conductive, and antimicrobial composites, and analyzes how their compositions influence pore morphology and biological performance. By combining precise structural control with multifunctional materials, PIPS-based 3D printing supports the development of next-generation biomedical scaffolds with enhanced adaptability, biocompatibility, and potential for smart, sustainable designs.

Keywords: Polymerization-induced phase separation (PIPS), 3D printing, Porous scaffold polymers, Tissue engineering.

1. Introduction

With the rapid progress of tissue engineering and personalized medicine, there is increasing demand for advanced manufacturing technologies in the biomedical field. Three-dimensional (3D) printing, with its digital precision and on-demand fabrication capabilities, has significantly advanced biomedical material development. Its ability to build complex structures and customize medical devices makes it a key enabler in regenerative medicine and tissue engineering.

Traditional 3D printing materials and methods still face several challenges, including a limited range of printable materials, weak interlayer connectivity, and difficulty in simultaneously controlling macro- and micro-scale pore structures. Additionally, the bio-adaptability of printed products at the cellular level remains insufficient, hindering their broader application in demanding medical fields such as bone tissue engineering, nerve repair, and vascular scaffolds.

Recently, Polymerization-Induced Phase Separation (PIPS) has emerged as a promising strategy for fabricating porous scaffold functional materials. Without requiring sacrificial agents, PIPS offers

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precise control over pore size, distribution, and connectivity, while enhancing scaffold permeability and cell compatibility—opening new avenues for the development of advanced biofunctional materials [1].

Combining the PIPS mechanism with high-resolution light-curing 3D printing (e.g., DLP) enables the simultaneous construction of porous scaffold structures during the printing process, breaking the limitations of the traditional "print first, pore later" approach [2].

This fusion strategy has garnered significant attention in materials science and bioengineering. Studies show it enables dynamic control of pore sizes across nano- to millimeter scales, while offering excellent molding stability and structural reproducibility. This makes it a versatile platform for fabricating high-performance bioscaffolds, tissue models, and drug delivery systems.

This paper focuses on porous scaffold polymers fabricated by Polymerization-Induced Phase Separation (PIPS) combined with 3D printing. It introduces the underlying principles and preparation strategies, compares pore-forming techniques, discusses material development and structure–function relationships, and explores applications in tissue engineering, regenerative medicine, and environmental treatment. Finally, it outlines current challenges and future development directions.

2. Polymerization-Induced Phase Separation principle and technology development

Polymerization-Induced Phase Separation (PIPS) is an advanced material preparation method that induces microscopic phase separation and the formation of porous scaffold structures due to the thermodynamic destabilization of the system during the polymerization reaction. The process is essentially a synergistic combination of chemical polymerization and physical phase separation, and its formation mechanism involves the gradual growth of polymer chains in solution and the decrease of compatibility with the solvent, which triggers the separation of the polymer-enriched phase from the diluted phase [1].

2.1. Phase separation mechanisms and classification

PIPS can be categorized into two main mechanisms based on thermodynamic driving and kinetic pathways:

(1) Transient Phase Separation (Nucleation and Growth, N&G): during polymerization, the system rapidly enters a thermodynamically unstable region, leading to the local generation of multiple polymer-rich nuclei that continue to grow with the reaction. This process typically results in a dispersed pore structure with small, uniformly distributed pore sizes [3].

(2) Continuous Phase Separation (Spinodal Decomposition, SD): When the system slowly traverses the spinodal decomposition region, the whole forms a continuous interconnected phase separation network, making it easier to construct porous scaffold materials with well-connected, bicontinuous structures, which are suitable for the needs of cell permeation and material exchange in tissue engineering [3].

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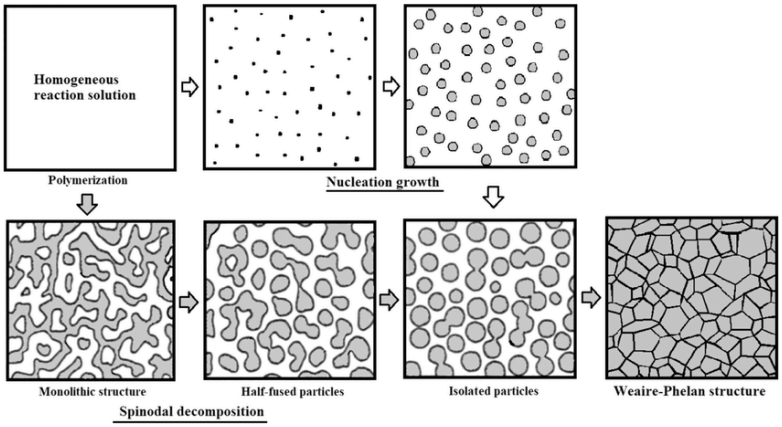

Figure 1. Microstructure formation pathways in PIPS: nucleation growth vs. spinodal decomposition [4]

Figure 1 illustrates the two main phase separation pathways in PIPS—nucleation and growth (N&G) and spinodal decomposition (SD)—highlighting how each leads to distinct porous scaffold scaffold structures that support applications like controlled drug release and tissue engineering.

