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Review Article

Low-Temperature Deposition Manufacturing: A Versatile Material Extrusion-Based 3D Printing Technology for Fabricating Hierarchically Porous Materials

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Low-temperature deposition manufacturing (LTDM) is a technology that combines material extrusion-based 3D printing and thermally induced phase separation (TIPS) into one process. With this feature, both the merits of 3D printing and TIPS can be incorporated including complex geometries with tailorable ordered macroporous features facilitated by 3D printing and microporous/nanoporous features endowed by TIPS. These macroporous/microporous/nanoporous combined structures are important to some important applications such as tissue engineering scaffolds, porous electrodes for electrochemical energy storage, purification, and filtering applications. However, the unique advantages and potential applications of LTDM have not been fully recognized and exploited yet. In this review, we will discuss the origin, principle, advantages, processes, and machine setup of LTDM technology with an emphasis on its unique advantages in fabricating porous materials. Then, current applications of LTDM including porous tissue engineering scaffolds and emerging porous electrodes for electrochemical storage will be described. The versatility of LTDM including its capability of processing a wide range of materials, multimaterial and gradient structures, and core-shell structures will be introduced. Finally, we will conclude with a perspective and outlook on the future development and applications of LTDM technology.

1. Introduction

Porous materials play an indispensable role in a wide range of applications such as tissue engineering scaffolds [1–4], electrodes for lithium-ion batteries, supercapacitors and fuel cells [5–14], oil/water separation, filters, and catalytic applications. One of the advantages of 3D printing is its capability of fabricating 3D objects with highly complex geometries. With this feature, 3D printing has unique advantages over other technologies for fabricating objects not only with complex 3D geometries but also with controllable porous characteristics, thereby offering an unparalleled tool for fabricating porous materials. The geometry and size of pores can be easily designed using computer-aided design (CAD) tools in a wide range of dimensions with minimum pore size down to tens of microns depending on the type of 3D printing technology. Some technologies such as two-photon polymerization (2PP) can even fabricate delicate controllable porous structures down to hundreds of nanometers [15].

However, few of 3D printing technologies are able to fabricate macroporous/microporous/nanoporous combined 3D objects. For those technologies able to fabricate nanoporous structures, it will be time-consuming to fabricate macrostructures. While for those technologies able to fabricate macroporous structures, it might be difficult to obtain microporous and nanoporous structures. While in some cases, macroporous/microporous/nanoporous combined structures are highly desired. For example, in bone tissue engineering, biodegradable scaffolds function as the template for cell attachment and proliferation [16]. Interconnected macroporous structures with a pore size of hundreds of microns are crucial for cell growth, nutrient transport, and

extraction of metabolites. Microporous structures and nanoporous structures are very important for cell attachment. Therefore, macroporous/microporous/nanoporous combined scaffolds with interconnected macropores provide an ideal template for bone tissue engineering [17, 18].

Inspired by the need for such scaffolds, a novel 3D printing process, namely, low-temperature deposition manufacturing (LTDM) was proposed [19]. LTDM combines material extrusion-based 3D printing and thermally induced phase separation (TIPS) into one process to fabricate macroporous/microporous/nanoporous combined 3D objects. Using this approach, the merits of both material extrusion-based 3D printing and TIPS can be incorporated. With material extrusion-based 3D printing, highly ordered precise macroporous features with a pore size of tens of microns to hundreds of microns may be fabricated in a layer-upon-layer fashion. While with TIPS, the unique advantage of fabricating microporous and nanoporous architectures can also be included. Due to these unique features, LTDM is especially suitable for fabricating porous tissue engineering scaffolds as a powerful bioprinting tool. The scaffolds fabricated via LTDM have been used as templates for cell culture, bone replacement, and other tissue engineering applications. In addition to tissue engineering applications, LTDM has also been applied to the fabrication of porous electrodes for lithium-ion batteries. Although the process was developed over 10 years ago, the unique advantages and its potential applications have not been fully recognized and exploited yet. In this minireview, we will discuss the origin, principle, advantages, and potential applications of LTDM and hopefully provide new insights into this technique.

