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Recent advances in polymer-modified poly(lactic acid) for tissue engineering applications

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Poly(lactic acid) (PLA) is one of the most widely used biodegradable polymers for tissue engineering due to its biocompatibility, processability, and favorable mechanical strength. However, its intrinsic brittleness, hydrophobicity, and limited control over degradation and biological signaling require extensive modification. This review summarizes recent advances in polymer-based modification strategies that tailor PLA for tissue engineering applications. We systematically discuss physical blending, chemical copolymerization, and bulk and surface grafting, emphasizing how each approach regulates mechanical behaviour, degradation kinetics, surface bioactivity, and process compatibility across films, fibres, and three-dimensional scaffolds. Particularly, we discuss emerging liquid crystalline modification strategies that introduce intrinsic molecular order beyond conventional isotropic composites. By comparing structure–property–function relationships of molecularly programmed, multifunctional PLA platforms across various modification routes and fabrication methods, this review highlights current limitations and outlines future opportunities capable of meeting the complex demands of tissue engineering applications.

1. Introduction

Poly(lactic acid) (PLA) is a thermoplastic polymer derived from renewable resources such as corn and sugarcane through the fermentation of plant starch.[1] It is commonly synthesized by either direct polycondensation of lactic acid or ring-opening polymerization of lactide.[2] Direct polycondensation involves dehydration and condensation of lactic acid monomers. However, the water generated during the reaction is difficult to remove, thereby limiting the achievable molecular weight and resulting in inferior material performance.[3] Consequently, this route is rarely used for the production of high-performance medical-grade PLA.[4] Ring-opening polymerization employs the conversion of lactic acid into the cyclic dimer lactide, followed by polymerization using catalysts such as stannous octoate. This method represents the primary industrial route for medical-grade PLA, as it allows precise control over molecular weight and chain architecture, thereby tuning degradation behaviour and mechanical strength.[5,6] PLA exists in several stereochemical forms, including poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA), and racemic poly(D,L-lactic acid) (PDLLA), each with physical properties that strongly depend on their stereochemistry and molecular weight.[7] Unless otherwise stated, the modifications discussed herein pertain to PLLA.

From the discovery of lactic acid in 1780, through the development of PLA by Wallace Carothers in 1932, and to the recognition of its medical potential in 1966, PLA has gradually emerged as one of the most widely used polymers in biomedical applications. The macroscopic mechanical properties of PLA are fundamentally governed by its molecular weight and polydispersity index.[8] Robust mechanical performance requires the molecular weight to significantly exceed the entanglement threshold ($\sim$9000 g mol^{-1}).[9,10] Tsuji established molecular weight as the primary determinant for stereocomplex crystallization. While low-molecular-weight PLLA and PDLA readily form exclusive stereocomplex crystals with high melting points ($\sim$230 °C) that markedly enhance macroscopic thermal resistance, high-molecular-weight variants ($>$100 000 g mol^{-1}) suffer from chain entanglement.[11] This chain entanglement impedes molecular diffusion and pairing, resulting in a mixture of homocrystals and stereocomplex crystals that compromises the polymer's overall thermal stability. However, PLA is highly susceptible to thermal degradation during processing, which can drastically reduce its molecular weight to below 40 000 g mol^{-1} and lead to a severe drop in tensile strength.[12] Utilizing stabilizers such as polycarbodiimides can effectively maintain the molecular weight above 90 000 g mol^{-1}, thereby preserving the tensile strength at approximately 60 MPa.[13] Furthermore, polymer chain architectural modifications that alter the molecular weight distribution play a crucial role.

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Modifying linear PLA (typical polymer dispersity <2.0) *via* reactive extrusion to introduce long-chain branching broadens the polydispersity index. This structural evolution significantly induces melt strain-hardening and enhances solid-state elongation while largely maintaining the high elastic modulus.[12]

Due to its biocompatibility, biodegradability, favourable processability, and relatively high mechanical strength, PLA is now considered as a representative biodegradable material for medical use.[7,14] *In vivo*, PLA degrades into lactic acid, which enters normal metabolic pathways and is safely eliminated, resulting in minimal toxicity.[2,5,15–18] PLA exhibits a tensile strength in the range of 50–70 MPa,[19] comparable to that of bone and higher than that of many other biodegradable polymers.[20,21] As a thermoplastic polymer, PLA is compatible with conventional and advanced processing techniques, including injection moulding, extrusion, fibre spinning, and three-dimensional (3D) printing. PLA is a semicrystalline polymer with good optical transparency. Notably, PLLA exhibits piezoelectric behaviour arising from the orientation of C=O dipoles within its crystalline structure.[22,23] Under mechanical stress, PLLA generates electrical charges, a property that is particularly relevant to bone and nerve regeneration, where electrical cues have been shown to promote cell growth and differentiation.[24]

Despite these advantages, pristine PLA suffers from several intrinsic limitations, including low impact toughness, low hydrophilicity, a narrow processing window, and slow degradation rates.[25] Pristine PLA typically shows a low elongation at break of approximately 5%, reflecting pronounced brittleness and poor impact resistance that restrict its use in load-bearing applications.[26] The polymer surface is highly hydrophobic, with water contact angles of approximately 75–80°, and PLA fibrous membranes often exhibit contact angles exceeding 120° that lead to poor cell adhesion and an increased risk of inflammatory responses.[27,28] As a semicrystalline polymer, the degradation behaviour of PLA is strongly influenced by crystallinity. Molecular weight governs degradation kinetics by modulating end-group density and chain entanglement, with high-molecular-weight PLA exhibiting a prolonged induction period.[29,30] In contrast, low-molecular-weight PLA features a higher density of carboxyl end-groups, facilitating the rapid formation of localized acidification and triggering non-linear autocatalytic acceleration. Polydispersity further regulates this process: a broad molecular weight distribution introduces short-chain oligomers that hydrolyze and diffuse rapidly, causing premature loss of mechanical integrity.[29] Furthermore, stereocomplexation between PLLA and PDLA creates a dense physical barrier. This crystalline structure effectively retards the penetration of water and enzymes, significantly extending the degradation cycle compared to amorphous or homocrystalline PLA.[31] Highly crystalline PLA may degrade very slowly over periods of up to 2–3 years,[11] which is unsuitable for tissues that require rapid healing.[32,33]

With the continuous increase in human life expectancy, the urgency of addressing diverse medical challenges has become increasingly apparent. Tissue engineering, as an interdisciplinary field integrating engineering and biology, aims to maintain, restore, or enhance tissue function through the synergistic integration of scaffolds, chemical cues, and biologically active cells.[34] In this context, biomaterials play a central role by providing mechanical support while simultaneously acting as 3D templates for cell adhesion and proliferation,[35,36] followed by controlled degradation upon the formation of new tissue.[5,35,37] Consequently, materials used for tissue engineering must meet exceptionally stringent criteria. Foremost among these criteria is biocompatibility, along with antimicrobial properties and the absence of toxicity, mutagenicity, teratogenicity, antigenicity, and carcinogenicity, to avoid inducing local or systemic pathological responses.[38–41]

PLA has emerged as one of the most widely used biodegradable polymers in medical applications because its degradation product, lactic acid, can be naturally metabolized by the human body, ensuring a high level of biosafety.[42] However, to meet the multifunctional demands of tissue engineering, extensive efforts have been devoted to modifying PLA to overcome its intrinsic brittleness, hydrophobicity, and mismatch between degradation rate and tissue regeneration.[19,43] Recent studies have shown that incorporation of low molecular weight plasticizers, such as citrate esters and glycerol, can effectively reduce the glass transition temperature (T_g) and increase chain mobility and toughness.[44] In parallel, inorganic nanofillers, including hydroxyapatite,[45] bioactive glass,[46,47] carbon nanotubes,[48,49] and carbon fibres[50,51] have been frequently incorporated into PLA matrices to enhance osteoconductivity and mechanical strength.[52]

Although these approaches have demonstrated certain benefits in drug delivery systems and specific orthopedic applications,[18] their limitations become increasingly evident when extended to complex tissue engineering applications. Low molecular weight plasticizers diffuse, migrate and leach under physiological conditions,[53] leading not only to time-dependent embrittlement but also to the release of small molecules that may induce cytotoxicity and inflammatory responses that impair tissue regeneration.[54] Likewise, while organic and inorganic nanofillers have shown promising performance in bone tissue engineering,[39,55] their interfacial compatibility with the PLA matrix is often insufficient,[16] resulting in aggregation and stress concentration that ultimately compromise the overall mechanical integrity of the composite.[56,57] Moreover, high filler loadings typically deteriorate processability and limit the applicability of advanced fabrication techniques, such as 3D printing, for constructing finely resolved biomimetic architectures.

In comparison, polymer-based modification of PLA is widely regarded as a more suitable strategy for tissue engineering applications.[58] Although the selection of medical grade polymers is constrained by stringent regulatory requirements, the introduction of high molecular weight polymer chains offers distinct advantages. Their long chain architecture and high degree of entanglement greatly reduce the probability of migration from the matrix, thereby supporting long term biosafety and mechanical stability of implanted devices.[57] By selecting

polymers with complementary properties, such as hydrophilic poly(ethylene glycol) (PEG)[59,60] or highly ductile poly(ε-caprolactone) (PCL),[61,62] the degradation behaviour, surface wettability, and mechanical performance of PLA can be tuned at the molecular level to better accommodate the complex environment of the extracellular matrix. Furthermore, fabrication techniques not only define the macroscopic geometry of a construct but also regulate its microscopic topography,[57] porosity, and surface energy,[63] which collectively govern cell adhesion, migration, differentiation, and *in vivo* degradation kinetics.[64,65] Polymer-modified PLA systems generally retain more favourable processing windows and are compatible with advanced manufacturing methods, including electrospinning, microfluidics, and 3D bioprinting.[63,66]

On this basis, this review focuses on recent advances over the past five years in fully polymer-modified PLA systems for tissue engineering applications. According to the underlying modification mechanisms, these strategies are categorized into physical blending, chemical copolymerization, and polymer grafting. Each category is discussed in relation to the final material form and its application within specific tissue engineering architectures. Through a systematic analysis of these polymer-based modification strategies, combined with relevant fabrication techniques and application contexts, this review aims to provide a clearer framework for designing PLA-based biomaterials that meet the stringent demands of modern tissue engineering.

2. Polymer blending for PLA modification

Polymer blending represents the most accessible and scalable physical strategy to tailor the performance of PLA without altering its covalent backbone, relying instead on thermodynamic mixing while preserving the intrinsic chemical identity of each component.[43,53,61,67–69] Due to its high stiffness and strength, PLA has been extensively explored for load-bearing biomedical applications, particularly tissue engineering scaffolds. However, its inherent brittleness, hydrophobic surface chemistry, and relatively slow degradation kinetics significantly constrain its biological integration and functional lifetime *in vivo*.

Blending PLA with secondary polymers provides a versatile route to address these limitations.[19,43,61,67,70–73] For instance, hydrophilic polymers enhance surface wettability and protein adsorption, elastomeric or low T_g polymers improve toughness and compliance, and degradable polymers allow modulation of hydrolytic degradation profiles. In addition, naturally derived polymers such as chitosan, collagen, and gelatin exhibit superior bioactivity, allowing PLA-based blends to combine the mechanical integrity of synthetic polymers with the biological functionality of natural macromolecules. This combination makes them more attractive for tissue engineering applications that require the simultaneous provision of mechanical support and biological signalling.

2.1. Polymer blend films: coupling mechanical compliance and surface biointeractions

PLA-based blend films have been widely investigated as model systems to understand how composition and processing collectively regulate mechanical compliance, surface wettability, and degradation behaviour.[68,69,74–77] Rather than acting independently, these parameters are often strongly coupled through phase morphology and crystallization kinetics.[78–80] For example, blending PLA with ductile polymers such as PCL or PEG enhances elongation at break while simultaneously altering surface hydrophilicity.[81,82] Weng *et al.* demonstrated that electrospun PLA/PCL and PLA/PEG blend films exhibited suppressed microphase separation and reduced crystallinity relative to solvent-cast counterparts, resulting in highly porous morphologies and improved flexibility.[83] These results highlight a theme in PLA blending: mechanical softening and surface wettability are often achieved at the expense of increased processing sensitivity, particularly in solvent choice and evaporation kinetics, as shown in Fig. 1a.

Beyond aliphatic polyesters, functional blends incorporating electroactive polymers further expand the utility of PLA films. Suresh *et al.* reported that PLA/poly(vinylidene fluoride-*co*-trifluoroethylene) (P(VDF–TrFE)) blends exhibited composition-dependent molecular ordering with a 50 : 50 ratio balancing tensile stiffness and electroactive phase formation (Fig. 1b).[84] Such systems demonstrate how blending can introduce multifunctionality that is relevant to bioelectronic interfaces and smart wound dressings (*i.e.*, mechanical compliance coupled with electromechanical responsiveness).

Ternary blending strategies provide an additional degree of freedom. Tuancharoensri *et al.* employed optical ternary phase diagrams to rapidly screen PLA/PCL/cellulose acetate butyrate systems, identifying a broad compositional window (55–85 wt% PLA) that delivered exceptional ductility (>350% elongation) while retaining biodegradability.[85] Similarly, Baimark and Phromsopha reported that block copolymer blends containing PEG, such as PLLA–PEG–PLLA/PEG systems, function primarily as internal plasticizers by lowering T_g and enhancing chain mobility.[86]

In addition, functional additives can further enhance PLA films containing antimicrobial activity. Demir *et al.* incorporated imidazole-functionalized cyclotriphosphazenes into PLA/PEG matrices, achieving strong antimicrobial efficacy (*e.g.*, against *Escherichia coli* and *Staphylococcus aureus*) despite moderate losses in mechanical strength (Fig. 1c).[87] This trade-off between biological function and mechanical integrity remains a central challenge in blend film design.