2.2. Phase separation triggers and regulators

The occurrence of PIPS is highly dependent on the regulation of multiple parameters, and the key causal factors and regulatory pathways mainly include: [2,5]

(1) Polymerization reaction rate plays a key role in determining the phase separation behavior. A fast polymerization rate accelerates solvent incompatibility, enabling the system to quickly enter the phase separation window, while a slower rate allows for the development of smoother and more structurally regular pores.

(2) Changes in system composition, such as variations in monomer concentration, cross-linker ratio, solvent type, and solvent volatility, can significantly shift the phase diagram and influence the nature and timing of phase separation.

(3) External stimuli, including light intensity, temperature fluctuations, and solvent exchange, can alter both the polymerization rate and the viscosity of the solution, thereby affecting the morphology and size distribution of the resulting porous scaffold structures.

(4) Polymerization pathways coupled to solvent behavior also play a crucial role. In systems containing partially volatile solvents, selective solvent evaporation or diffusion may occur alongside polymerization, guiding the self-assembly of the pore network and enhancing structural control.

In addition, the visualization experiments and simulations of the PIPS process in novel studies reveal the effects of different reaction parameters on the phase structure evolution. For example, Merenda et al. utilized a multi-material DLP printing platform to construct functional gradient membrane materials containing both dense and porous scaffold regions, enabling structurally partitioned programmable fabrication [6].

2.3. Comparison with traditional porous scaffold fabrication techniques

Compared with other porous scaffold fabrication techniques, PIPS offers the following outstanding advantages:

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Table 1. Comparison of porous scaffold fabrication techiques in terms of procress, structure control, and biocompatibility

Technique	Process Workflow	Requires Pore-Forming Agent	Pore Structure Control	Biocompatibility	Drawbacks
Template Removal	Molding → Leaching → Sintering	Yes	Medium	Medium	Complex process
Foaming	Add foaming agent → Solidify	Yes	Poor	Poor	Uneven pore size
Freeze-Drying	Freezing → Sublimation	No	Medium	Good	High cost, long cycle
PIPS (This study)	Polymerization-Induced Phase Separation	No	High (multi-scale layered)	Excellent	High system design requirements

Table 1 summarizes key differences between traditional porous scaffold techniques and PIPS.

While methods like template removal and foaming rely on pore-forming agents and often suffer from poor control or biocompatibility, PIPS stands out with agent-free processing, high multi-scale pore control, and excellent biocompatibility. These advantages, as emphasized in the accompanying text, make PIPS especially powerful when integrated with DLP-based 3D printing, enabling precise, efficient, and structurally continuous scaffolds—ideal for biomedical applications like controlled drug delivery and tissue regeneration.

PIPS not only avoids the problem of sacrificial agent residue, but also forms a structure with more connectivity and mechanical continuity; especially after combining with Digital Light Processing (DLP) technology, it can realize the synchronous process of “photopolymerization-phase separation-setting”, which greatly improves the printing accuracy and manufacturing efficiency. Precision and Manufacturing Efficiency [2,5]

In summary, PIPS, as a highly integrated and adaptable means of structural control, provides a new fabrication paradigm for 3D printing porous scaffold polymer construction, and becomes one of the key technologies to drive the development of next-generation biofunctional materials.

3. Development and optimization of functional materials for 3D printing

In the process of fusion of Polymerization-Induced Phase Separation (PIPS) and three-dimensional printing technology, the rational construction and performance regulation of material systems are the core of realizing structural design and functional output. Whether it is a light-curing printing platform or a heat-induced melt-printing process based on thermal induction, the performance of functional polymer materials directly determines the formation mechanism of pore structure, the stability of print molding, and the bio-responsiveness in subsequent applications. Therefore, the development of tunable high-performance resin systems, the construction of multi-component composite platforms, and the realization of the synergistic design of materials and process parameters are the key breakthroughs to promote the application of PIPS-3D printing technology in the direction of biomedical applications [7].

3.1. Optimization of formulations and performance enhancement of light-curing systems

Light-curing based printing methods such as digital light processing (DLP) and stereolithography (SLA) are widely used in PIPS structure printing due to their high precision, high resolution and

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scalability. Among them, the bisphenol A-based epoxy acrylate resin system has excellent photosensitivity and molding stability, which makes it one of the current mainstream basic formulations. The polymerization rate and the degree of synergy of the phase separation process can be significantly affected by adjusting the monomer species and functional group ratio.