2. Origin, Principle, and Processes of Low-Temperature Deposition Manufacturing

Low-temperature deposition manufacturing (LTDM) was initially proposed to satisfy the need for porous tissue engineering scaffolds [19]. In the early stage of tissue engineering, biodegradable scaffolds are usually fabricated via traditional fabrication methods such as solvent casting and particulate leaching, fiber bonding, phase separation, melt molding, solution casting, freeze drying, and gas foaming [16]. Although these processes are able to fabricate porous structures, they offer little capability of precisely controlling the pore size, geometry, and interconnectivity [3]. The random spatial distribution of pores within the scaffold matrix had been a major challenge. Consequently, researchers tried to pursue new technologies to address these challenges. This encouraged the use of 3D printing (also known as rapid prototyping and solid freeform fabrication) technologies to allow the digital CAD design and digital manufacturing of tissue engineering scaffolds [1].

Figure 1 shows the schematic of CAD-designed scaffolds with interconnected macropores and examples of scaffolds fabricated by fused deposition modelling (FDM) [20–30] and stereolithography (SLA) [31–44]. In these scaffolds, the line width W and line spacing S (Figure 1(a)) can be easily tuned, thereby achieving controllable pore geometry, size, and interconnectivity. This pioneering work has greatly advanced this field of tissue engineering. In addition to FDM and SLA, many other 3D printing technologies have also been explored to fabricate tissue engineering scaffolds such as binder-jetting [45–47], selective laser sintering (SLS) [48–53], microstereolithography (μ-SLA) [54–59], and direct ink writing [14, 60–62]. However, these conventional 3D printing processes have certain drawbacks that limited their use in tissue engineering scaffolds. For FDM process, raw materials must be processed into filaments and the high temperature during the extrusion process might have adverse effects on the bioactivities of scaffolds. For stereolithography-based 3D printing process, photocurable polymers are required and the addition of photoinitiators usually results in toxic byproducts. As a result, available stereolithography resins for biomedical applications have been quite limited. For binder jetting-based 3D printing process, available binders are also limited due to the restriction of biocompatibility. In addition, postprocessing including heat treatment is required to improve the mechanical properties and durability of scaffolds. For SLS-based 3D printing process, powdered materials are required and they have to withstand the high-energy density of lasers during the fabrication process. More importantly, all of the processes are difficult to fabricate macroporous/microporous/nanoporous combined scaffolds.

To overcome the challenges faced by various conventional 3D printing technologies, LTDM was proposed. LTDM is a combination of material extrusion-based 3D printing and thermally induced phase separation (TIPS). By incorporating TIPS into 3D printing process, the merits of TIPS can be utilized. TIPS has been a traditional fabrication process for tissue engineering scaffolds and also has been widely used in the fabrication of porous membrane for water treatment, filtering, purification, etc. The principle of TIPS is shown in Figure 2(a). In TIPS, polymer is dissolved into solvents (e.g., mixtures of 1,4-dioxane and water) to make a uniform and homogeneous solution. During this period, other components such as ceramic particles such as hydroxyapatite (HA), tricalcium phosphate (TCP), and porogens can be dispersed or added into polymer solution by ultrasonication process. Then, the polymer solution is heated to a temperature above its cloud point. After that, the solution is cooled down to the desired quenching temperature. During the cooling process, the homogeneous solution separates into a polymer-rich phase and a polymer-lean phase. Finally, solvents are removed by a freeze-drying or freeze extraction process.

As shown in the temperature-composition phase diagram for the polymer-solvent system illustrated by Figure 2(a), there are two typical curves: the binodal curve and the spinodal curve. Above the binodal curve, polymer and solvents form a homogeneous solution. Below the binodal curve, the homogeneous solution becomes metastable and phase separation may take place. Below the spinodal curve is the unstable zone. In this zone, the polymer solution forms a bicontinuous structure composed of a polymer-rich and polymer-lean phase. Therefore, phase separation can be induced by cooling the polymer solution from above the cloud point down to the unstable zone. The scaffold or