The key limitation of physical blend films is their morphological instability, which fundamentally originates from high interfacial free energy that thermodynamically drives droplet coalescence and macroscopic phase coarsening. Building on this thermodynamic framework, Fredi and Dorigato highlighted that block and graft copolymers can selectively localize at the phase boundaries, acting as macromolecular surfactants to significantly reduce interfacial tension and

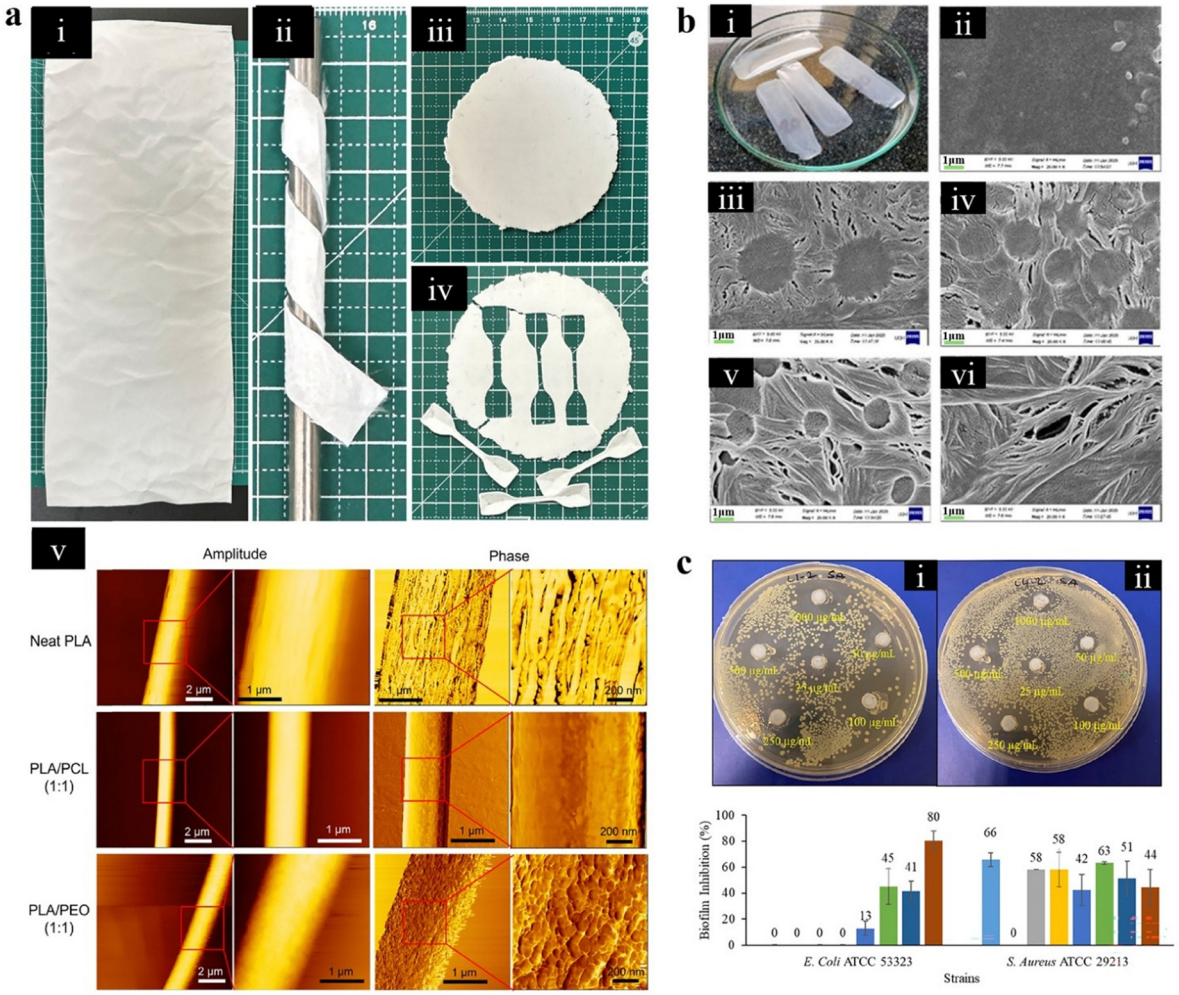

Fig. 1 Morphologies and functional performances of PLA blend films prepared by electrospinning and solvent casting. (a) Photographs of electrospun (i) and (ii) and solvent-cast (iii) and (iv) films comprised of PLA/PEO (1 : 1) blend. Atomic force micrographs of a single electrospun PLA blend fiber (v). Reprinted with permission from ref. 83. Copyright 2025, Elsevier. (b) Photograph of micrometer-thick PLA blend films (i) and scanning electron micrographs of 0P(VDF–TrFE):100PLA (ii), 25P(VDF–TrFE):75PLA (iii), 50P(VDF–TrFE):50PLA (iv), 75P(VDF–TrFE):25PLA (v), and 100P(VDF–TrFE):0PLA (vi). Reprinted with permission from ref. 84. Copyright 2025, Elsevier. (c) Screening of antibacterial activity of MCp and BCp compounds against *S. aureus* ATCC 29213 strains (i). Antibiofilm activity of PLA, PLA/PEG, PLA/PEG/MCp, and PLA/PEG/BCp composite films against *E. coli* ATCC 53323 and *S. aureus* ATCC 29213 (ii). Values are mean of triplicate measurements; error bars represent standard deviations. Reprinted with permission from ref. 87. Copyright 2025, American Chemical Society.

suppress macrophase separation.[88] In glassy PLA systems, Li *et al.* and Larson *et al.* demonstrated this concept using amphiphilic diblock copolymers.[89,90] They revealed that the PLA-miscible blocks (such as poly(ethylene oxide)(PEO)) thermodynamically anchor into the PLA matrix while the rubbery blocks form submicron segregated cores, effectively lowering the interfacial energy and driving the spontaneous self-assembly of stable micellar networks. Furthermore, the specific thermodynamic phase behavior is highly dependent on polymer architecture; as elucidated by Lee *et al.*, introducing graft-block polymers allows for precise control over the long-range order and uniform nanoscale dispersion of the rubbery domains within the PLA matrix.[91] Coote *et al.* demonstrated that such surfactant-like interfacial stabilization allows persistent phase morphology and long-term toughness retention (for over nine months), effectively counteracting the thermodynamic drive for physical aging in PLA.[92] Even under severe post-processing deformation, such as uniaxial stretching, these thermodynamically stable domains remain intact to achieve unique biaxial toughening mechanisms.[93] Overall, these studies establish that the effectiveness of PLA toughening is governed not only by the physical identity of the dispersed phase, but more fundamentally by the thermodynamic stabilization of the interfacial morphology through engineered block and graft architectures.

Challenges and opportunities: the key limitation of blend films is their morphological instability and processing dependence, where moderate variations in solvent system, drying rate, or composition can induce phase separation and property variability. Opportunities lie in developing blending strategies

that decouple surface bioactivity from bulk mechanics, for example, through gradient structures, surface segregating additives, or post-processing treatments.

2.2. Electrospun fibrous scaffolds with microstructures

Electrospinning has emerged as a main fabrication strategy for PLA-based fibrous scaffolds due to its ability to generate nano- to microscale architectures that closely resemble the extracellular matrix.[94–97] Through control of processing parameters such as applied voltage, solution concentration, and collector geometry, electrospinning can regulate fibre diameter, porosity, and scaffold alignment, all of which influence cell adhesion and migration.[98] We note here that several Reviews have summarized the use of electrospun PLA and PLA/PCL blends in regenerative medicine.[24,99–101] While these reviews comprehensively catalogue applications across vascular, neural, and bone tissues, they primarily emphasize correlations between processing and properties rather than the coupling of structure and function.

Recent experimental studies reveal how blend composition governs microstructure evolution during electrospinning. Karpova *et al.* identified a composition-dependent phase inversion in PLA/PCL fibres, which significantly altered segmental mobility, diffusivity, and drug release kinetics.[102] Blending PLA with biologically active polyesters further enhances scaffold–cell interactions. Solarz *et al.* developed PLA/polyhydroxyoctanoate fibrous scaffolds with experimental setup shown in Fig. 2a. The results exhibited improved hydrophilicity and cytocompatibility (Fig. 2b) relative to pristine PLA alongside reduced fibre diameters that are favourable for soft tissue regeneration (Fig. 2c).[103] Importantly, processing strategy itself can override compositional effects. Goreninskii *et al.* demonstrated that multichannel electrospinning preserved the crystallographic identity of PLA and PCL phases, resulting in enhanced multipotent mesenchymal stem cell adhesion compared to single channel mixed-solution spinning.[104] Thermoresponsive behaviour can also be introduced through blending. Sringam *et al.* reported that high molecular weight PEG–PLAs displayed excellent shape memory performance near physiological temperatures, allowing minimally invasive deployment strategies such as self-expanding stents.[105] Composite yarn architectures integrating PLA fibres with drug-loaded chitosan/PVA nanofibres[106] or gelatin[107] further illustrate how hierarchical blending improves antimicrobial activity (*e.g.*, L929 fibroblast cells) and degradation rates without catastrophic mechanical compromise.

At the macroscale, reinforcement strategies offer partial solutions to the intrinsic limitations of fibre blending. Deng *et al.* achieved highly aligned PLA short fibre reinforcement within a PCL matrix *via* vacuum-assisted resin infusion, resulting in substantial gains in tensile modulus suitable for tendon and ligament repair (Fig. 2d).[108] Nevertheless, such alignment arises primarily from external processing fields rather than intrinsic molecular ordering.

Challenges and opportunities: electrospun PLA blends are fundamentally process-driven systems, where microstructure, alignment, and anisotropy are imposed rather than encoded. However, this technique limits spatial programmability and long range order. Opportunities exist in material systems that intrinsically generate ordered architectures to achieve reproducible anisotropy and dynamic biological function rather than relying exclusively on processing.

2.3. Additive manufacturing of functional PLA blends

Additive manufacturing allows fabrication of patient specific PLA-based scaffolds with controlled porosity, geometry, and mechanical gradients, which makes it particularly attractive for bone and cartilage repair.[45,109–111] Blending PLA with secondary polymers improves printability, impact resistance, and degradation kinetics, as well as allowing incorporation of bioactive fillers and therapeutic agents. Several Reviews have summarized 3D-printed PLA-based scaffolds in bone regeneration models.[112–115] These studies confirm PLA's osteogenic potential but also highlight a lack of standardized evaluation protocols and limited translation beyond small animal models.

Recent experimental efforts have therefore focused on composition-driven strategies to enhance the intrinsic limitations of pristine PLA, particularly its brittleness, hydrophobicity, and narrow processing window. For instance, Dominguez-Candela *et al.* reported that blending PLA with poly(3-hydroxybutyrate) and functional plasticizers induces multiphase softening and interfacial lubrication, resulting in a substantial increase in impact resistance while simultaneously reducing water contact angles.[116] These coupled effects improve melt processability and promote cell–material interactions, highlighting the blend design in balancing mechanical robustness and biological performance.

Živčák *et al.* reported the use of plasticization strategies (oligomeric lactic acid or citrate-based additives) to provide composition-dependent control over chain mobility, degradation kinetics, and local pH stability during implantation, which are critical parameters for long term tissue compatibility.[117,118] Notably, these additives act primarily through bulk plasticization and do not introduce long range structural organization, yielding materials with largely homogeneous and isotropic responses. Furthermore, Culenova *et al.* used more complex formulations (*e.g.*, ternary PLA/poly(3-hydroxybutyrate)/thermoplastic starch systems) to synergistically tune hydrophilicity, porosity, and degradation behaviour through component selection and phase distribution while maintaining cytocompatibility across relevant cell types such as human chondrocytes (Fig. 3a).[119] However, these improvements are achieved through compositional averaging at the bulk level rather than through spatially programmable control, limiting the ability to locally regulate degradation behaviour within the scaffold (Fig. 3b).[120]

Shahverdi *et al.* reported the use of advanced fabrication routes such as melt electrowriting to enhance resolution in fibre placement and localize mechanical reinforcement, thereby expanding the applicability of PLA-based blends toward load-bearing tissue defects, as shown in Fig. 3c.[121] In these cases, structural anisotropy is introduced primarily through processing-induced alignment rather than intrinsic molecular ordering.

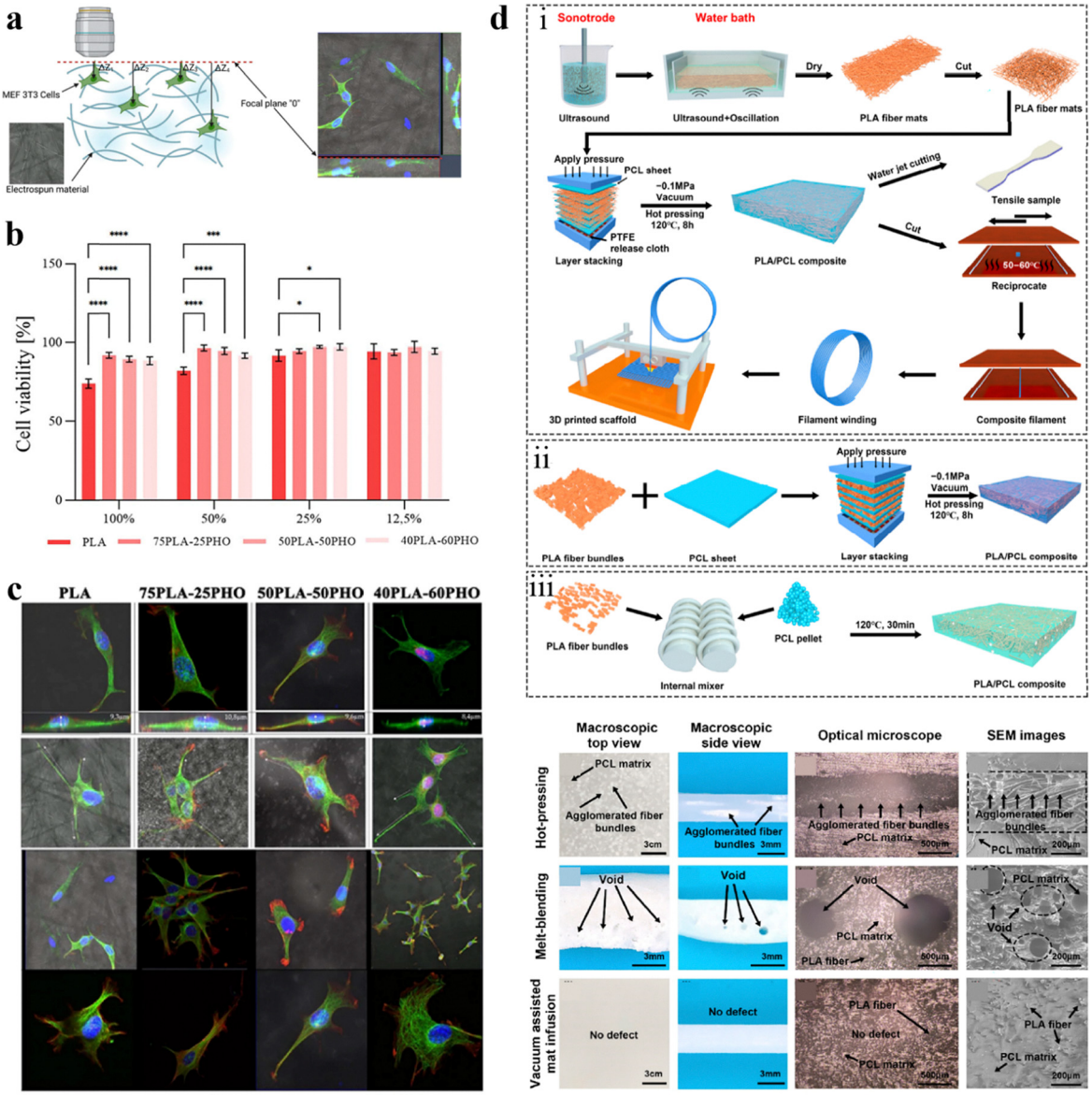

Fig. 2 Evaluation of PLA blend fibres regarding cell viability, 3D cell migration, and cytoskeletal organization. (a) Experimental setup for 3D cell tracking and migration analysis. (b) Cell viability as a function of biomaterial formulation and extract volume concentration (%, v/v); significant differences compared to the control, the neat PLA fiber sample, for the same dilution are indicated by asterisk (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p \leq 0.0001$). (c) Confocal fluorescence micrographs of a 3D reconstruction of cells incubated in different formulations of PLA/polyhydroxyoctanoate biomaterial fibres (microtubules: green; actin filaments: red; 3D reconstructed nuclei: blue). Reprinted with permission from ref. 103. Copyright 2023, Royal Society of Chemistry. (d) Schematic illustration and optical and scanning electron micrographs of composites formed by VARI process that adapts and prepares PLA/PCL composites for FDM printing (i), conventional hot pressing (ii), and melt blending (iii). Reprinted with permission from ref. 108. Copyright 2025, Elsevier.