For example, dilute monomers with flexible chain segments can help relieve crosslinking shrinkage stress and improve interlayer adhesion, while structural monomers with high crosslink density can enhance thermal stability and final mechanical properties [8].

In addition, variations in initiator type (e.g., TPO vs. 1176) and concentration significantly affect the light curing rate and phase separation window width, thus indirectly regulating the scale and distribution of the final pore structure [9].

To further enhance the structural integrity of the cured structure, the researchers developed a dual photo-thermal curing system, i.e., initial curing of the morphology by DLP printing, and then applying a heat treatment to achieve a further increase in cross-linking degree. This strategy not only enhances the interlayer bonding strength but also improves the structural integrity of the aperture edges, which is particularly suitable for the stable fabrication of large-sized and complex scaffolds [10]. The construction of this dual-curing system also broadens the material applicability and enhances the adaptability to resins with different viscosities or polarities.

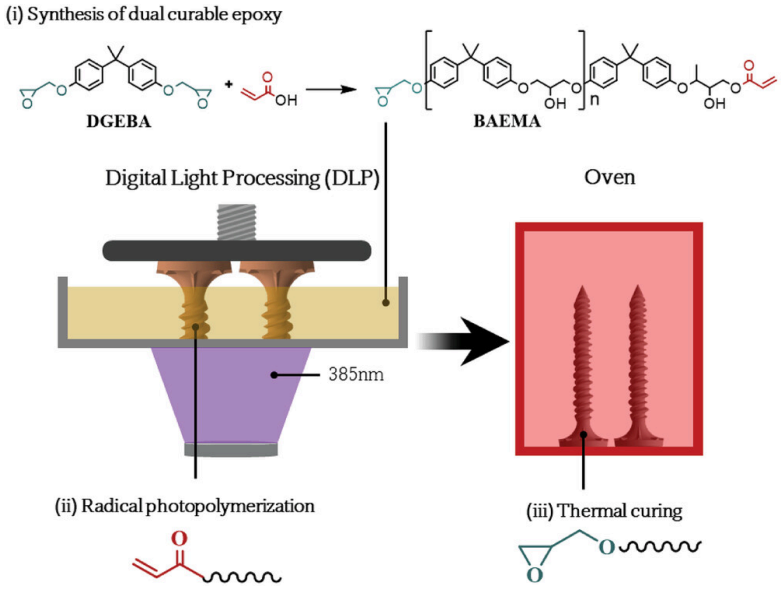

Figure 2. Schematic illustration of dual-curable epoxy fabrication and processing via DLP printing and thermal curing [11]

Figurec 2 illustrates the dual-curing strategy described in the text, where DLP printing enables precise initial photopolymerization, followed by thermal curing to enhance cross-linking. This process improves interlayer bonding, pore edge integrity, and material adaptability—key for producing robust, large-scale porous scaffolds with fine-tuned microstructures.

3.2. Composite applications of thermosetting and degradable polymers

Single synthetic polymers often have shortcomings in terms of biocompatibility, degradability, or functional responsiveness, so in recent years a great deal of research has turned to composite design to enhance the biomedical suitability of systems by synergistically integrating thermoset polymers with natural or functional materials [12].

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Polyethylene glycol (PEG) has been widely introduced into PIPS systems not only as a good phase separation inducer, but also to improve the hydrophilicity and cellular affinity of the materials.

Polycaprolactone (PCL), on the other hand, is used as a structural support framework due to its slow and controlled degradation and good thermoplasticity, which is particularly suitable for bone tissue engineering applications. When composite with hydroxyapatite (HA), the scaffolds not only have good osseointegration, but also can guide the migration and mineralization of osteoblasts [13].

In addition, natural macromolecules such as collagen and gelatin are rich in biorecognition sequences that promote cell adhesion, proliferation and exosome activity, and are often added to scaffolds as a functional layer wrapping or composite phase [14].Two-dimensional nanomaterials such as graphene and MXene are also gradually being introduced into the PIPS printing system to enhance the conductivity, antimicrobial properties and mechanical strength of the scaffolds, which is particularly suitable for scenarios with special requirements for signaling in neural or skin tissue engineering.

The strategy of multi-component composite not only realizes the multi-dimensional regulation of mechanical, thermal, optical, and biological properties, but also makes the PIPS phase behavior richer. For example, material systems with large hydrophilic and hydrophobicity differences and polarity differences can easily induce clear interfacial structures and form pore networks with a high degree of order, which is favorable for nutrient transport, cell migration and drug delivery [15].