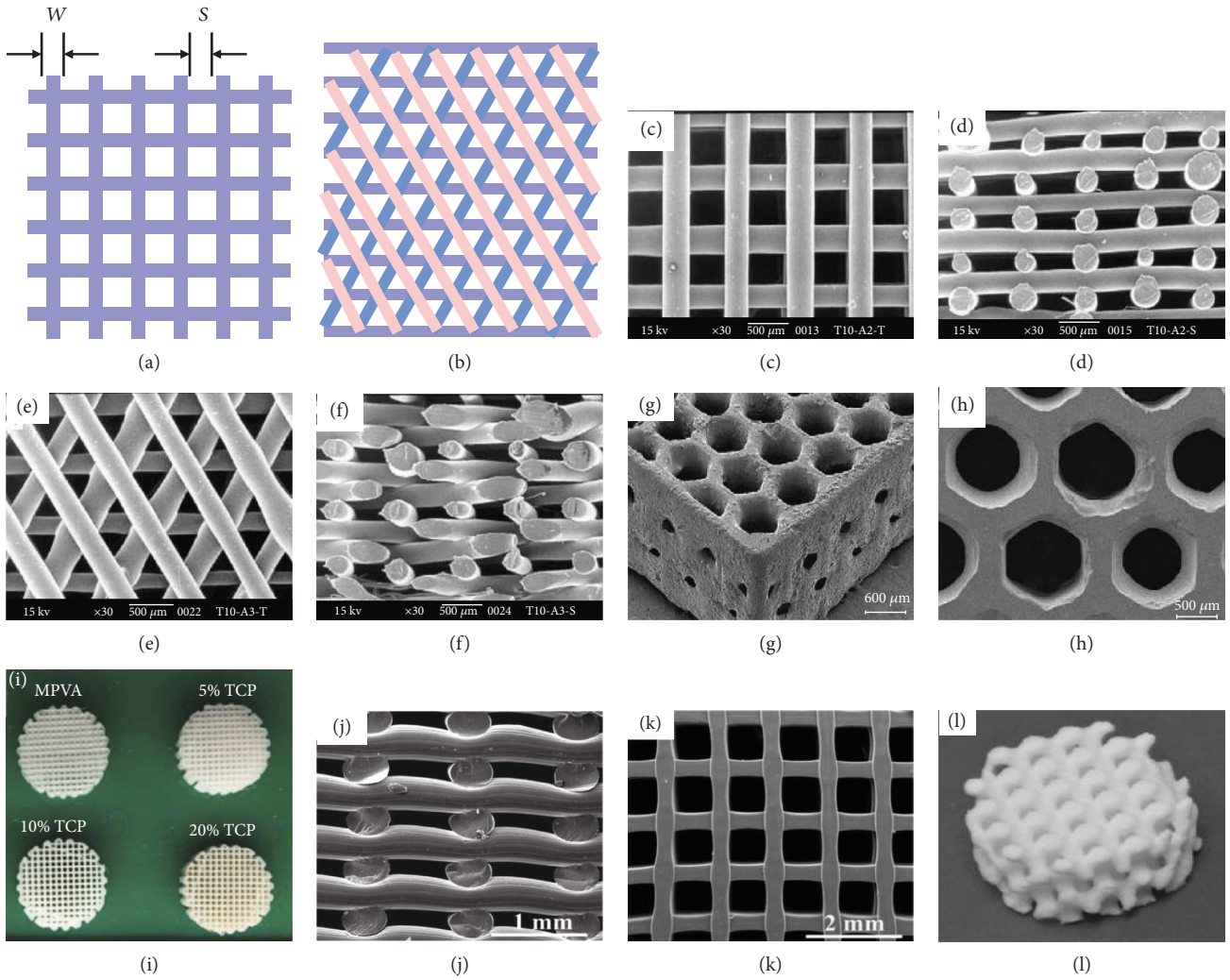

Figure 1: Examples of interconnected porous tissue engineering scaffolds fabricated by 3D printing technologies. (a) 0°-90° crossing, (b) 0°-60°-120° crossing, (c, d) PCL scaffolds (0°-90° crossing) by fused deposition modelling (FDM), (e, f) PCL scaffolds (0°-60°-120° crossing) by FDM [20], (g, h) poly(D,L)-lactide (PDLLA) scaffolds by stereolithography [32], (i–k) poly(vinyl alcohol)/β-tricalcium phosphate composite scaffold (PVA/β-TCP) by FDM [21], and (l) porous 45S5 bioglass scaffold by SLA [33]. Reproduced with permission.

membrane architectures can be effectively controlled by manipulating several process parameters including polymer concentration, ceramic content, addition of porogens, quenching temperature, cooling rate, and solvent/nonsolvent ratio. With TIPS, a large variety of polymers has been processed into porous scaffolds or membranes including poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(D,L-lactic acid) (PDLLA), and poly(lactic-co-glycolic acid) (PLGA).