Beyond filament-based printing, supercritical CO_2 foaming and thermally induced phase separation techniques have been employed to generate highly interconnected porous architectures with tunable pore size and permeability. Lv *et al.* demonstrated that PLA/PCL foams supported human umbilical vein endothelial cell viability and migration, emphasizing the relevance of porous blend scaffolds for vascular tissue engineering and mass transport-sensitive applications.[122]

Challenges and opportunities: despite impressive geometric control, additive manufacturing of PLA blends remains largely composition-driven rather than structurally programmed. Mechanical anisotropy, degradation gradients, and biological signaling are primarily dictated by printing path and blend ratio. This limitation motivates emerging strategies that embed ordering or responsiveness at the molecular level, enabling scaffolds whose function is not only defined by printing geometry.

2.4. Injection-moulded PLA blends: shear-induced reinforcement

Injection moulding remains the industrial standard for producing dense, high strength orthopedic components such as screws and fixation plates. Recent advances exploit

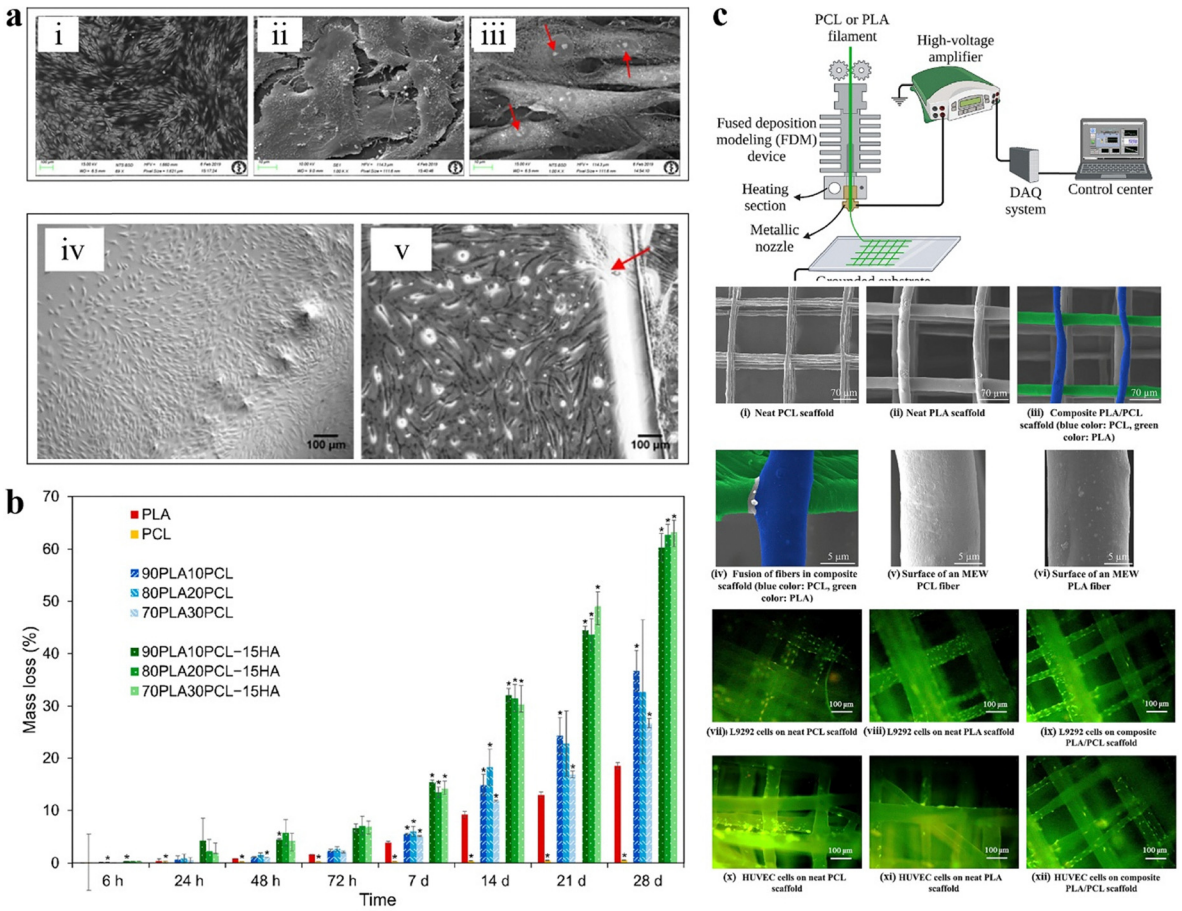

Fig. 3 Degradation behaviour and *in vitro* cytocompatibility of PLA blend composites. (a) Morphological analysis of the cell culture (i) and detailed shape analysis (ii). Backscattered electron detector revealed multiple nuclei present in the cells, which indicated protein translation activity (iii, red arrows). Evaluation of the cytotoxic potential of the sample according to direct contact cytotoxicity test. The control group was presented as a standard culture of chondrocytes with fibroblast-like morphology (iv). The PLA/polyhydroxybutyrate (PHB)/thermoplastic starch scaffold did not alter cell morphology or viability (v, arrow depicting the edge of the 2D film). Reprinted with permission from ref. 119. Copyright 2021, SAGE Publications. (b) Percentage of mass lost for all materials during the four-week degradation period presented as mean ± standard deviation values. * denotes statistical significance compared to PLA ($p < 0.05$) in the same time point. Reprinted with permission from ref. 120. Copyright 2022, Elsevier. (c) Schematic of experimental setup and scanning electron micrographs of melt elecrowritten scaffolds for neat PCL (i), neat PLA (ii), and composite PLA/PCL scaffolds (iii), bonding and connection of two fibres (iv)–(vi). LIVE/DEAD staining results of L929 cells/HUVEC cells for neat PCL (vii) and (x), neat PLA (viii) and (xi), and composite PLA/PCL scaffolds (ix) and (xii). Reprinted with permission from ref. 121. Copyright 2022, Springer Nature.

shear-dominated processing environments to enhance mechanical performance in PLA blends.[123,124] Past studies of injection-moulded PLA systems emphasize crystallinity control and impact resistance as the primary levers for mechanical optimization.[125–130] These studies have reported how cooling rate, mould temperature, and nucleating agents influence spherulitic morphology and bulk stiffness, which provide a solid foundation for understanding relationships between structures and properties in moulded PLA. However, these results focus on bulk responses and did not discuss the spatial heterogeneity or biological implications of flow-induced microstructures.

Microinjection moulding, in particular, generates extreme shear and elongational flow fields during melt filling, which can induce fibrillation and elongation of secondary phases.[131–134] Chen *et al.* demonstrated this effect in PLA/PCL/bioactive glass composites where shear-induced fibrillar morphologies lead to a pronounced enhancement in Young's modulus and load transfer efficiency.[135] Importantly, such mechanical reinforcement arises from processing-driven morphology rather than molecular-level alignment of the PLA chains themselves.

Ultrasonic moulding represents a complementary processing strategy that reduces residence time and overall thermal exposure by coupling localized heating with high frequency vibration, thereby improving energy efficiency while allowing the fabrication of complex micro-implants with minimal thermal degradation.[136,137] As shown in Fig. 4, Garcia-Ferrer *et al.* showed that these advantages are particularly relevant for PLA, where excessive thermal histories can compromise molecular weight and degradation behaviour.[138]

Porosity can be further introduced through microcellular injection moulding,[139–141] yielding lightweight, interconnected scaffold architectures without sacrificing manufacturing speed.

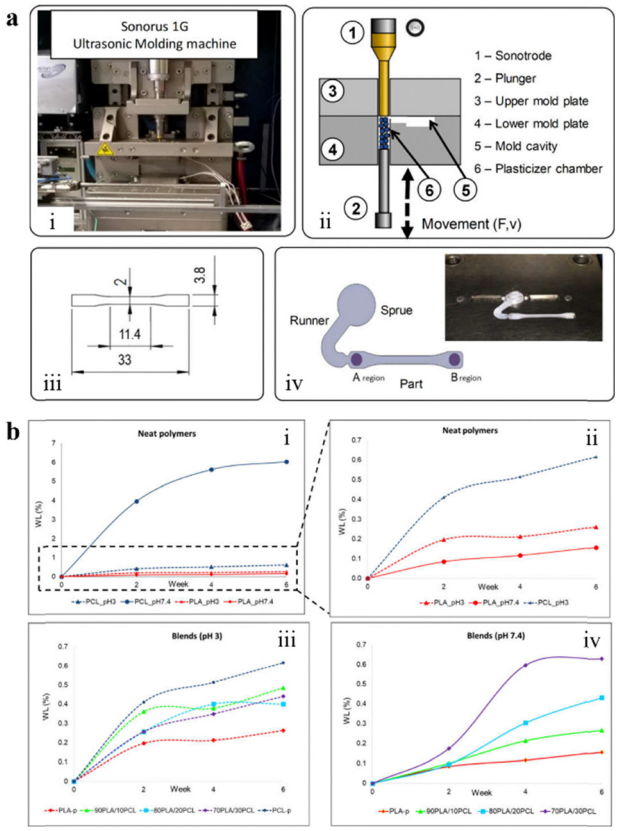

Fig. 4 Ultrasonic moulding process and degradation behaviour of PLA blends. (a) Ultrasonic moulding technology: Sonorus 1G machine (i), main elements (ii), specimen (iii), and specimen regions (iv). (b) Degradation of neat PLA (i) and (ii) and PLA blends at pH 3 (iii) and pH 7.4 (iv) in terms of weight loss. Reprinted with permission from ref. 138. Copyright 2021, Elsevier.

For example, Mi *et al.* produced PLA/thermoplastic polyurethane scaffolds shown to support 3T3 mouse fibroblast proliferation and maintain high production efficiency and dimensional fidelity *via* this approach.[142] Pore formation and mechanical performance are governed by gas nucleation and flow-induced structuring rather than intrinsic ordering within the polymer matrix.

Challenges and opportunities: injection moulding is advantageous in mechanical reinforcement but offers limited control over biological gradients and surface functionality. Future opportunities lie in integrating moulding-compatible materials that encode biological cues or anisotropy at the molecular scale, thereby reducing reliance on extreme processing conditions.

2.5. Incorporation of liquid crystalline fillers: ordered blending beyond isotropic composites

Conventional polymer blending strategies primarily rely on compositional averaging and processing-induced morphology to tailor the mechanical and biological performance of PLA. As discussed in Sections 2.1–2.4, improvements in toughness, wettability, and degradation behaviour are typically achieved through plasticization, phase dispersion, or flow-induced alignment. However, these approaches mainly regulate local structure or composition, and any anisotropy that arises is usually weak and highly dependent on processing conditions. As a result, most blended PLA systems remain largely isotropic, with limited ability to generate stable, directional cues at biologically relevant length scales. In this context, the incorporation of liquid crystalline (LC) fillers represents an advanced extension of blending strategies in which mesoscopic order is introduced intrinsically through phase behaviour rather than imposed by processing.[143–146] In PLA-based systems, LC blending has been primarily realized through low molecular weight LC mesogens and lyotropic colloidal fillers, both of which can self-organize into ordered domains and generate anisotropic, bioactive interfaces without covalent modification of the polymer backbone.[147–154]

2.5.1. Low molecular weight LCs. Low molecular weight LCs can be directly blended with PLA to generate thermotropic LC phases within isotropic matrices. These small molecule LCs are widely used in liquid crystal displays (LCDs), chemical sensors, and biosensors, where their molecular order and responsive phase behaviour allow precise modulation of optical, electrical, and transport properties.[149,155–168] In LC phases, molecules exhibit long range orientational order, often with layered or helical arrangements (*e.g.*, nematic, smectic, or cholesteric), which can mediate anisotropic interactions and dynamic responsiveness.[169–180]

Zheng *et al.* prepared PLLA/LC composite films using a one-pot solution casting approach with cholesteryl oleyl carbonate and cholesteryl pelargonate (Fig. 5a).[181] By regulating the proportion of these two substances in the polymer matrix, the resulting films maintained a stable LC phase at physiological temperature. In this regime, molecular ordering and fluidity facilitated directional mass transport and signal transduction, distinguishing these systems from conventional plasticized blends. Biologically, these PLLA/LC composites promote M2 macrophage polarization (RAW264.7) and enhanced osteogenic differentiation of bone marrow mesenchymal stem cells in co-culture. In a rat calvarial defect model, PLLA–30%LC scaffolds exhibited significantly greater new bone formation than pristine PLLA, indicating that LC ordering can regulate tissue regeneration through immunomodulatory and bioinstructive pathways rather than only mechanical reinforcement.[182]

Nasajpour *et al.* reported a related strategy that electrospun cholesteryl ester mesogens into a PCL matrix to maintain a LC mesophase at 37 °C (Fig. 5b).[183] Atomic force microscopy revealed characteristic fingerprint-like surface patterns while the Young's modulus (3–16 kPa) closely matched that of native muscle tissue. In this system, the polymer matrix provided bulk elastic support whereas the dispersed LCs generated a viscoelastic, fluid-like surface interface that promoted myogenic differentiation of C2C12 myoblasts. Although demonstrated in PCL, this work provides a clear design blueprint for PLA-based systems in which LC mesophases function as dynamic, cell-instructive interfaces rather than passive fillers.