3.3. Material-dominant factors in the regulatory mechanisms of phase separation

In the PIPS process, the material system dictates the phase separation mechanisms such as spinodal decomposition or nucleation and growth—which in turn influences pore formation rate, morphology, and connectivity. Systems like PEG/DEX or epoxy acrylates allow dynamic pore size regulation (10 nm to 1000 μm) by adjusting monomer types, hydrophilic–hydrophobic balance, viscosity, and thermodynamic parameters. Cross-linking density also plays a crucial role: higher densities enhance structural rigidity for load-bearing applications like bone or cartilage scaffolds, while lower densities favor elastic networks suited for soft tissue engineering and injectable designs [5].

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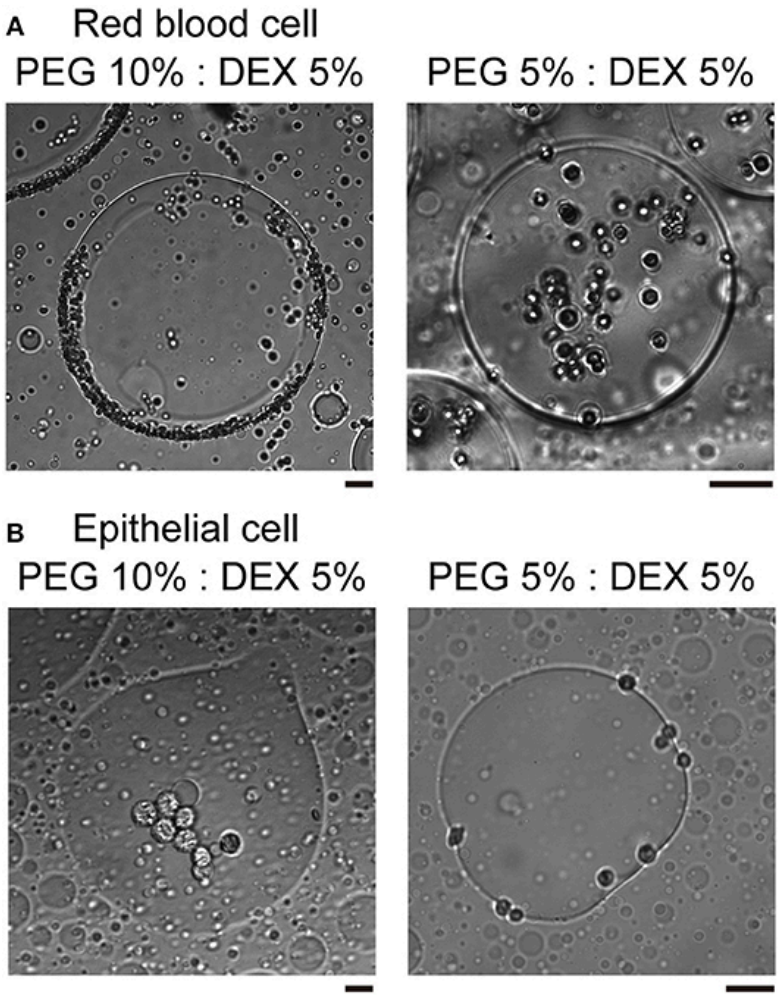

Figure 3. Visualization of phase separation and cell distribution in PEG/DEX aqueous two-phase systems with varying compositions [16]

Figure 3 supports the text by showing how varying PEG/DEX compositions influence phase separation and cell localization, emphasizing that material composition and crosslinking density directly impact pore structure and biological performance—critical for designing application-specific scaffolds in PIPS systems.

The latest research also combines real-time optical imaging with PIPS to "visualize phase separation" using fluorescent markers and phase-separating dyes to optimize formulation design and process windows. Such strategies enhance the predictability of the phase behavior of the system, and provide theoretical support and practical access to personalized structural design and stable batch manufacturing [7].

4. Modulation of porous scaffold structure and design of pore size structure

Porous scaffold structure is not only the core expression of Polymerization-Induced Phase Separation (PIPS) systems, but also the basis for scaffolds to realize their functions in biomedical scenarios. The pore size, pore connectivity, hierarchical structure and its arrangement significantly affect the physiological processes such as cell adhesion, diffusion, migration, angiogenesis, nutrient transport and so on [17]. Therefore, realizing precise regulation of pore structure, especially cross-

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scale and multifunctional synergy, is one of the core objectives of the current 3D printing-phase separation composite manufacturing strategy [18].

4.1. Correspondence between pore size classification and biological functions

Different sizes of pores have different functions in tissue engineering, and studies have generally concluded that micropores (<10 μm) are mainly beneficial for cell adhesion, providing anchoring sites and initial signaling pathways; mesopores (10-100 μm) are suitable for cell migration, intercellular communication, and microtissue formation; and macropores (>100 μm) are crucial for angiogenesis, tissue reconstruction, and exchange of macromolecular nutrients and waste products [17].