It is worth noting that TIPS has some advantages that current 3D printing technologies cannot compete against. Firstly, TIPS has the capability of tailoring pore size in a wide range from microns to hundreds of microns in a simple and scalable manner, while current 3D printing technologies are difficult to fabricate micropores with the diameter of below 10 microns. Secondly, TIPS has the capability of fabricating nanofibrous architectures within the matrix that current 3D printing technologies are incapable of. It will be a technological improvement if 3D printing and TIPS can be integrated into one process by combining the merits of both technologies. By doing so, macroporous/microporous/nanoporous combined structures can be fabricated.

However, how to combine TIPS and 3D printing into one process is a technological challenge. As shown in Figure 2(b), conventional material extrusion-based 3D printing utilizes a heated extrusion nozzle to extrude polymer filaments to form 3D-printed objects. However, in TIPS, polymers must be processed into a homogeneous solution. Firstly, the nozzle design should be modified to enable the extrusion of polymer solution, while not polymer filaments. Secondly, the initial temperature of polymer solution should be maintained above the cloud point before extrusion; therefore, it is inevitable that a heating unit is incorporated in the nozzle. Thirdly, a cooling process is required to induce phase separation by cooling the polymer solution from above the cloud point down to the unstable zone. Once the three aspects are satisfied, 3D printing and TIPS can be integrated into one process. As shown in Figure 3(c), polymer solution can be loaded into a syringe with a heating unit to control its