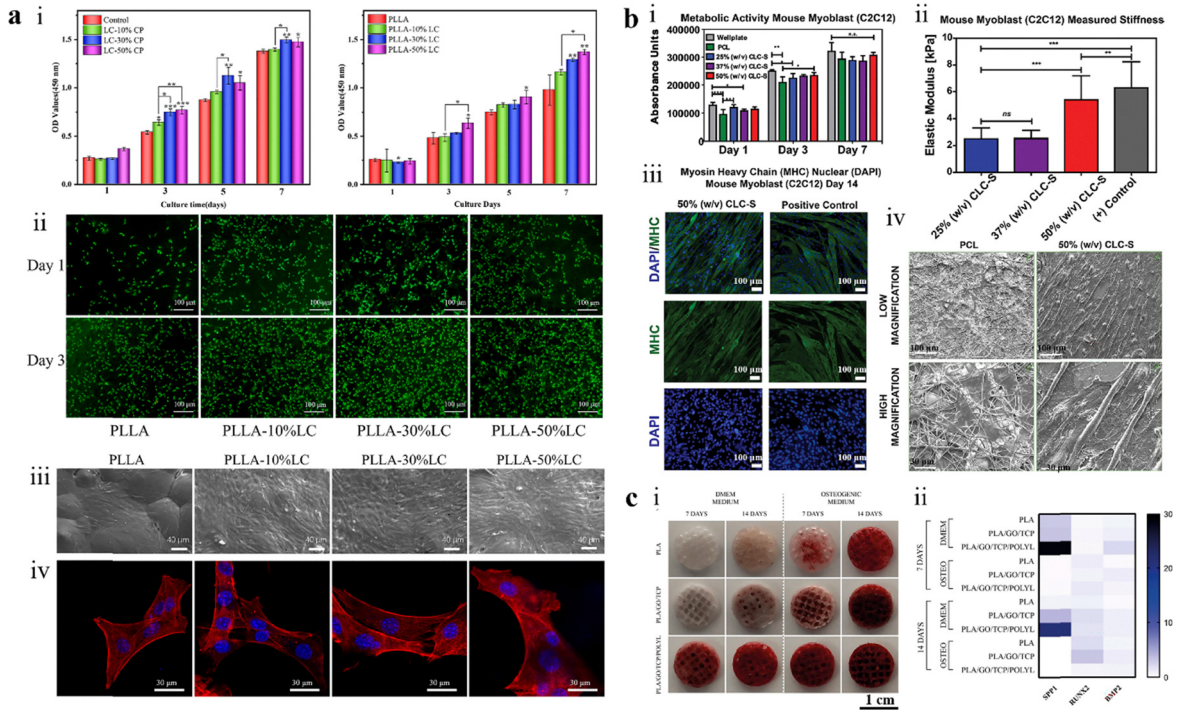

Fig. 5 *In vitro* cellular responses and osteogenic-related performance of LC/PLA composite. (a) Cell proliferation in COC/CP LC and PLLA/LC composites for 7 days* refer to statistically significant proliferation $p < 0.05$ (i). Fluorescence micrographs of AO-EB-stained MC3T3-E1 cells seeded on PLLA films (ii). Scanning electron micrographs (iii) and fluorescence micrographs (iv) of morphologies of MC3T3-E1 cells cultured on PLLA films. Reprinted with permission from ref. 181. Copyright 2022, Frontiers Media SA. (b) *In vitro* biocompatibility of muscle cells with cholesteryl ester LC scaffolds (CLC-S). Presto Blue metabolic analysis of the C2C12 mouse myoblast cells cultured over 7 days (i). Atomic force microscopy measurements of C2C12 mouse myoblast cellular stiffness on tested scaffolds (ii). Immunohistochemistry staining of myosin heavy chain (MHC) and 4′,6-diamidino-2-phenylindole (DAPI) of C2C12 mouse myoblast cells cultured on CLC-S scaffold compared to positive control at Day 14. White arrow highlights multinucleated phenotype of mouse myoblast (iii). Scanning lectron micrographs of cultured C2C12 mouse myoblast cells on scaffolds at Day 14 (iv) (n = 6 for C2C12 metabolic activity assays, n = 4 for elastic modulus measurements, $^{**}P < 0.01$, $^{***}P < 0.001$.) Reprinted with permission from ref. 183. Copyright 2020, American Chemical Society. (c) PLA scaffolds seeded with hWJ-MSCs in a supplemented culture media (DMEM) medium and an osteogenic differentiation medium (i). Gene expression of SPP1, RUNX2, and BMP2 of hWJ-MSCs seeded on PLA films with supplemented DMEM medium and osteogenic differentiation medium (ii). Reprinted with permission from ref. 188. Copyright 2024, Royal Society of Chemistry.

2.5.2. Colloidal LC fillers. Colloidal fillers capable of forming lyotropic LC phases represent another biologically relevant class of LC blending strategies.[146,184–186] Graphene oxide (GO) is a representative example, exhibiting nematic phase above critical concentrations due to its high aspect ratio and strong inter-sheet interactions.[187] Sanchez-Cepeda *et al.* exploited this property to fabricate PLA/GO/tricalcium phosphate composite scaffolds in which the LC alignment of GO sheets promoted epitaxial crystallization of PLA chains.[188] This LC ordering-mediated crystallization distinguishes LC filler incorporation from conventional nanoparticle reinforcement where crystallization effects are typically isotropic and localized. The resulting scaffolds exhibited enhanced surface wettability and microscale roughness, leading to improved adhesion and proliferation of human Wharton's jelly mesenchymal stem cells, as shown in Fig. 5c. Moreover, GO incorporation promoted osteogenic marker expression, demonstrating the role of ordered interfaces in directing cellular responses.

Cellulose nanocrystals (CNCs) provide another biologically relevant class of LC fillers.[189–191] Owing to their rod-like geometry and surface hydroxyl groups, CNCs can form chiral nematic phases and simultaneously enhance stiffness and hydrophilicity when dispersed in PLA matrices. While CNC-reinforced PLA systems are often discussed in the context of mechanical reinforcement,[192–195] their LC ordering introduces an additional level of structural hierarchy that bridges bulk mechanics and interfacial bioactivity.

Challenges and opportunities: LC blending provides a versatile route to move beyond isotropic composites by introducing self-organized order into PLA-based biomaterials without covalent modification of the backbone. However, LC-blended systems remain highly sensitive to composition, processing history, and dispersion quality, with limited control over long term phase stability and degradation-coupled evolution. Beyond low molecular weight LC mesogens and colloidal fillers, blending strategies based on LC polymers represent an intriguing but underexplored extension. LC polymers can undergo shear-induced alignment or *in situ* fibrillation, imparting strong anisotropic reinforcement, and have demonstrated promising applications in soft actuators, robotics, and responsive biomedical devices.[196–201] Nonetheless, their biocompatibility, degradation behaviour, and long term structural stability in

PLA-based tissue scaffolds remain underexplored. Future opportunities lie in hybrid strategies that integrate LC blending, potentially combining LC polymer components with compatibilization, surface grafting, or copolymerization.

2.6. Clinical translation of blended PLA

The clinical translation of PLA has been most successful in application scenarios where intrinsic brittleness and limited toughness are mitigated through multiphase material design. Polymer blending and composite formulation, particularly *via* the incorporation of ductile secondary phases or bioactive inorganic fillers, represent industrially accessible approaches that preserve the regulatory familiarity and chemical identity of PLA-based systems.

In orthopedic fixation, commercial bioresorbable devices such as Delta+ resorbable implant system (Stryker), Biosteon (Stryker), and ComposiTCP (Zimmer Biomet) provide representative, albeit indirectly disclosed, examples of this design paradigm. While these products are generally described as PLA-based materials in regulatory filings, research papers and a registered study (NCT07080450) suggest the incorporation of secondary phases consistent with blending or composite strategies, including osteoconductive fillers such as hydroxyapatite (HA) and β-tricalcium phosphate.[202,203] These heterogeneous material systems exhibit enhanced bioactivity and more favorable osteointegration compared to neat PLA, thereby supporting their widespread use in load-sharing orthopedic and craniomaxillofacial applications.

Beyond rigid fixation, PLA-based composite formulations have also been explored in wound management and regenerative interfaces. Platforms such as COLLACOTE developed by Integra LifeSciences illustrate how biodegradable polymer matrices can be integrated with structural or functional phases to achieve coupled mechanical compliance and biological performance.[204–206] In such systems, PLA typically functions as a structural matrix within a multiphase architecture, consistent with blend-like design principles.

From a translational perspective, PLA-based blends composed of synthetic and well-characterized components are generally well-suited for the U.S. Food and Drug Administration 510(k) pathway due to their compositional reproducibility and well-established degradation behavior.[207] However, increasing compositional complexity, particularly through the incorporation of poorly defined phases or biologically derived components, can substantially elevate regulatory barriers. This constraint, coupled with materials performance, remains a key factor in limiting the broader clinical adoption of advanced PLA blending strategies.

3. Copolymerization for PLA modification

In contrast to physical blending, copolymerization represents a chemical modification strategy that introduces distinct monomer units into the PLA backbone through covalent bonding.[208–211] By directly altering chain sequence and architecture, and segmental mobility, copolymerization achieves molecular-level regulation of crystallinity, hydrophilicity, degradation kinetics, and mechanical behaviour.[212–214] As a result, copolymerization provides a fundamentally different design principle from blending, allowing functional attributes to be encoded intrinsically rather than imposed through processing or phase morphology.

PLA-based copolymers are typically synthesized by incorporating monomers such as glycolide (GA), ε-caprolactone (CL), or ethylene glycol-derived segments to form random, block, or graft architectures. These modifications reduce crystallinity, broaden thermal transitions, and increase chain flexibility, thereby expanding the applicability of PLA to soft tissues and dynamic biological environments.[215–217] Importantly, copolymerization offers improved morphological stability compared to blends, as the functional segments are chemically tethered rather than physically mixed, mitigating phase separation during processing and degradation.[218,219]

3.1. Copolymer films with stable flexibility and controlled degradation

Copolymer-modified PLA films have been widely explored as guided tissue regeneration membranes, anti-adhesion barriers, and substrates for wound dressings and flexible biointerfaces.[220–223] In these applications, copolymerization is primarily used to suppress crystallinity and lower the T_g, thereby improving flexibility, swelling behaviour, and biological interactions while maintaining sufficient mechanical integrity. Poly(lactic-*co*-glycolic acid) (PLGA)-based systems exemplify this strategy. Sirek *et al.* fabricated multifunctional wound-dressing films by solvent casting PLGA matrices loaded with abietic acid and the photosensitizer chlorin e6.[224] Compared to pristine PLA, the amorphous nature of PLGA allowed rapid swelling and efficient exudate absorption, and its predictable hydrolytic degradation supported coordinated release of antimicrobial and photodynamic agents. This study shows that degradation-mediated release profiles can be programmed through monomer composition rather than additive diffusion alone.

Electrospun PLGA membranes further illustrate the advantages of copolymerization in moist and dynamic biological environments. Chor *et al.* examined PLGA (85 : 15) fibrous membranes for oral mucosal regeneration and showed that, despite progressive mass loss and molecular weight reduction, the fibrous architecture remained sufficiently intact to support cell infiltration.[225] Relative to PLA, glycolide incorporation enhanced hydrophilicity and accelerated degradation without eliciting significant inflammatory responses, demonstrating the suitability of PLGA for soft tissue barrier applications in mouse pre-osteoblast cells (MC3T3-E1), as shown in Fig. 6a.

Beyond standalone films, copolymers are frequently employed as surface modification layers. Maadani *et al.* reviewed PLGA-based coating strategies for porous scaffolds, demonstrating that uniform coatings improve compressive strength and surface wettability and modulate the local

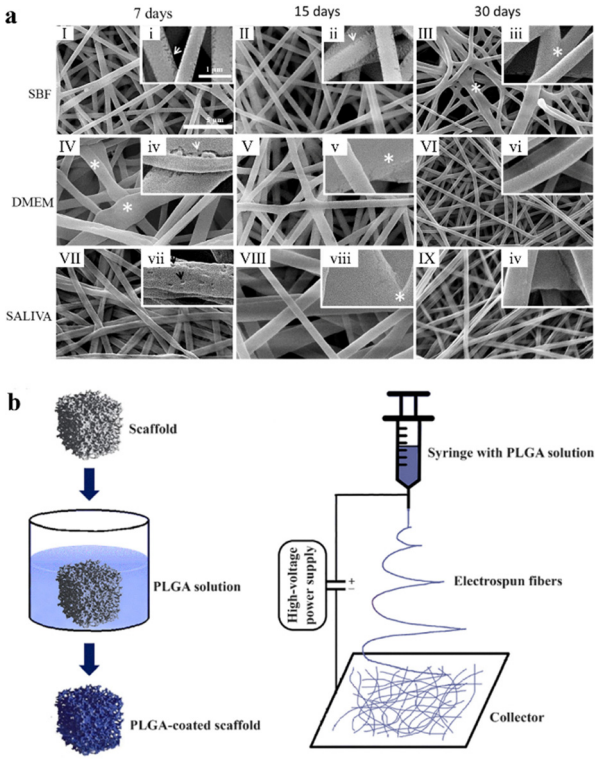

Fig. 6 Morphological evolution of electrospun PLGA fibrous films in physiological media. (a) Scanning electron micrographs of non-irradiated, electrospun PLGA after immersion in simulated body fluid (SBF), culture media (DMEM), and artificial saliva for 7, 15, and 30 days. In SBF, fibres exhibited border fissures at Days 7 and 15 (i, ii, arrows), which became less pronounced at Day 30, accompanied by inter-fibre connections (III, iii, asterisks). In DMEM, fibres swelled at Day 7 (IV, asterisks) with elongated fissures (iv, arrow), followed by hydration-induced fusion at Day 15 (v, asterisks) and narrowing with reduced fissuring at Day 30 (VI). In saliva, fibres showed initial shrinkage and surface pores at Day 7 (VII, vii, arrows), swelling and partial fusion at Day 15 (VIII, viii, asterisks), and narrowed, pore-free morphology at Day 30 (IX, ix). Reprinted with permission from ref. 225. Copyright 2020, Elsevier. (b) Setup of dip coating and electrospinning. Reprinted with permission from ref. 226. Copyright 2023, Elsevier.

biochemical microenvironment through degradation products (Fig. 6b).[226] However, as discussed in past work, acidic byproducts from PLGA degradation can interfere with mineral deposition, indicating that copolymer composition must be optimized to balance mechanical reinforcement and biological compatibility.

Block and graft copolymers provide additional control over phase stability.[227–229] Baimark and Phromsopha demonstrated that PLLA–PEG–PLLA triblock copolymer films exhibit rubber-like elasticity and stable morphology, effectively suppressing PEG phase separation observed in physically blended systems.[230] Similarly, Mekpothi *et al.* synthesized graft copolymers with tunable side chain density, achieving precise control over crystallization and degradation behaviour.[231] These studies demonstrate how copolymerization permits decoupling of flexibility and morphological stability.

Challenges and opportunities: while copolymer films offer improved stability and programmable degradation, their properties remain spatially homogeneous and limit the ability to encode gradients in mechanics or bioactivity. Opportunities lie in sequence-controlled copolymers and surface segregating architectures that introduce functional heterogeneity without sacrificing film integrity.

3.2. Copolymer fibres: matching degradation and elasticity to tissue-specific demands

In fibrous scaffolds, copolymerization is primarily employed to tune elasticity and degradation kinetics to better match the requirements of nerve, tendon, vascular, and bone tissues.[96,232–235] Compared to PLA blends, PLA copolymer fibres offer more predictable mechanical evolution during degradation, as chain composition rather than phase morphology governs material response.

Poly(L-lactic acid-*co*-ε-caprolactone) (PLCL) copolymers exemplify this approach in nerve regeneration. Mao *et al.* developed a bilayer nerve conduit incorporating an electrospun PLCL outer layer and an inner decellularized extracellular matrix layer.[236] The PLCL copolymer balanced the stiffness of PLA with the elasticity of PCL, providing sufficient mechanical integrity as well as accommodating dynamic deformation. *In vivo* studies demonstrated regeneration outcomes comparable to autografts, which highlights how copolymer elasticity directly translates to functional performance.