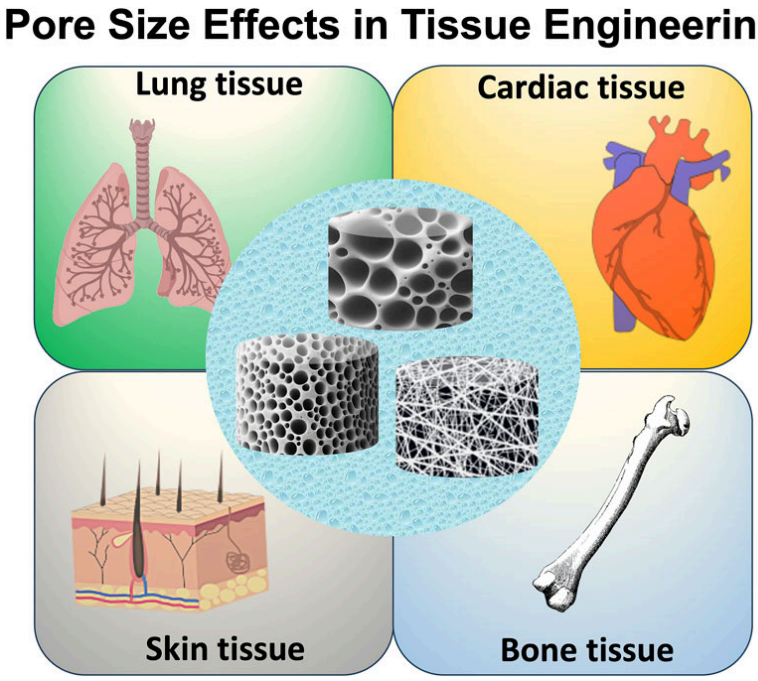

Figure 4. Pore size effects on different tissue types in tissue engineering [19]

This figure visually reinforces the text by showing how different pore sizes serve distinct biological roles across tissue types—highlighting the importance of designing scaffolds with multi-scale, interconnected pores to support cell adhesion, communication, and tissue regeneration in applications like bone or cardiac repair.

Taking bone tissue engineering as an example, macropores can form a good basis for vascularization, mesopores facilitate the spatial extension of bone progenitor cells, and micropores promote the formation of early calcification and mineralization. Therefore, an ideal bone scaffold should contain multiple size levels of pores that are highly interconnected in three dimensions to mimic the functional and structural hierarchy of natural bone tissue [20].

4.2. Importance of pore connectivity and hierarchical structure

In many natural tissues, pores are not homogeneous and isolated, but present a multi-layered, multi-scale hierarchical structure that simultaneously fulfills the physical support and biological transport functions required for cell survival. The liver, alveoli, or spongy bone, for example, have a complex

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network of channels that provide spatial scaffolding for material exchange, cellular arrangement, and tissue regeneration [21].

The multistage phase separation mechanism of PIPS can naturally form such hierarchical nature, especially in low polymerization rate, gradient solvent volatilization or multi-monomer systems, where the phase separation can exhibit spontaneous hierarchical gradation, leading to the formation of microporous-medium-porous-macroporous coexisting structural units. It is shown that this bionic hierarchical structure, built from the bottom-up, can more effectively guide cell chemotaxis behavior and enhance the tissue integration of the scaffolds [16].

In addition, to further improve the connectivity, some studies have adopted a dual network strategy, i.e., a two-step PIPS process or composite light-field printing to guide the formation of a pore network with a main channel and side-branch structure for distributed nutrient flow and cell invasion [6].

4.3. Pore size dynamic regulation strategies and programmable structure generation

Porous scaffold structures constructed by traditional static template or sacrificial agent methods often lack flexibility in pore size control. In contrast, PIPS combined with 3D printing enables “dynamically programmable” control of pore size through the modulation of multiple process parameters. The main parameters include: [5]

(1) Light intensity and exposure time directly influence the photopolymerization rate, which in turn determines the initiation and termination of phase separation, thereby enabling control over the resulting pore size.

(2) Monomer type and ratio govern the tendency for phase separation and compatibility with the solvent, ultimately shaping the distribution and morphology of the pore structure.

(3) Temperature and viscosity change rate affect the diffusion dynamics and the formation rate of phase boundaries, which influences the fineness and complexity of the pore architecture.

(4) Multi-field or multi-material printing technologies enable spatial zoning of the printed structure, allowing for the simultaneous fabrication of regions with varying pore sizes to meet diverse functional needs within a single scaffold.

For example, a recent study has realized the formation of functional gradient scaffolds with multilevel pore sizes ranging from 10 μm to 300 μm in the same layer of structure by adjusting the light intensity in real time in DLP printing, which can be used to model structural transitions from cortex to cancellous bone [6].