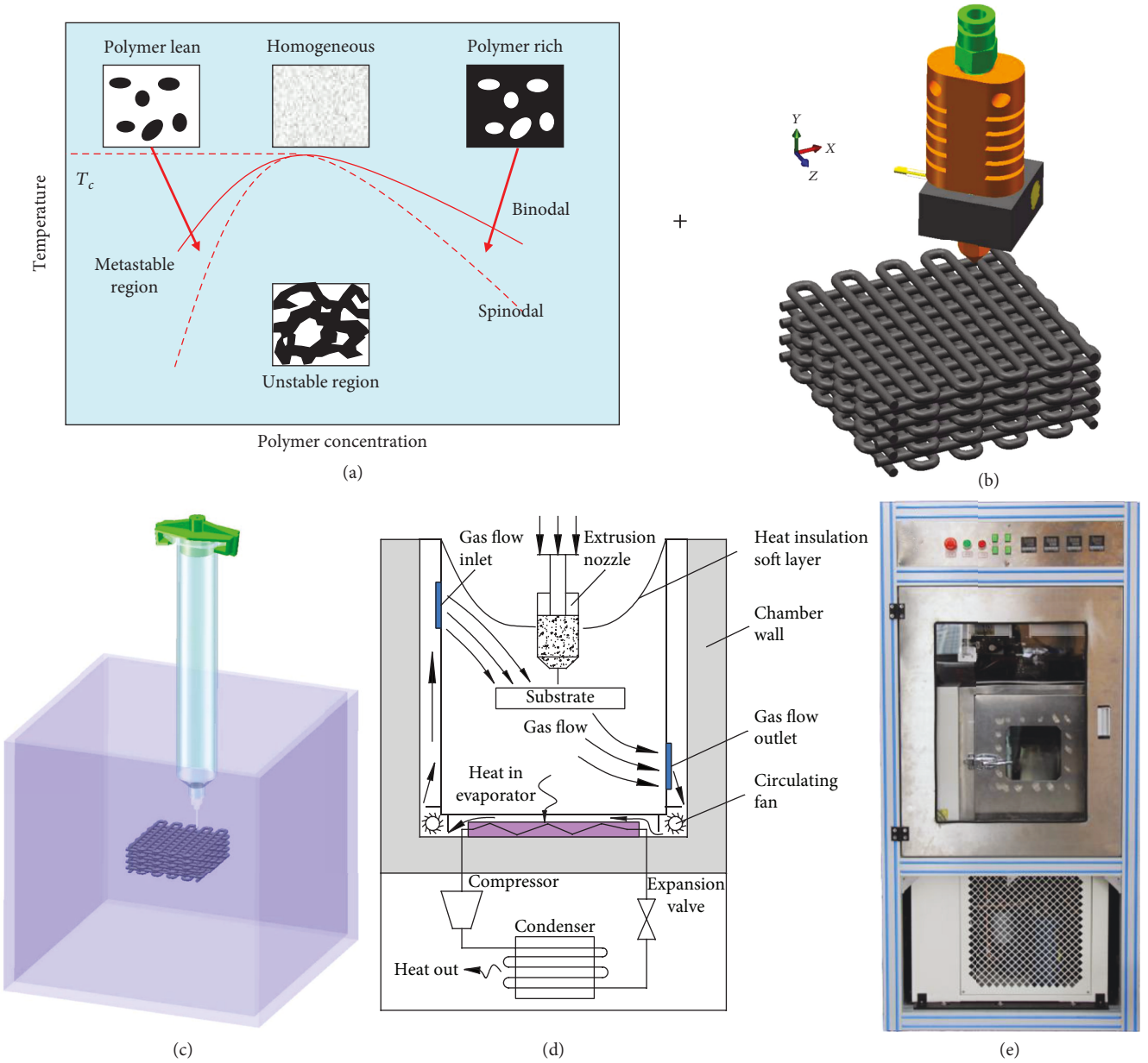

Figure 2: Origin and principle of low-temperature deposition manufacturing. (a) Temperature-composition phase diagram for TIPS, (b) conventional material extrusion-based 3D printing process, (c) principle of LTDM process, (d) schematic of LTDM machine, and (e) LTDM machine [63].

temperature and extruded pneumatically or by a piston into a low-temperature chamber to form 3D-printed objects. Based on this idea, LTDM process was proposed. The schematic of LTDM machine and developed LTDM machine are shown in Figures 2(d) and 2(e).

Based on the LTDM technology, the fabrication process of porous materials by LTDM usually includes (1) CAD design of 3D objects, (2) preparation of printable inks that were usually a mixture of homogeneous polymer solution, ceramic particles, and/or other additives, (3) deposition of inks into the low-temperature chamber to obtain 3D-printed objects, and (4) removal of solvents by freeze-drying or freeze extraction. Figure 3 shows the fabrication process of porous electrodes for lithium-ion batteries by LTDM.

3. Applications of LTDM Technology

To date, LTDM technology has been mainly used to fabricate tissue engineering scaffolds. Recently, some researchers used this technology to fabricate porous electrodes for lithium-ion batteries. We anticipate that this technology may find more applications where functional devices or components with hierarchical porous features are required.

3.1. Porous Tissue Scaffolds for Bone Tissue Regeneration. Xiong et al. fabricated poly(L-lactic acid) (PLLA)/tricalcium phosphate (TCP) composite porous scaffolds by LTDM for the first time [19]. The initial homogeneous polymer solution was composed of 15 wt% PLLA, 15 wt% TCP, and 70 wt%