PLGA fibres have been extensively explored for soft- and hard-tissue regeneration due to their tunable degradation rates. Das *et al.* used cryo-milled PLGA fibres as injectable reinforcement for fat grafting, as shown in Fig. 7a, significantly improving graft retention and vascularization as shown in Fig. 7b.[237] In bone-related applications, Suarez-Lopez *et al.* showed that PLGA/calcium phosphate composite fibres accelerated biomineralization and osteogenic differentiation (MC3T3-E1), with degradation rates better synchronized to new bone formation than PLA-based counterparts.[238]

Copolymerization also facilitates integration with bioactive and conductive components. Guzman-Soria *et al.* combine mechanical reinforcement with biological recognition such as human cervical cancer cell line and mouse embryonic fibroblast cell line in PLGA/collagen fibres.[239] In addition, Castro *et al.* showed that PLGA effectively encapsulates conductive polypyrrole, which preserves electrical functionality and guides neurite outgrowth of rat adrenal pheochromocytoma cell line.[240] More complex terpolymer systems, such as poly(L-lactic acid-*co*-caprolactone-*co*-glycolic acid), further expand the design space by independently tuning strength, elasticity, and degradation.[241]

Shi *et al.* reported that tuning PLLA fiber diameters (ranging from 293 nm to 1.3 μm) precisely guides the directional outgrowth of axons in chick dorsal root ganglia.[242] Their findings demonstrate that large-diameter fibers drive parallel axonal elongation, whereas small-diameter fibers induce vertical growth, effectively mimicking the extracellular matrix through topographic contact guidance to provide physical orientation for neural regeneration. For skeletal muscle tissue engineering, Wang *et al.* utilized ultrathin electrospun PLGA scaffolds (thickness ~6 μm) to cultivate C2C12 myoblasts, constructing

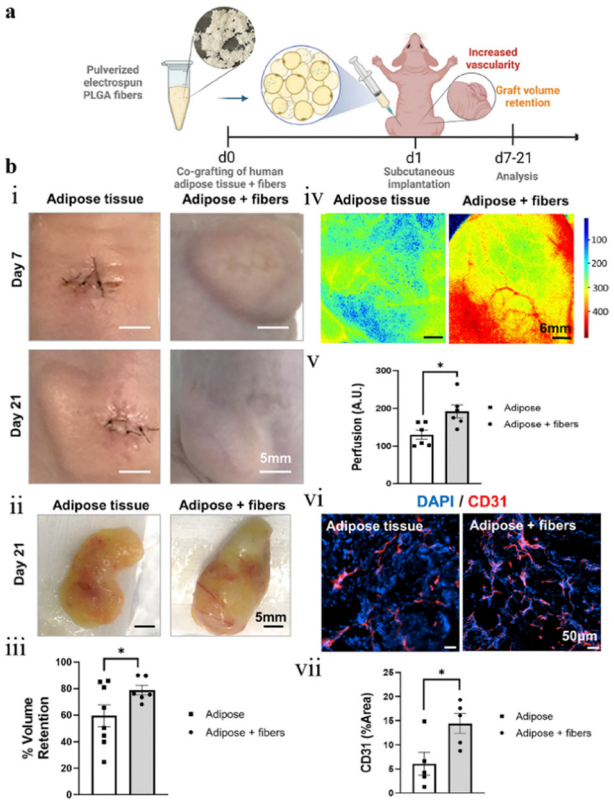

Fig. 7 *In vivo* evaluation of adipose tissue grafts incorporating milled PLGA fibres. (a) Schematic demonstrating the process of combining adipose tissue collected *via* liposuction with pulverized PLGA fibres. (b) The dorsal tops of mice were engrafted with a treatment of adipose-fibre tissue combination, and the dorsal bottoms of mice were engrafted with adipose tissue only (n = 9) (i). Adipose-only engraftments and adipose-fibre combination engraftments harvested at Day 21 (ii). Volume retention by Day 21 in adipose-fibre engraftment compared to adipose engraftment (P = 0.040) (iii). Perfusion levels of adipose-only engraftments and adipose-fibre engraftments (iv). Perfusion levels in adipose-fibre samples compared to adipose-only engraftment samples (P = 0.015) (v). CD31 immunohistochemistry of adipose tissue from control and PLGA-fibre treated mice (n = 5) (vi). CD31 expression in control and PLGA fibre-treated adipose grafts (P = 0.028) (vii). All error bars are shown as SEMs. *P < 0.05 (t-test). A.U., arbitrary units. Reprinted with permission from ref. 237. Copyright 2023, Wiley.

millimeter-scale 3D muscle tissues through unique stacking and rolling techniques.[243] The results demonstrate that the ultrathin architecture ensures a high cell-to-mass ratio (42%) by allowing cells to form high-density layers without deep migration. Furthermore, this process allows for precise control over fiber orientation in order to mimic the parallel alignment of native muscle fibers, significantly promoting myotube differentiation and maturation.

Beyond tissue engineering, PLA-based materials demonstrate exceptional potential in vaccine delivery and immunoregulation. Xu *et al.* developed amino-terminated chiral PLA nanoparticles (50–80 nm) as nanovaccines to electrostatically adsorb ovalbumin (OVA) antigens.[244] Their results confirm that when compared to L-enantiomer and traditional alum adjuvants, D-enantiomer (PDLA) nanoparticles more effectively activate dendritic cell maturation, facilitate antigen cross-presentation, and stimulate $CD8^+$ T cell activation, achieving a 65% tumor inhibition rate in melanoma models. In the domain of smart targeted drug delivery, Chen *et al.* designed size-transformable micelles composed of PEG-*b*-PLA that shrink from 150 nm to 40 nm within the tumor microenvironment, thereby synergistically optimizing blood circulation time and deep tumor penetration.[245] Expanding this "tumor blockade" repertoire, Sun *et al.* delineated a strategy to construct artificial extracellular matrices *via* biomaterial-mediated fibrogenesis and gelation, establishing a robust physical barrier to inhibit tumor invasion and metastasis.[246] Complementing this finding, Liu *et al.* used metabolic glycoengineering to facilitate selective biomineralization within the tumor, effectively starving malignant tissues by cutting off essential nutrient and oxygen supplies.[247]

Additionally, Xu *et al.* encapsulated protein vaccines and mRNA vaccines within PLA/PLGA nanoparticles to mimic virus-like particles, inducing potent humoral and cellular immunity.[248] Wei *et al.* exploited the slow degradation profile of these polymers to develop immunomodulatory carriers that induce regulatory T cells for treating autoimmune diseases.[249] Finally, Luo *et al.* prepared mPEG-*b*-PMet thermosensitive hydrogels that utilize a reactive oxygen species scavenging mechanism to protect H9c2 cardiomyocytes and L929 fibroblasts from oxidative stress, highlighting their cytoprotective potential in treating ischemic diseases.[250]

Challenges and opportunities: copolymer fibres offer superior degradation matching and elasticity but remain largely isotropic unless coupled with external alignment strategies. Future directions include copolymers that intrinsically promote chain orientation or hierarchical assembly during spinning, reducing reliance on processing-induced alignment.

3.3. Copolymer-based 3D printing: expanding the printable window and functionality

In additive manufacturing, copolymerization primarily addresses the brittleness, narrow thermal window, and unfavourable degradation behaviour of printed PLA constructs.[251–254] PLCL and PLGA copolymers are particularly attractive due to their reduced melting temperatures, improved rheology, and enhanced post-printing mechanical resilience.[255–257] PLCL-based systems have been extensively studied for elastic tissue engineering. Rahul *et al.* demonstrated that PLCL copolymers with optimized monomer ratios exhibit printing fidelity and mechanical properties closely matching native tracheal cartilage (Fig. 8a and b).[258] Liu *et al.* further showed that PLCL scaffolds maintain elasticity and fatigue resistance under cyclic loading for applications in vascular and cardiac tissues (*e.g.*, *in vitro* cell tests with human umbilical vein endothelial cells and human smooth muscle cells).[259]

PLGA copolymers expand printing strategies beyond melt processing. Song *et al.* fabricated protein-functionalized PLGA scaffolds *via* fused deposition modelling, achieving controlled degradation and enhanced osteogenic differentiation (*e.g.*, *in vitro* cell tests with rabbit bone marrow mesenchymal stem cells).[260] Solvent-based printing approaches further mitigate thermal degradation. Hatt *et al.* demonstrated extrusion of

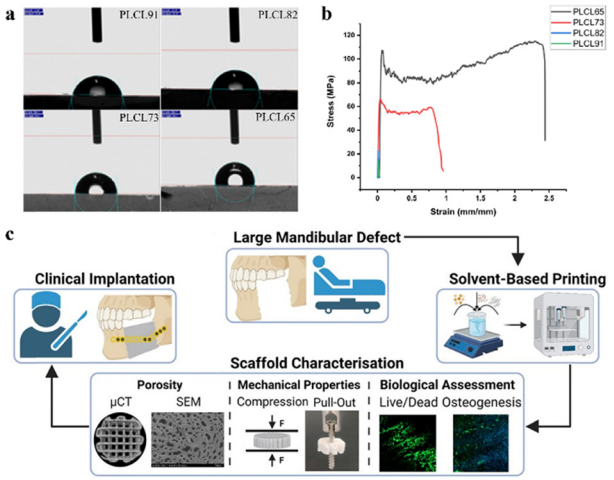

Fig. 8 Surface wettability, mechanical properties, and patient-specific fabrication of copolymer PLA scaffolds. (a) Water contact angles showing the hydrophilicity of PLA copolymers. (b) Stress–strain curve of the synthesized PLCL. Reprinted with permission from ref. 258. Copyright 2022, American Chemical Society. (c) Workflow of the creation of a patient-specific 3D-printed scaffold. Reprinted with permission from ref. 261. Copyright 2023, Oxford University Press.

PLGA at low temperatures using non-toxic solvents that can both preserve molecular weight and incorporate heat-sensitive bioactive compounds, allowing patient-specific fabrication of PLGA scaffolds (Fig. 8c).[261]

Powder extrusion and direct ink writing strategies further illustrate how copolymer chemistry expands both printable modalities and functional integration in PLA-based systems.[262–264] Annaji *et al.* exploited the relatively low melting temperature and favourable flow characteristics of PLGA copolymers to achieve powder extrusion of drug-loaded scaffolds, which effectively protects heat-sensitive therapeutics during processing.[265] The infill density, wall thickness, and drug release kinetics of the printed constructs could be precisely modulated by tuning the molecular weight of PLGA. Similarly, Sonthithai *et al.* integrated PEG–PLA diblock copolymer synthesis with a powder extrusion and direct ink writing printing strategy to fabricate photocurable composite hydrogels for cartilage repair.[266] In this system, hydrophobic PLA segments provided mechanical reinforcement through physical association, and hydrophilic PEG domains maintained high water content and print fidelity. The resulting scaffolds exhibited well-defined pore architectures and supported porcine articular chondrocyte redifferentiation.

Challenges and opportunities: while copolymerization expands printability and degradation control, printed structures remain geometry-defined rather than molecularly programmed. Opportunities lie in copolymers that couple printability with stimulus responsiveness or self-organization, expanding functionality beyond static architectures.

3.4. Copolymer hydrogels: injectable and responsive platforms

PLA is frequently incorporated into hydrogel systems in the form of block copolymers to impart mechanical reinforcement, injectability, and programmable degradation, making these materials particularly attractive for minimally invasive therapies and localized tissue regeneration.[267–270] In contrast to chemically crosslinked hydrogels, PLA-containing copolymer hydrogels rely primarily on physical interactions, allowing reversible sol–gel transitions and reducing concerns associated with residual crosslinkers.

PEG–PLA-based block copolymers dominate this space due to their well-defined amphiphilic architecture and thermosensitive sol–gel transitions under physiological conditions.[271–273] Upon heating, hydrophobic PLA segments aggregate to form physically crosslinked domains whereas hydrophilic PEG chains maintain water retention and cytocompatibility. As reported by Sun *et al.*, these assemblies create micellar cores capable of encapsulating hydrophobic drugs, and the PEG-rich corona enhances colloidal stability and minimizes nonspecific protein adsorption.[274] Such architecture allows injectable delivery followed by *in situ* gelation, providing spatial confinement of therapeutic payloads without surgical implantation.

PLGA–PEG–PLGA triblock copolymer systems further extend this concept by allowing independent tuning of gelation temperature, mechanical stiffness, and degradation kinetics through copolymer composition and block length. Zhao *et al.* demonstrated that subtle variations in lactide to glycolide ratio and molecular weight could shift gelation windows to near body temperature, as well as simultaneously controlling recombinant protein hMetrnl release profiles over clinically relevant time scales.[275] These features translated directly into improved wound healing outcomes, highlighting the functional relevance of copolymer architecture beyond simple injectability as shown in Fig. 9a.

Beyond conventional block copolymers, sequence-controlled copolymerization introduces an additional design dimension. Jo *et al.* reported that gradient *versus* block sequence distributions within PLA-containing copolymers greatly influence gel strength, sol–gel transition temperature, and degradation behaviour (Fig. 9b).[276] Unlike traditional block architectures, gradient sequences generate more heterogeneous hydrophobic domains, leading to broader gelation windows and tunable viscoelastic responses. This level of control provides a route to decouple mechanical integrity from degradation rate.

Beyond simple compositional variation, chain sequence distribution provides copolymer systems with an additional thermodynamic handle that allows the decoupling of segregation strength from interfacial width. In contrast to block copolymers, where a sharp junction between A and B blocks leads to strong segregation and narrow interfaces under a given effective Flory–Huggins parameter χN, gradient copolymers distribute the compositional transition over a finite chain contour. This spatial averaging reduces local segregation strength, broadens the order–disorder transition, and creates more diffuse phase boundaries, thereby stabilizing heterogeneous domain structures over wider processing and compositional windows.[277]

The underlying physics has been quantitatively established. Brown *et al.*, using self-consistent field theory, demonstrated

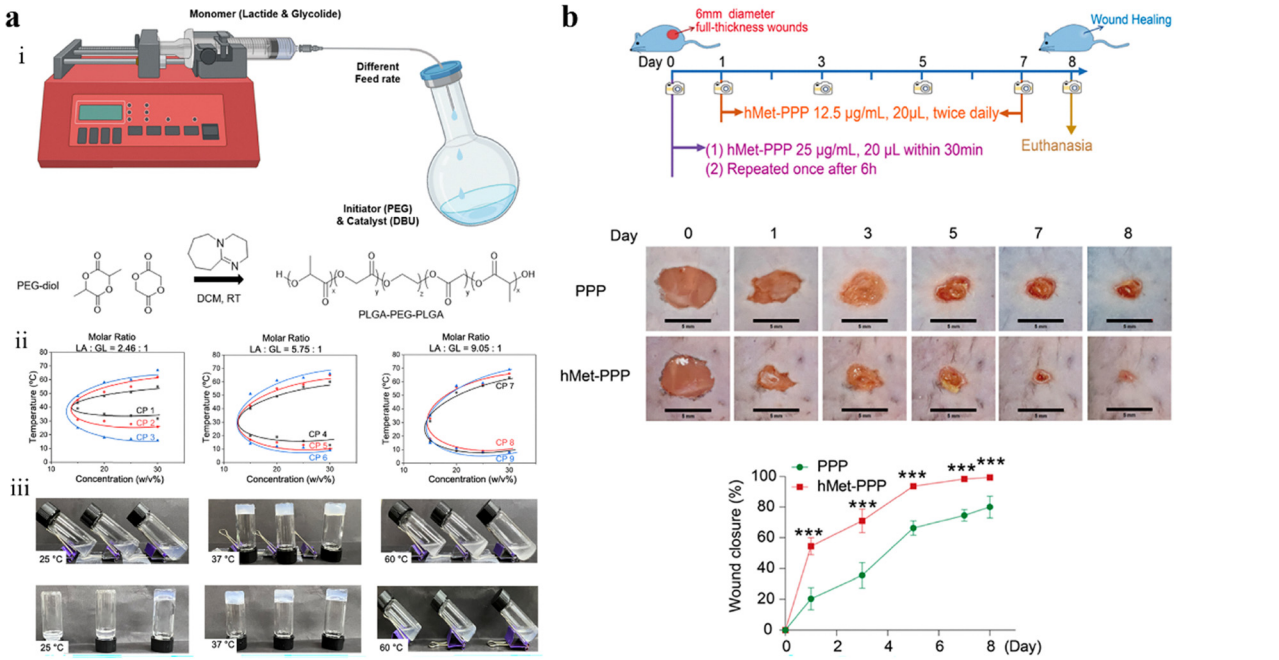

Fig. 9 Wound healing using PLA copolymeric gels. (a) Schematic of PLGA–PEG–PLGA triblock copolymer synthesis, with controlled PLGA sequences achieved by manipulating feed rates and molar ratio between lactide and glycolide (i). Sol–gel transition curves for copolymers synthesized at varying feed rates and molar ratios of lactide to glycolide (ii). Photographs of sols and gels at various temperatures (iii). Reprinted with permission from ref. 275. Copyright 2024, American Chemical Society. (b) The administration of hMet-PPP promotes skin wound healing in mice. (n = 6–10). Data are presented as mean ± SD. *** $p < 0.001$, as analyzed by two-way ANOVA. Reprinted with permission from ref. 276. Copyright 2025, MDPI.