5. Progress in biomedical applications

The emergence of Polymerization-Induced Phase Separation (PIPS) in combination with 3D printing technology has brought a completely new structural fabrication strategy and functional realization to the biomedical field. The porous scaffold polymer materials fabricated through this technology not only achieve breakthroughs in geometric scale and structural complexity, but also endow the materials with unique mechanical, biological and chemical properties, which enable them to be widely used in a variety of directions, such as in vitro 3D cell cultures, tissue-engineered scaffolds, neural and cartilage regeneration, targeted drug release, and antimicrobial therapeutics. In addition, the high specific surface area and tunability of porous scaffold polymers also show great potential in emerging cross-cutting areas such as environmental treatment and biosorption [2].

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5.1. In vitro three-dimensional cell culture and disease modeling

Compared with traditional 2D culture, 3D culture systems can more realistically simulate the in vivo microenvironment, reflecting the spatial behavior, mechanical responses, and gene expression patterns of cell [22]. Porous scaffolds prepared using PIPS-3D printing can promote cell adhesion, migration and differentiation in three-dimensional space due to their good connectivity and pore size distribution [23].

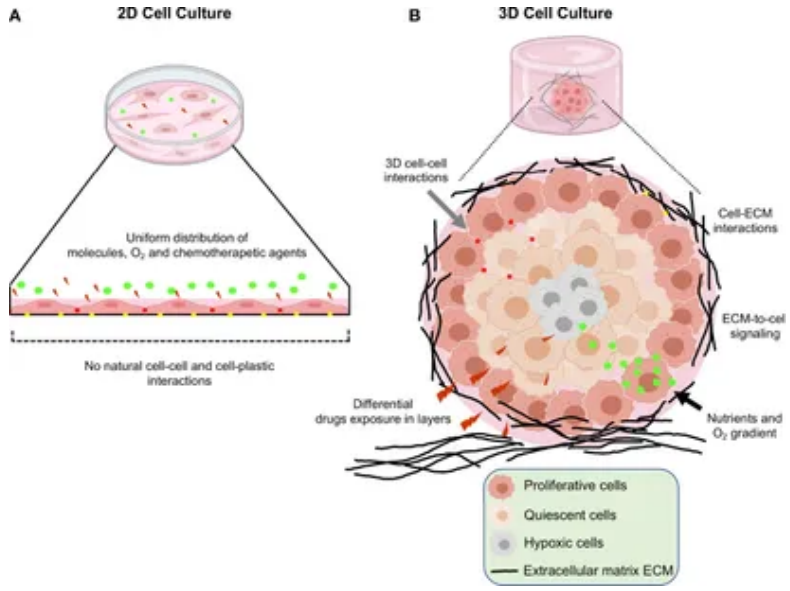

Figure 5. Comparison between 2D and 3D cell culture models in terms of structure and biological behavior [24]

This figure supports the text by illustrating how 3D cell culture—enabled by PIPS-printed porous scaffolds—better mimics in vivo environments than 2D models, allowing more realistic cell–ECM interactions, nutrient gradients, and spatial cell behaviors essential for disease modeling and tissue engineering.

5.2. Tissue engineering scaffolds and regenerative medicine applications

PIPS structural scaffolds are promising for a wide range of applications in the field of tissue engineering such as bone, cartilage, nerve and skin. Its excellent pore connectivity and mechanical suitability make it an ideal template for mimicking natural tissue structures [19].

In bone tissue engineering, PCL/HA/Collagen multicomponent scaffolds constructed multi-scale pore structures through synergistic phase separation, which not only improved the adhesion and expansion of bone progenitor cells (BMSCs), but also enhanced the mineralization deposition rate. In addition, by introducing a gradient pore design into the printed scaffolds, the mechanical and nutritional gradients between cortical and cancellous bone could be simulated to enhance the integration ability and mechanical stability of the scaffolds [20].

In nerve repair, the combination of conductive composites and lamellar pores promotes axonal regeneration of nerve cells under applied electrical stimulation, and the scaffold not only provides physical guidance, but also enhances electrical signaling and functional recovery [25].

For cartilage or skin tissues, PIPS scaffolds provide suitable microenvironmental support for soft tissue regeneration by modulating the flexible network and pore pliability, which can reduce scar

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formation and promote inward migration of endogenous cells [26].

5.3. Smart drug delivery and anti-infective applications

The large specific surface area, tunable structure, and high interfacial activity of porous scaffold polymers make them high-quality candidates for drug-carrying systems. Fine regulation of drug release rate can be achieved by modulating the pore size and surface chemical modification [27].

Recent studies have developed multiple responsive drug release platforms: temperature-responsive scaffolds to accelerate drug release upon local warming of body temperature or inflammation; pH-responsive scaffolds to precisely release anticancer drugs in the micro-acidic environment of tumors, thereby enhancing targeting efficiency and reducing toxic side effects [28].