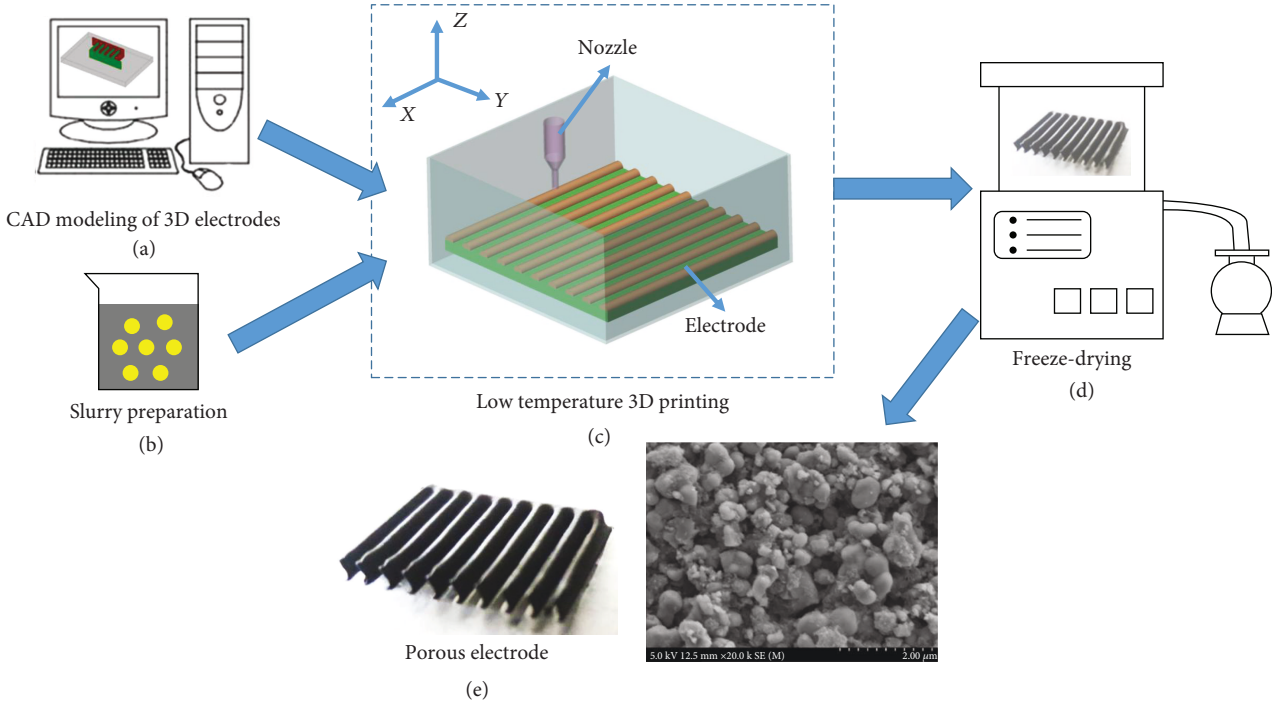

Figure 3: LTDM fabrication process [63].

dioxane. Figure 4 shows the fabricated cylindrical, femoral, and cubic porous scaffolds. It can be seen that interconnected pores in the diameter range of hundreds of microns were obtained. From the scanning electron microscope (SEM) image (Figures 4(e) and 4(f)), micropores in the diameter range of 5 microns to 10 microns and nanofibrous architectures can be observed. The porosity of these scaffolds was 89.6%. The mechanical properties of these scaffolds were measured and found to be very similar to that of 40~49-year-old human lumbar. Implantation experiments were carried to repair 20 mm segmental defects in canine radiuses by these scaffolds (Figures 4(g) and 4(h)). It was found the large bone defect was completely repaired with regenerated new bone at 24 weeks after implantation (Figure 4(i)).

In addition to synthetic biomaterials such as PLLA and PLGA, LTDM can also be used to fabricate natural-derived biomaterial scaffolds such as collagen, chitosan, and gelatin. Figure 5 shows the collagen, chitosan, and gelatin scaffolds fabricated via LTDM by Liu et al. [64]. These natural-derived biomaterial scaffolds have hierarchical porous structures with nanofibrous surface morphologies. In addition, various composite scaffolds including PLGA/pearl [65], PLGA/collagen [66], and chitosan/nano-HA [67] were also fabricated by LTDM and validated by cell seeding and implantation experiments. To further enhance the performance of scaffolds, various components can be added into the initial homogeneous solution so that special desirable properties may be achieved. For example, by adding magnesium (Mg) into PLGA/TCP composite, anti-infection scaffolds were fabricated by Ma et al. and the PLGA/TCP/Mg composite scaffold was proven to have the capability of inhibiting bacterial adhesion [68]. Lai et al. fabricated a superior PLGA/TCP/Icariin composite scaffold by incorporating a unique phytomolecule icariin to achieve improved biodegradability, biocompatibility, and osteogenic capability [69]. To conclude, LTDM is able to process a large variety of materials including synthetic biomaterials, natural-derived biomaterials, and composites and also able to incorporate various bioactive molecules to fabricate tissue engineering scaffolds with superior properties.

LTDM is also capable of fabricating multimaterial scaffolds via a multinozzle system. Both syringe-driven and screw extrusion-based multinozzle system have been developed to fabricate multimaterial scaffolds (as shown in Figures 6(e) and 6(f)). Figures 6(a)–6(d) show scaffolds with two different materials including cubic scaffolds, scaffolds with internal blood vessel, and cone-shaped scaffolds (red and white represents two different materials). These heterogeneous and gradient scaffolds are important for the repairment of multitissue defects. As an example, the articular cartilage and subchondral bone defects require two or more different biomaterials to repair the two regions simultaneously.