that adding a tapered (gradient) region between blocks shifts the order–disorder transition to lower temperatures relative to the neat diblock, an effect that scales with taper length and is more pronounced in inverse tapers.[277] Tapered systems do not simply behave as diblocks at a shifted effective temperature: normal tapering systematically widens the bicontinuous gyroid region of the phase diagram whereas inverse tapering narrows this region, reflecting asymmetry in chain organization at the interface. More recently, Li *et al.* employed particle-based simulations to show that fine-tuning monomer sequence distribution along gradient copolymers permits independent control over microdomain size, interfacial mixing, and mechanical response, establishing sequence as a distinct design variable rather than a binary block *vs.* random choice.[278]

For PLA-based copolymers, the significance of sequence distribution is twofold. On the synthetic front, Cheng *et al.* developed stereogradient PLA *via* controlled ring-opening polymerization of *meso*-lactide/L-lactide mixtures, achieving gradient sequences that systematically grade stereochemistry along the polymer backbone.[279] This structural feature modulates crystallization kinetics, thermal stability, and degradation profiles in ways unattainable by simple block or random architectures. On the application side, sequence-controlled multiblock copolymers of PLA have been shown to improve mechanical performance dramatically. For instance, sequence-defined six-arm star-block copolymers of PCL-*b*-PLA undergo phase separation that results in a two- to three-fold enhancement in tensile toughness without sacrificing modulus, demonstrating the direct influence of block sequence on bulk mechanical properties. These examples illustrate that the desired sequence architecture, whether blocky for strong microphase separation and periodic nanostructures, or gradient/tapered for broader processing windows and enhanced interfacial stability, is inherently application-specific. Emerging self-consistent field theory formalisms capable of treating arbitrary monomer sequences, coupled with advances in sequence-controlled PLA synthesis, now provide the theoretical and synthetic framework to rationally design copolymer sequences tailored to specific biomedical requirements, from load-bearing scaffolds to stimuli-responsive delivery systems.[280]

Challenges and opportunities: despite this progress, copolymer hydrogels generally lack long range structural anisotropy and spatial organization, limiting their ability to recapitulate direction-dependent mechanical and biological cues present in native tissues. Opportunities lie in integrating PLA-based copolymer chemistry with self-assembling motifs, supramolecular interactions, or external fields to introduce directionality, hierarchical structuring, and dynamic remodelling.

3.5. LC copolymerization: molecularly-encoded order

Conventional PLA copolymerization strategies, as discussed in Sections 3.1–3.4, primarily aim to regulate crystallinity, elasticity, and degradation kinetics through the incorporation of flexible or hydrophilic comonomers. While highly effective in matching bulk mechanics and degradation to tissue-specific demands, these copolymers generally remain structurally

isotropic with a limited capacity to encode directional order or long range molecular organization. In this context, LC copolymerization introduces an additional design dimension in which mesogenic units are incorporated directly into the polymer backbone, enabling spontaneous molecular ordering that is intrinsic rather than processing-induced.[149,154,281–311]

Oca *et al.* introduced LC phase behaviour through the synthesis of aromatic–aliphatic LC copolyesters, which exhibited a nematic mesophase below 165 °C.[312] Injection-moulded specimens showed pronounced molecular orientation along the flow direction, resulting in a Young's modulus of 5.7 ± 0.3 GPa, compared to 2.3 ± 0.3 GPa for compression-moulded samples. The degradation behaviour of these materials showed reduced temperature sensitivity relative to other biodegradable polyesters. Direct and indirect contact assays with MC3T3-E1 osteoblasts indicated favourable cytocompatibility without detectable cytotoxic leachables, comparable to poly(glycolic acid). Wei *et al.* designed and prepared biobased LC copolyesters as shown in Fig. 10a, which also demonstrated that the combined degradability, mechanical performance, and biological compatibility of these materials support their potential for biomedical device applications (Fig. 10b and c).[313]

Challenges and opportunities: despite their promise, LC copolymers often require complex synthesis and a careful balance between mesophase stability and biodegradability. Opportunities lie in developing biodegradable LC monomers compatible with lactide polymerization and in sequence-controlled copolymerization strategies that achieve programmable anisotropy without sacrificing processability.

3.6. Commercial platforms of PLA copolymers

Distinct from physical blending, the copolymerization of PLA with comonomers such as glycolide and ε-caprolactone, or with polymeric segments such as polyethylene glycol, introduces covalent linkages that suppress macroscopic phase separation while allowing controlled nanoscale organization. This molecular-level integration allows for the systematic tuning of crystallinity, mechanical compliance, and degradation kinetics across a broad spectrum of material architectures. From a translational perspective, PLA-based copolymers represent one of the most mature classes of synthetic biodegradable materials, demonstrated by a wide range of clinically approved medical devices and drug delivery systems.

The commercial landscape is predominantly anchored by PLGA, particularly in the field of controlled drug delivery. Its widespread adoption is exemplified by globally marketed products such as Lupron Depot developed by AbbVie, as well as standardized excipient platforms including the RESOMER series from Evonik Industries.[314,315] These systems use the predictable hydrolytic degradation and tunable release characteristics of PLGA to achieve sustained and controlled therapeutic delivery. Similarly, widely used bioresorbable sutures such as Vicryl (Ethicon) are based on PLGA copolymer systems.[316]

For applications requiring high elasticity and fatigue resistance, copolymers such as PLCL have been developed to better match the dynamic mechanical environment of soft tissues. These materials have achieved clinically relevant implementations in flexible, implantable devices, including peripheral nerve conduits and soft tissue support structures. Representative examples include nerve repair products from Polyganics and Gunze, as well as elastomeric biodegradable systems used in aesthetic lifting threads, such as Aptos threads based on PLLA–PCL copolymers.[317,318]

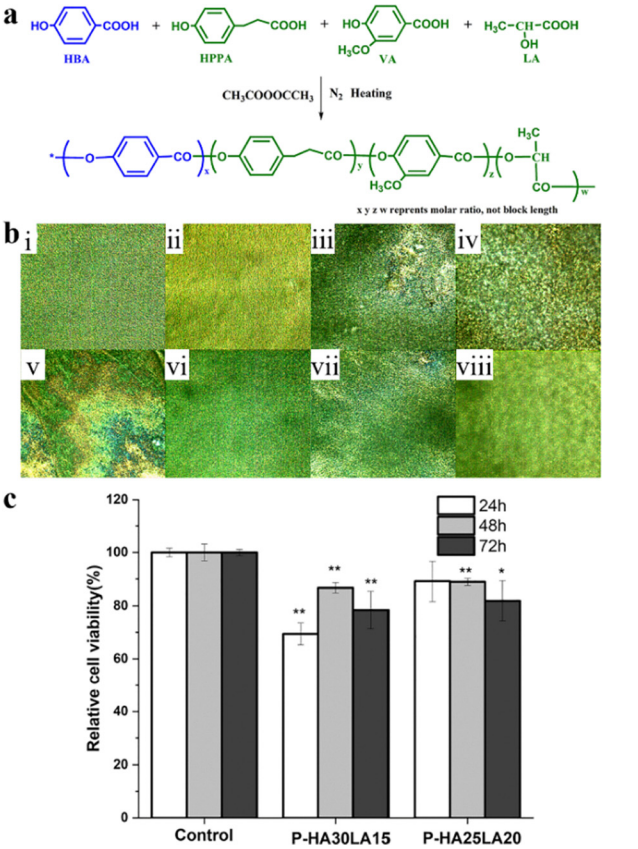

Fig. 10 Phase behaviour and cytotoxicity of lactide-based LC copolyesters. (a) Reaction route of LC lactide-based copolyesters. (b) Polarized light micrographs of synthesized LC copolyesters: P-HA35LA10, 200 °C (i); P-HA30LA15, 230 °C (ii); P-HA25LA20, 225 °C (iii) and 350 °C (iv); P-HA26LA23, 210 °C (v); P-HA35LA25, 250 °C (vi); P-HA30LA28, 190 °C (vii) and 300 °C (viii). (c) Cytotoxicity assessment of LC copolyesters (*$P < 0.05$, **$P < 0.01$). Reprinted with permission from ref. 313. Copyright 2022, Elsevier.

Meanwhile, amphiphilic block copolymers based on PEG–PLA architectures are driving continued innovation in advanced pharmaceutics. These materials can self-assemble into nanostructures such as micelles or thermoresponsive hydrogels, permitting injectable formulations with *in situ* gelation and spatiotemporally controlled drug release. Such systems are being actively translated by pharmaceutical developers with advanced delivery platforms, including Luye Pharma, which has established expertise in PLGA-based microsphere technologies for long-acting injectables. Commercial products such as Rykindo and Jinyouping further highlight the expanding role of PLA-based copolymer systems in next-generation therapeutic modalities.[319]

4. Bulk and surface grafting for PLA modification

Grafting modification can be regarded as an interfacial ''precision surgery'' for improving the biomedical performance of PLA. Grafting strategies mainly fall into two categories. The first is bulk grafting (*e.g.*, maleic anhydride-grafted PLA(PLA-*g*-MAH)), which is primarily used as a compatibilizer to improve interfacial bonding between PLA and hydrophilic fillers such as bone powders or natural fibres.[320–326] The second is surface grafting (*e.g.*, surface grafting of polymers), which aims to impart hydrophilicity, antibacterial properties, or specific cell recognition capability to the inherently hydrophobic PLA surface.[327–332]

In recent years, research emphasis has shifted from purely improving mechanical performance toward imparting biological activity (through grafting peptides or growth factors) and electrical conductivity (through grafting CNTs or polypyrrole), among other emerging functionalities. However, both *in vitro* and *in vivo* studies remain limited. Therefore, this section mainly focuses on more established grafting strategies and provides guidance for future applications in tissue engineering.

4.1. Grafted PLA films: interfacial toughening and bioactive surfaces

In film systems, grafting modification is mainly applied to improve toughness, optical transparency, and surface functionalization, such as antibacterial and anti-adhesion properties.[333–338] PLA-*g*-MAH plays a critical role in the fabrication of high-performance films. Park *et al.* employed PLA -*g*-MAH as an *in situ* compatibilizer in PLA/poly(butylene terephthalate-*co*-butylene sebacate) blends.[339] The MAH groups reacted with terminal hydroxyl groups of poly(butylene terephthalate-*co*-butylene sebacate) *via* esterification, forming graft copolymers *in situ* and significantly reducing interfacial tension. This interfacial grafting modification increased the elongation at break compared with the brittle failure of pristine PLA and improved film transparency. Such modified films combine the strength of PLA with the toughness of the rubbery phase, making them promising candidates for flexible anti-adhesion membranes or barrier layers in soft tissue repair.

Surface grafting of bioactive organic acids is another effective strategy to improve the surface properties of PLA films. Juarez-Moreno *et al.* grafted fumaric acid and ascorbic acid onto PLA film surfaces using dielectric barrier discharge cold plasma treatment.[340] After fumaric acid and ascorbic acid grafting, the water contact angle decreased from $\sim 76^{\circ}$ (pristine PLA) to $\sim 40^{\circ}$ and $\sim 28^{\circ}$, respectively, indicating a substantial enhancement in surface hydrophilicity. Through fumaric acid and ascorbic acid grafting, the surface wettability and chemical activity of PLA were significantly improved without altering bulk material properties, providing a new modification route for tissue engineering scaffolds and biomedical implants.

Natural polymers such as chitosan can also be grafted onto PLA to enhance bioactivity.[341–344] Vamvakaki *et al.* synthesized chitosan-grafted PLLA using a ''grafting-to'' strategy in which PLLA polymer chains were chemically bonded to the chitosan backbone.[345] The resulting films retained the mechanical support of PLA with introduced amino groups from chitosan, which improved hydrophilicity and cell affinity as shown in Fig. 11a and b. *In vitro* studies demonstrated that MC3T3-E1 preosteoblasts exhibited significantly higher adhesion and proliferation on chitosan-*g*-PLLA films than on pristine PLA films. These graft copolymer films show strong potential as guided bone regeneration membranes, effectively preventing soft tissue invasion (Fig. 11c and d) while promoting bone repair.[346]

Challenges and opportunities: grafting modification effectively improves toughness, transparency, and surface bioactivity of PLA films, but functional effects are largely limited to interfacial regions. Challenges remain in maintaining long term stability of grafted functionalities under physiological conditions. Opportunities exist in combining bulk compatibilization with stable surface grafting to produce multifunctional films for anti-adhesion and soft tissue repair applications.

4.2. Grafted PLA fibres: bioactive and conductive interfaces

In electrospinning, grafting modification is commonly used for post-spinning surface functionalization or as an additive to improve the dispersion of inorganic fillers within fibres.[347–352] Castro *et al.* formed a tightly adhered conductive polypyrrole layer on PLGA fibre surfaces through *in situ* oxidative polymerization of pyrrole monomers, representing a generalized form of surface grafting.[240] This modification imparted excellent electroactivity to the scaffold without disrupting the aligned fibre structure, as shown in Fig. 12a. When PC12 cells were cultured on the scaffolds under electrical stimulation, graft-modified fibres significantly promoted directional neurite outgrowth compared to simple physical blends.

Carbon-based materials can also be grafted onto polymers to impart conductivity.[353–357] Roca *et al.* grafted carboxylated carbon nanotubes (CNTs-COOH) onto surface-activated electrospun PLA nanofibres.[358] After oxidative treatment of PLA fibres, CNTs were covalently immobilized *via* esterification. The nanofibrous architecture facilitated current guidance and increased specific surface area, providing abundant anchoring sites for CNTs. Compared with physical adsorption, grafted CNTs were more resistant to detachment during ultrasonication or *in vivo* conditions, significantly improving biosafety (Fig. 12b). The grafted fibrous membranes exhibited enhanced conductivity, surface roughness, and hydrophilicity.