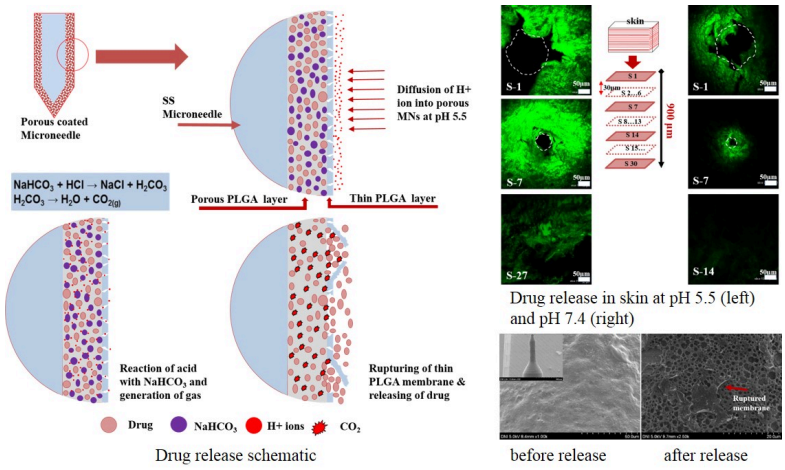

Figure 6. Schematic and visualization of pH-responsive porous scaffold microneedle drug release and skin penetration behavior [29]

This figure illustrates the pH-responsive drug release mechanism described in the text, showing how porous scaffold microneedles release drugs in acidic environments and effectively penetrate skin—supporting smart delivery and antimicrobial applications through tunable porosity and surface chemistry in PIPS-based scaffolds.

In addition, loading antimicrobial peptides, silver ions or zinc oxide nanoparticles into the porous scaffold structure of PIPS can endow the scaffolds with long-term bacteriostatic properties, which are widely used in postoperative infection prevention and control, chronic wound dressing and oral implant materials. The study shows that these scaffolds can effectively inhibit the growth of Staphylococcus aureus and Escherichia coli without affecting cellular activity [30].

5.4. Cross-cutting applications of biosorption and environmental medicine

In addition to traditional medical applications, the structural advantages of PIPS porous scaffold polymer materials have been expanded to the fields of biosorption and environmental pollution control. high porosity scaffolds constructed by Dong et al. show excellent adsorption of oil pollutants, with an oil absorption rate as high as 15-30 times of their own mass and good selectivity. These materials are expected to be used as functional materials for medical waste liquid treatment devices and operating room liquid removal devices, which will promote the technological progress of green healthcare [31].

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Some studies have also combined the specific surface area of porous scaffold polymers with the immobilization capacity of biological enzymes to develop microreaction platforms for in vitro assays and molecular sieving, providing a new material base for biosensors and lab-on-a-chip systems [32].

6. Current challenges and future directions

Although the convergence of Polymerization-Induced Phase Separation (PIPS) and 3D printing technology has opened up a new path for the application of porous scaffold polymers in the biomedical field, there are still a series of engineering, biological, and systemic challenges to move from laboratory research to clinical application and industrialization.

These issues involve multidimensional design of material formulations, molding mechanisms, bio-adaptability, manufacturability at scale, and functional integration, and must be considered comprehensively for practical applications [33].

6.1. Material system suitability and print window limitations

Current material systems suitable for PIPS-3D printing are still limited, in particular, there are still bottlenecks in materials that combine photosensitivity, phase separation capability, biosafety and mechanical suitability [34]. For example, some monomers with good phase separation (e.g., some epoxy resins) may suffer from incomplete light-curing reactions, poor print stability, or degradation product biotoxicity.

In addition, differences in viscosity, charge density, thermal conductivity and other physical parameters between different materials often lead to delamination, interfacial discontinuities or differences in the degree of curing in multi-material co-printing, thus affecting the molding accuracy and long-term stability of the overall structure.In the future, it is necessary to develop new monomers and cross-linkers with triple control of structure-reaction-biology for PIPS systems, so as to form a broader platform for material adaptation [35].

6.2. Interlayer bond strength and macrostructural stability issues

As the 3D printing process usually adopts a layer-by-layer construction method, the quality of inter-layer fusion directly affects the overall mechanical properties and long-term stability of the scaffold [36]. Microphase separation in the PIPS process is prone to form stress concentration zones at the interlayer interfaces, especially in complex structures or gradient porous scaffold regions, and if the phase separation does not match the photopolymerization kinetics, defects such as delamination, bubble entrapment, or pore closure are prone to occur.