MAH can act as an intermediate to graft bioactive components such as collagen or CNCs onto PLA matrices. Ospina-Orejarena *et al.* used MAH as an intermediate species to covalently graft collagen onto PLA backbones.[359] In electrospun fibres, fibre diameter decreased with increasing collagen content without introducing defects. Compared to blend-spun fibres, graft-modified scaffolds exhibited a higher Young's modulus due to strengthened interfacial interactions and showed a fourfold increase in cell adhesion. In addition, Zhou *et al.* prepared CNC-reinforced electrospun nanocomposite scaffolds using MAH-grafted PLA as the matrix, effectively

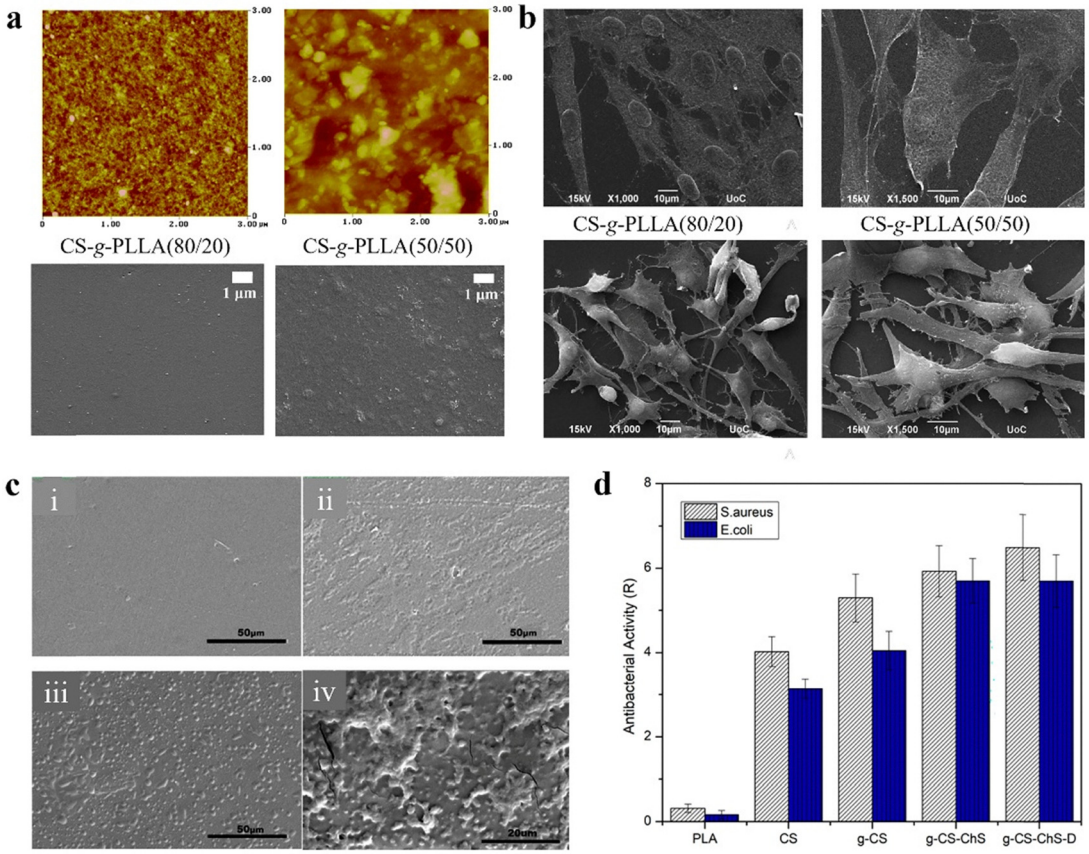

Fig. 11 Cellular adhesion and antibacterial performance of chitosan-grafted and surface-modified PLA films. (a) Atomic force micrographs and scanning electron micrographs of CS-*g*-PLLA (80/20) and CS-*g*-PLLA (50/50). (b) Scanning electron micrographs illustrating the morphology of MC3T3-E1 pre-osteoblastic cells cultured for 2 days on CS-*g*-PLLA (80/20) and CS-*g*-PLLA (50/50) films. Reprinted with permission from ref. 345. Copyright 2020, Elsevier. (c) Scanning electron micrographs of untreated PLA (i), plasma treated PLA (ii), and CS (iii) and CS-chondroitin sulfate (ChS) (iv) grafted films. (d) Antibacterial activity of untreated, CS and/or ChS coated, and lomefloxacin loaded PLA samples. Reprinted with permission from ref. 346. Copyright 2022, MDPI.

preventing CNC aggregation in the hydrophobic PLA matrix.[360] Esterification between MAH groups and CNC hydroxyl groups formed robust chemical interfaces. The resulting nanofibres exhibited tensile strengths exceeding 10 MPa and improved *in vitro* degradation stability. These scaffolds showed no cytotoxicity and effectively supported the proliferation of human adipose-derived stem cells.

Furthermore, Uda *et al.* investigated the influence of grafting architecture on fibre properties.[361] Although based on PCL systems, the findings are highly relevant to PLA. Copolymers with varying graft densities and side chain lengths were synthesized and electrospun into fibres. High grafting density forced the main chains into a distinctive bottlebrush conformation, significantly altering crystallization behaviour and fibre surface potential. This molecularly designed grafting strategy provides precise control over degradation rate and cell interactive interfaces, with potential applications in bioelectronic interfaces and neural repair.

Challenges and opportunities: grafted PLA fibres exhibit enhanced bioactivity, conductivity, and interfacial reinforcement without compromising fibrous morphology, but precise control over graft distribution and long term stability remains challenging. Opportunities include molecularly designed graft architectures that regulate crystallization, degradation, and cell–material interactions while remaining compatible with scalable electrospinning processes.

4.3. 3D Printing of grafted PLA: reactive and post-printing functionalization

In 3D printing, graft-modified PLA acts as a key compatibilizer for fabricating high strength, bioactive composite scaffolds.[362–366] Dominguez-Candela *et al.* investigated 3D-printed PLA/poly(3-hydroxybutyrate) scaffolds using various reactive graft copolymers and compatibilizers, including petroleum-based polyethylene derivatives (ethylene–glycidyl methacrylate copolymer and ethylene–methyl acrylate–glycidyl methacrylate terpolymer), styrene–MAH copolymer, and epoxidized linseed oil.[116] During melt processing, these additives underwent *in situ* reactions, significantly improving ductility and impact resistance, with impact absorption energy increasing by approximately 31–47%. The printed scaffolds exhibited porosities of 50–53% and pore sizes of 675–718 μm, well suited

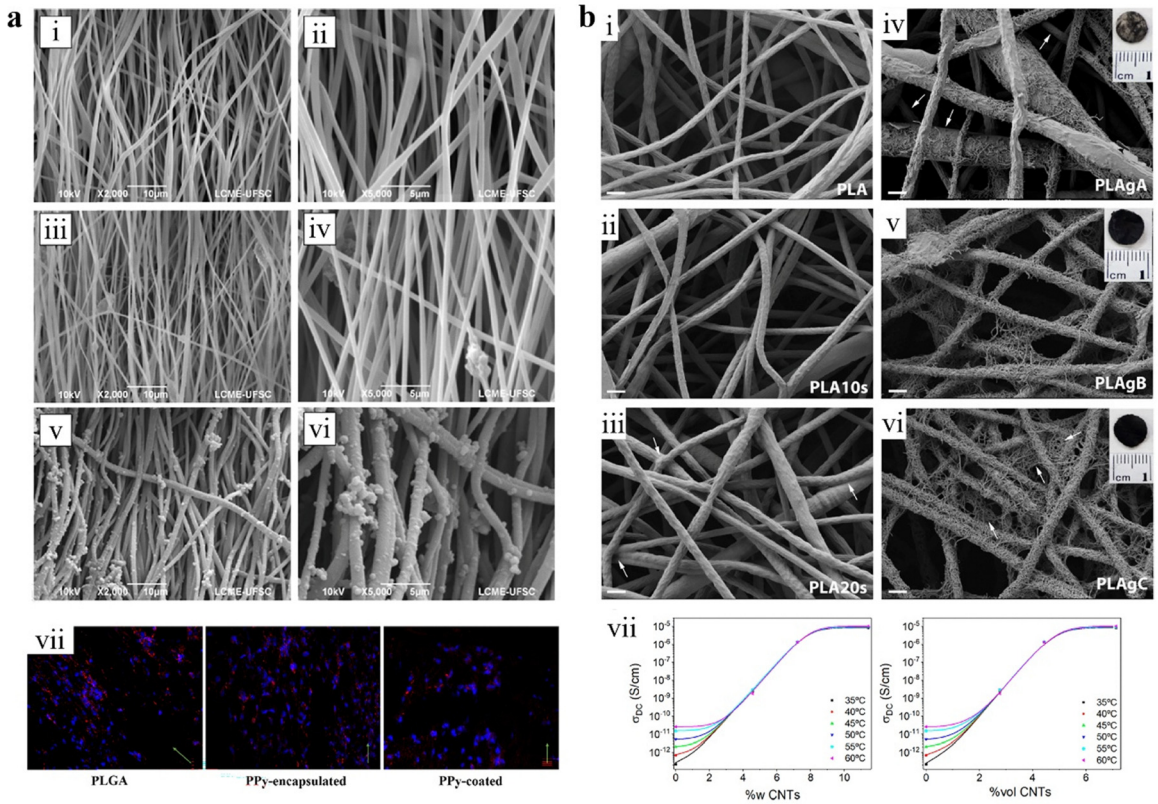

Fig. 12 Electrical conductivity and cellular responses of electrospun PLA grafting membranes. (a) Scanning electron micrographs of PLGA (i) and (ii), polypyrrole-encapsulated (iii) and (iv), and polypyrrole-coated electrospun mats (v) and (vi). Fluorescence micrographs of PC12 cells after 7 days on PLGA, polypyrrole-encapsulated, and polypyrrole-coated electrospun mats (vii). The blue staining was conducted by using 4′,6-diamidino-2-phenylindole, which labels cell nuclei, and the red staining used phalloidin, which shows the actin cytoskeleton. Reprinted with permission from ref. 240. Copyright 2025, American Chemical Society. (b) Scanning electron micrographs and photographs (insets) of membranes and characterization of their fibre diameter before and after CNTs grafting: a nontreated electrospun PLA membrane (i), an electrospun PLA membrane treated with 30% H_2SO_4 for 10 s (ii) and 20 s (iii). Electrospun PLA membrane grafted with CNTs after treated with 30% H_2SO_4 for 10 s (iv), membrane grafted with CNTs after treated with 30% H_2SO_4 for 10 s and subjected to water rinsing and drying (v), and membrane grafted with CNTs after treated with 30% H_2SO_4 for 20 s and subjected to water rinsing and drying (vi). White arrows indicate areas where the CNTs fill the gaps between nanofibers. Electrical conductivity as a function of both mass fraction and volume fraction of CNTs present in the PLA membranes (vii). Reprinted with permission from ref. 358. Copyright 2023, American Chemical Society.

for bone cell growth. The additives also reduced water contact angles ($<65^\circ$), enhancing surface hydrophilicity, as shown in Fig. 13a. These improvements in processability and cellular metabolic activity shown in Fig. 13b highlight the suitability of such systems for bone tissue engineering.

PLA-*g*-MAH also effectively improves interfacial bonding during 3D printing. Lendvai *et al.* demonstrated that adding only 0.25–2.0 wt% PLA-*g*-MAH allowed esterification between anhydride groups and hydroxyl groups on biofiller surfaces, significantly enhancing interfacial adhesion.[367] This grafting strategy increased tensile strength by 15% and impact strength by 45%. Although not directly tested in tissue engineering contexts, these findings offer insights into preventing premature failure of PLA-based composite bone screws or plates due to interfacial debonding after implantation.

Baran *et al.* discussed photografting and atom transfer radical polymerization grafting strategies on PLA scaffolds printed *via* fused deposition modeling.[368] Due to the complex internal porosity of printed structures, conventional coatings often fail to achieve uniform coverage. Surface grafting using monomer vapor or solution infiltration allows functional polymer brushes (*e.g.*, poly(methyl methacrylate) or poly(ethylene glycol) methacrylate) to grow on all internal surfaces. Such modifications impart antifouling properties or specific biological recognition, both of which are critical for vascular scaffolds and implantable sensor housing.[369–371]

Challenges and opportunities: in 3D printing, grafted PLA primarily improves interfacial bonding and surface functionality of composite scaffolds, but modification effects are often constrained by printing-induced heterogeneity. Opportunities exist in integrating grafting strategies with printing pathways to achieve uniform functionalization throughout complex porous architectures and to enhance long term biological performance.

4.4. Injection moulding PLA with reactive grafting

Injection moulding requires good melt flowability and thermal stability. Similar to 3D printing, grafting modification in this

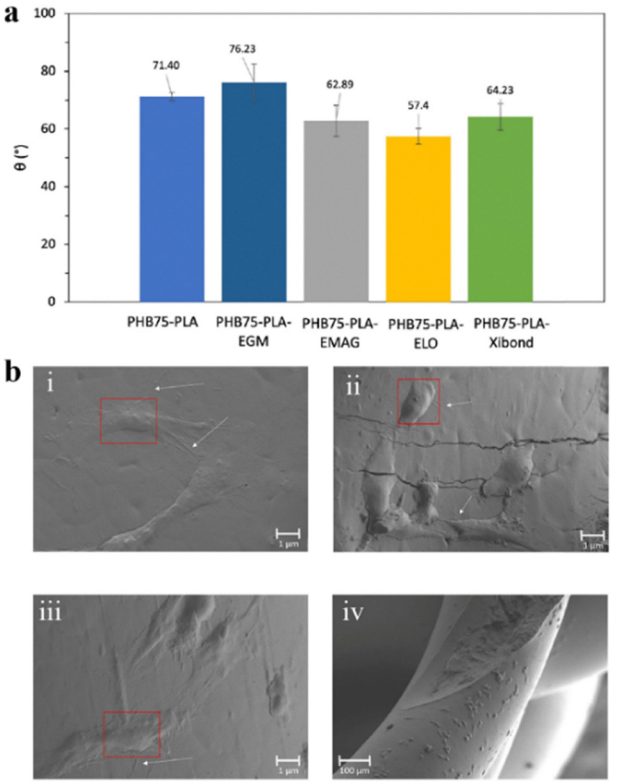

Fig. 13 Surface wettability and osteoblastic cell adhesion behaviour of 3D-printed scaffolds. (a) Water contact angle measurements of 3D printed scaffolds made of PHB75-PLA blend with different additives. (b) Scanning electron micrographs of human osteoblastic cell proliferation on 3D printed scaffolds after 7 days: PHB75-PLA-EMAG (i), PHB75-PLA-ELO (ii), PHB75-PLA-Xibond (iii), and PHB75-PLA-Xibond (iv). Red box indicates lamellipodia and white arrow a filopodia formation. Red box indicates lamellipodia and white arrow indicates a filopodia formation. Reprinted with permission from ref. 116. Copyright 2024, Elsevier.

process mainly enhances interfacial compatibility to produce high-strength composite implants.[372–374] Pérez-Fonseca *et al.* compared MAH-*g*-PLA and glycidyl methacrylate-grafted PLA (GMA-*g*-PLA) in injection moulding.[375] GMA-*g*-PLA contains highly reactive epoxy groups. During extrusion–injection processing, GMA-*g*-PLA exhibited higher reaction efficiency and more effective grafting onto natural fibre surfaces than MAH-*g*-PLA (Fig. 14). PLA composites modified with GMA-*g*-PLA achieved tensile strengths up to 67 MPa, exceeding that of pristine PLA. This study provides a clear pathway for improving the mechanical performance of injection-moulded orthopedic implants.

Standau *et al.* reviewed and experimentally investigated the use of PLA-*g*-MAH and peroxide-initiated chain extension/grafting reactions to improve PLA melt strength for microcellular injection moulding.[376] Pristine PLA exhibits low melt strength, leading to pore collapse during foaming. Long chain-branched PLA produced *via* reactive extrusion significantly increased low-shear viscosity. Using this modified PLA, microcellular injection moulding yielded porous scaffolds with uniform cell structures and high porosity. These scaffolds retained the

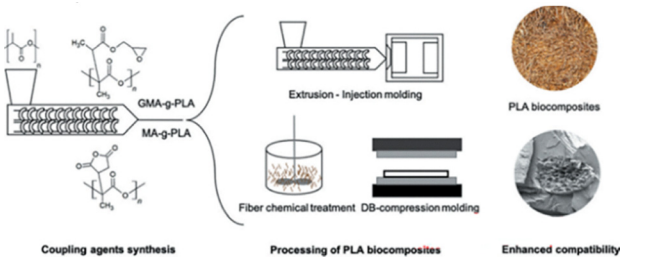

Fig. 14 Schematic illustration of the fabrication of PLA biocomposites using extrusion–injection moulding and dry blending–compression moulding with MA-*g*-PLA and GMA-*g*-PLA as compatiblizer. Reprinted with permission from ref. 375. Copyright 2021, Taylor & Francis.

geometric precision of injection-moulded parts and incorporated internal microporosity favourable for cell ingrowth, which represents an efficient manufacturing route for bone tissue engineering scaffolds.[377,378]

Challenges and opportunities: grafting modification significantly enhances interfacial compatibility and mechanical strength of injection-moulded PLA composites, but optimization is constrained by processing stability and melt rheology. Opportunities lie in reactive grafting strategies that balance flowability, mechanical reinforcement, and structural integrity for load-bearing orthopedic implants.

4.5. LC grafting through side chain and terminal architecture

As discussed in Sections 4.1–4.4, conventional grafting strategies improve toughness, hydrophilicity, conductivity, or bioactivity by introducing functional moieties at interfaces. LC grafting represents an advanced extension of this concept, in which mesogenic units are grafted onto PLA chains to generate self-organized, ordered interfaces rather than chemically uniform surfaces.[379–382]

Gong *et al.* reported this approach through the synthesis of ABA triblock copolymers consisting of a central PLLA block and terminal cholesterol-based dendritic LC segments.[383] In this architecture, the PLLA backbone provides mechanical support and biodegradability while the grafted cholesterol mesogens drive local ordering and self assembly, as shown in Fig. 15a. Although the introduction of hydrophobic LC segments increased surface hydrophobicity relative to pristine PLA, *in vitro* studies with 3T3-L1 fibroblasts revealed significantly enhanced cell adhesion and proliferation (Fig. 15b). This behaviour reveals that cellular responses are governed not only by surface chemistry, but also by the presence of ordered, dynamic interfacial structures.

Unlike physically blended low molecular weight LC molecules, grafted LC moieties are covalently tethered, minimizing leaching and improving structural stability under aqueous and physiological conditions. At the same time, because LC units are localized primarily at chain ends or side chains, LC grafting avoids the synthetic complexity and processing constraints associated with full backbone copolymerization.[384,385] This strategy allows for the decoupling of bulk mechanics from interfacial bioinstruction, which is advantageous for scaffolds

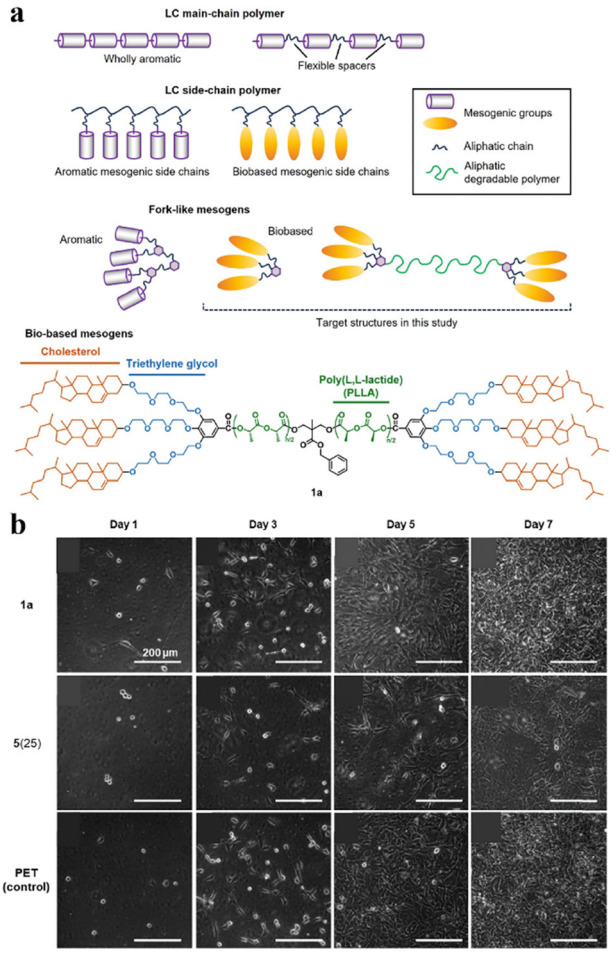

Fig. 15 Fibroblast adhesion and morphology of LC PLLA derivatives. (a) Molecular design for LC poly(L,L-lactide) derivative. (b) Phase contrast micrographs of 3T3-L1 mouse fibroblasts cultured on poly(L,L-lactide) derivative. Reprinted with permission from ref. 383. Copyright 2025, American Chemical Society.

where surface-mediated cell signaling dominates performance. More broadly, LC grafting transitions PLA surfaces from chemically functionalized interfaces to structurally organized, anisotropic biointerfaces, offering new opportunities for guiding cell alignment, differentiation, and mechanotransduction without altering bulk scaffold integrity.[386]

Challenges and opportunities: while LC grafting provides robust interfacial ordering with minimal impact on bulk properties, the strategy still limits precise control over graft density, spatial distribution, and long term evolution during triggered reorganization or stimuli responsiveness, allowing time-dependent and adaptive biointerfaces degradation. Opportunities lie in designing grafted architectures that couple LC ordering with degradation.

4.6. Translational gaps and future pathways for grafted PLA

Distinct from physical blending and covalent copolymerization, grafting and surface modification of PLA constitute a targeted interfacial engineering strategy aimed at decoupling bulk mechanical performance from surface-specific functionality. Broadly, these approaches can be categorized into bulk grafting, typically achieved *via* reactive processing, and surface grafting, which involves the functionalization of preformed substrates.

From a translational perspective, these two strategies exhibit markedly different levels of technological maturity. Bulk grafting systems, exemplified by PLA-*g*-MAH, are primarily investigated as macromolecular compatibilizers to enhance interfacial adhesion in PLA-based composites containing inorganic fillers (*e.g.*, hydroxyapatite, β-tricalcium phosphate) or elastomeric phases (*e.g.*, polycaprolactone). Despite extensive academic investigation, there is currently limited publicly disclosed evidence supporting their use as core technologies in clinically approved high-risk implantable devices. Key barriers include challenges associated with scalable manufacturing, precise control over grafting efficiency and distribution, batch-to-batch reproducibility, and the establishment of long-term *in vivo* safety profiles.

In contrast, surface grafting strategies, particularly those applied to electrospun fibers, porous scaffolds, and thin films, have been widely explored to introduce functionalities such as enhanced hydrophilicity, antimicrobial activity, and biorecognition. These are typically achieved through the immobilization of bioactive molecules (*e.g.*, RGD peptides), antimicrobial agents, or conductive polymers. However, the majority of such systems remain at the preclinical stage, with validation largely confined to *in vitro* studies and early animal models. Their clinical translation is constrained by several persistent challenges. First, maintaining the long-term chemical and structural stability of grafted layers *in vivo* (*e.g.*, under conditions involving enzymatic activity, fluid shear, and locally acidic degradation environments) remains nontrivial. Second, achieving uniform and conformal functionalization within complex three-dimensional porous architectures is technically challenging using conventional surface modification techniques. Third, the incorporation of biologically active components often introduces additional regulatory complexity regarding classification as combination products and more stringent requirements for demonstrating safety, efficacy, and manufacturing consistency under agencies such as the U.S. Food and Drug Administration.

The strategic value of grafting-based modification lies in achieving functional decoupling between bulk mechanical integrity and surface bioactivity. Future efforts should focus on developing grafting approaches compatible with scalable medical manufacturing processes, including solvent-free or vapor-phase techniques that facilitate deeper penetration into porous structures. In parallel, advances in macromolecular architecture design such as densely grafted or brush-like side chains may provide viable routes to improving the stability and durability of functional interfaces. Nevertheless, successful clinical translation will require not only materials innovation but also alignment with regulatory expectations, manufacturing robustness, and long-term biological validation. Progress across these dimensions is essential in advancing

grafting-modified PLA systems toward next-generation tissue engineering scaffolds and compliant biomedical interfaces.

5. Conclusion

Research on polymer-modified PLA for tissue engineering has progressively shifted from simple property enhancement toward structure- and function-oriented material design. Multiple parallel strategies have been established, including blending, copolymerization, grafting modification, and LC-related approaches, which are coupled with processing methods such as film casting, electrospinning, injection moulding, and additive manufacturing, as summarized in Table 1. Despite their diverse chemistries and fabrication routes, these strategies differ fundamentally in how structural order, spatial heterogeneity, and biological function are introduced within PLA-based systems.

Blended systems improve mechanical performance or surface bioactivity through the introduction of a second phase. However, their structure and properties are highly sensitive to processing conditions, resulting in limited morphological stability and pronounced variability in microstructure and macroscopic performance. Copolymerization offers clear advantages in improving phase stability, printability, toughness, and degradation controllability, yet the resulting materials are typically spatially homogeneous, which limits their ability to introduce gradient and directional biological cues. Grafting modification effectively enhances interfacial compatibility and surface bioactivity and is well suited for functional modification of films, fibres, and 3D printed structures, although its effects are largely confined to near-surface regions. Recently, LC-based modification provides an emerging route to introduce intrinsic order into PLA-based tissue engineering materials and has the potential to surpass conventional composite systems. Nevertheless, phase separation, nonuniform dispersion, and structural evolution during degradation remain difficult to control, and these systems are highly sensitive to composition and processing history.

From a fabrication perspective, electrospun fibres can generate anisotropic microstructures and improve cell guidance behaviour, but their ordering is primarily imposed by external processing. Additive manufacturing techniques, including 3D printing, offer precise geometric control over PLA-based composite scaffolds. However, functionality remains largely dictated by printing paths and composition ratios, with limited capability for molecular-level structural programming. Injection moulding provides advantages in mechanical reinforcement but offers relatively limited control over degradation gradients and surface functionality. Overall, most current systems rely on processing-induced structures rather than intrinsically encoding anisotropy or biological function at the molecular level, constraining reproducibility and long term performance consistency.

Future opportunities lie in the integration of material design, processing strategies, and biological function, shifting from reliance on external processing toward coordinated structural programming at molecular and supramolecular levels. Such integration may provide new routes for programmable degradation, improved interfacial stability, and enhanced cell–

Table 1 Comprehensive summary of representative polymer-modified PLA systems for tissue engineering applications

Modification strategy	Specific modification strategy	Primary fabrication technique	Key material form	Target tissue/application	Key outcome/performance highlight	Major challenges
Blending	PLA/cholesteryl ester LC[181,183]	Solvent casting/electrospinning	Film, fiber	Bone, muscle	Promotes M2 polarization, myogenesis, modulus 3–16 kPa	Phase separation, limited LC stability
Blending	PLA/PCL/PHB ternary[85,119]	Solution casting/melt blending	Film, foam	Chondrocytes, soft tissue	>350% elongation, cytocompatible	Property variability, processing sensitive
Blending	PLA/PEG or PLA/PCL binary[83,103]	Electrospinning	Nanofibrous mat	Soft tissue regeneration	High flexibility, hydrophilicity, cell adhesion	Process-driven alignment only
Blending	PLA/GO[188]	3D printing (FDM)	Porous scaffold	Bone (hWJ-MSCs)	Enhanced osteogenic markers (RUNX2, BMP2)	Dispersion uniformity, printability
Copolymerization	PLGA (85 : 15)[225]	Electrospinning	Fibrous membrane	Oral mucosa	Hydrophilic, accelerated degradation, cell infiltration	Acidic byproducts
Copolymerization	PLCL[236]	Electrospinning+ decellularized ECM	Bilayer conduit	Peripheral nerve	Regeneration comparable to autografts	Isotropic, batch variability
Copolymerization	PLGA–PEG–PLGA triblock[275]	Thermogelation	Injectable hydrogel	Skin wound healing	Thermoresponsive, sustained protein release	No anisotropy, limited spatial control
Copolymerization	Gradient PLGA–PEG–PLGA[276]	Thermogelation	Hydrogel	Soft tissue	Broad gelation window, tunable viscoelasticity	Synthetic complexity
Grafting	PLA-*g*-MAH[116,367]	Injection moulding/3D printing	Scaffold, implant	Bone	Increased tensile/impact strength (15%/45%)	Interface-confined effects
Grafting	Chitosan-*g*-PLLA[345]	Solvent casting	Film	Bone (pre-osteoblasts)	Hydrophilic (40°), improved cell adhesion	Long-term stability uncertain
Grafting	Carbon nanotube grafting[358]	Electrospinning	Fibrous membrane	Neural (PC12 cells)	Conductivity, directional neurite outgrowth	Graft density control, potential toxicity
LC-based	LC copolymerization (aromatic–aliphatic)[312,313]	Injection moulding	Dense implant	Bone (osteoblasts)	High modulus (5.7 GPa), cytocompatible	Complex synthesis, high processing temperature

material interactions. At the molecular level, sequence-controlled copolymerization, selective surface migration, and particularly the incorporation of LC moieties into PLA offers promising routes for constructing anisotropic and dynamically responsive structures while maintaining overall material stability and spatial control over mechanical and biological functions. At the material and structural levels, the synergistic integration of functional polymers and nanostructured components with advanced manufacturing techniques, including electrospinning, microfluidics, and 3D/4D printing, may achieve unified control over structure, properties, and biological function across multiple length scales. Through these advances, polymer-modified PLA can evolve from a passive biodegradable material into an actively programmable, multifunctional platform for tissue engineering.

Author contributions

CL and XW contributed to the conception of the review. CL performed the literature review and drafted the manuscript. XW supervised the work. All authors read and revised the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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