In addition, there is still a lack of systematic evaluation of the fatigue performance of scaffolds under deformation, compressive or shear loading conditions in wet environments. When used for applications such as in vivo mechanical supports (e.g., bone, cartilage), ensuring load-bearing capacity while maintaining porosity and permeability is a central challenge in material design and process optimization [37].

6.3. Lack of in vivo degradation behavior and biosafety assessment

Although many degradable polymers (e.g., PCL, PEG, PLA, etc.) have been used for 3D printing scaffold construction, there are still many unknowns about their degradation behavior in the PIPS system [38]. For example, do phase interfaces formed during polymerization alter degradation

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pathways? Do structural heterogeneities induced by phase separation lead to localized inhomogeneous degradation? Are scaffold degradation products likely to induce local acidification or immune responses? These questions still lack systematic validation in animal models and long-term follow-up evaluation [39].

In addition, for some composites (e.g., containing nano-additives such as graphene and nano-silver), their possible bioaccumulation and toxicological effects during degradation still need to be alerted. The future development needs to strengthen the research on the coupling mechanism of structure-property-biological response, introduce higher throughput cell/animal evaluation system and multi-scale simulation methods, and provide data support for clinical safety [40].

6.4. Difficulty in realizing multi-material synergistic printing and integrated functional structures

Most of the current functions of porous scaffold polymers rely on the passive properties of the materials themselves, and how to realize multi-material synergistic construction and integrated response functions (e.g., conductive, photosensitive, magnetically responsive, and antimicrobial, etc.) is still in the exploratory stage [41].

Ideally, the future 3D printing platform should have: multi-material synchronized feeding, spatially partitioned printing, multi-physical field control and self-feedback control system. For example, in the same scaffold integrated electrical response area (conductive polymers), drug release area (pH response), support area (high-modulus materials) and bioactive area (natural proteins), etc., to achieve “structure-function-response” integrated design [42].

6.5. Development needs for intelligent, adaptive and regenerative feedback systems

Future tissue engineering not only needs static scaffolds, but also “active scaffolds” with intelligent response, signal sensing and regeneration regulation. At present, preliminary attempts have been made to introduce smart hydrogels, dynamic crosslinked polymers and other materials into the PIPS structure to realize stress-induced pore size changes, drug release under electric field stimulation, etc., but they are still in the experimental verification stage.

At the same time, how to translate in vitro signals (e.g., microfluidics, mechanical stress) into real-time parameter adjustments during the printing process, realizing “closed-loop printing” (Closed-loop printing), is an important direction to promote high-throughput intelligent tissue fabrication [43]. For example, the adaptive regenerative scaffold system of “print-grow-regulate” can be realized by adjusting the evolutionary path of pore structure through the feedback of cell behavior.

6.6. Trends in technology development

With advances in material design and printing processes, PIPS has progressed beyond traditional thermotropic separation to incorporate photo-, field-, and electro-induced mechanisms. Emerging developments include intelligent PIPS systems responsive to stimuli like pH, temperature, or light for tunable pore structures; the incorporation of biomolecules such as gelatin or collagen to enhance cell affinity; and the use of visualization and simulation tools to guide precise structure design. As a versatile and integrated method for structural control, PIPS offers a promising strategy for fabricating next-generation biofunctional porous scaffold polymers via 3D printing [9,44].

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6.7. Trends in the integration of structural biomimicry and functional design

Pore structures serve not only as geometric frameworks but also as functional components in tissue regeneration. Bionic designs—such as bone-like spongy, lung-like honeycomb, or liver-inspired cavity-tube structures—enhance mechanical support and biological performance. Recent advances emphasize "structure-function integration," incorporating features like conductivity, antimicrobial activity, and responsiveness into scaffolds. For instance, conductive nanoparticles can enable electrical stimulation for nerve repair, while antimicrobial agents support localized immune regulation. These multifunctional, responsive porous scaffold systems offer promising directions for next-generation bioscaffold design in complex tissue engineering and regenerative medicine [45].

7. Conclusion

This review summarizes the mechanisms, material systems, and pore modulation strategies of PIPS-3D printed polymers, highlighting their biomedical applications in 3D cell culture, tissue regeneration, drug delivery, and infection control.

The integration of Polymerization-Induced Phase Separation (PIPS) with 3D printing represents a major advancement in the fabrication of porous scaffold functional materials. By coupling material phase behavior with digital layer-by-layer construction, this approach enables precise and programmable control of pore scale, morphology, and distribution, overcoming limitations of traditional methods and offering a flexible platform for multifunctional structure design [2].

Despite these advances, challenges remain in material compatibility, process stability, and long-term biosafety. Future development will focus on high-throughput manufacturing, intelligent response systems, AI-driven design, and sustainable materials. As the technology matures, PIPS-based porous scaffold polymers are expected to evolve into active, responsive platforms for precision medicine, tissue engineering, and environmental applications [38].

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