By equipping LTDM machine with a core-shell nozzle, core-shell porous structures can be manufactured. Zhang et al. developed such a core-shell nozzle to fabricate multilayered porous osteochondral scaffolds [70]. The core-shell nozzle is composed of an inner nozzle and outer nozzle that are used to dispense inner materials (PLGA/TCP composite) and outer materials (collagen) simultaneously (as shown in Figure 7(a)). With this core-shell nozzle, collagen-wrapped PLGA/TCP scaffold was fabricated (Figure 7(b)). The entire scaffold was composed of a collagen-wrapped PLGA/TCP scaffold, a compact layer, and an oriented cartilage layer fabricated via TIPS. Cell seeding experiments showed that cells were able to adhere to the surface of scaffolds and proliferate in the porous structures (Figures 7(c) and 7(d)). This

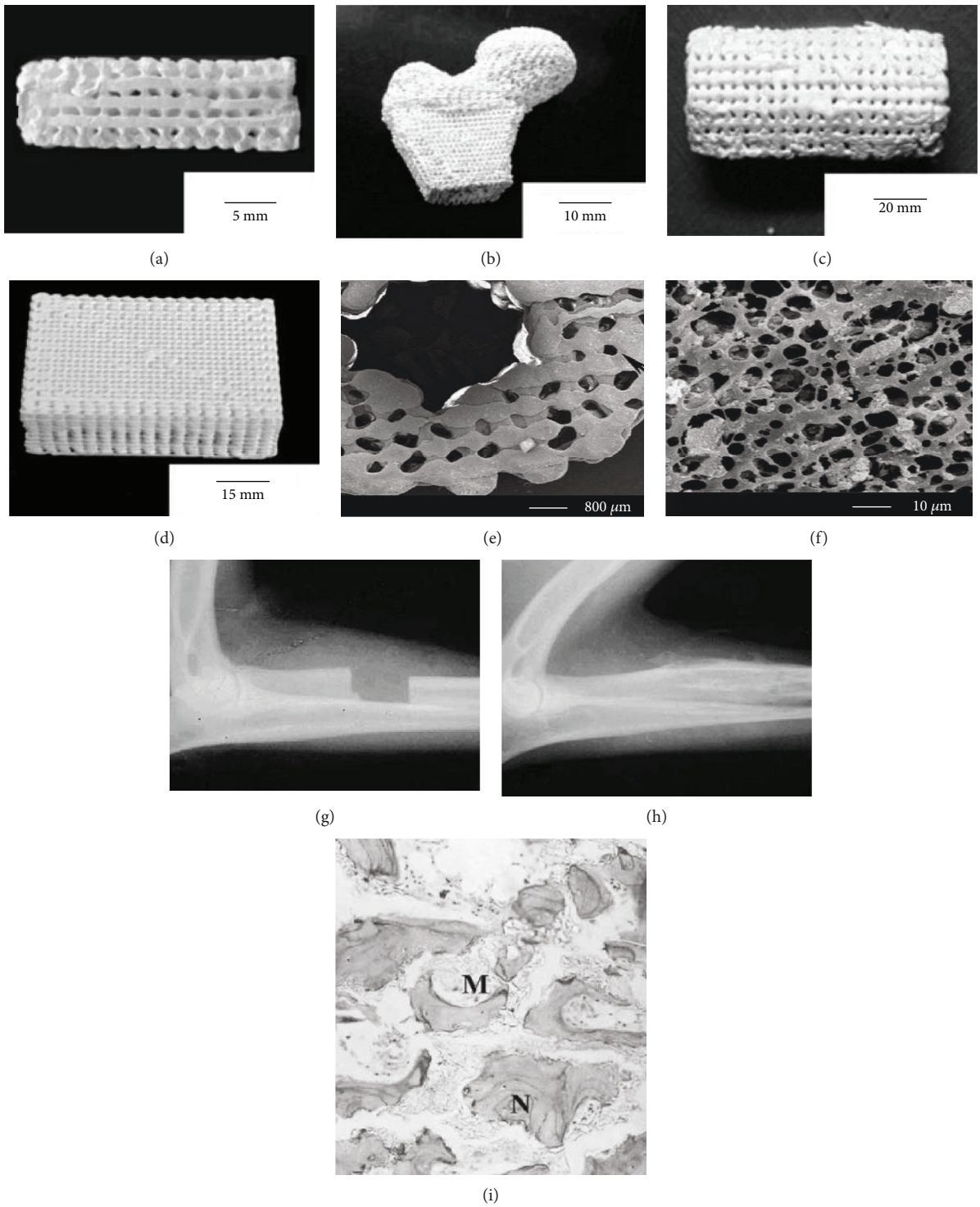

Figure 4: PLLA/TCP scaffolds fabricated by LTDM technology. (a, b) Cylindrical scaffolds, (c) femoral scaffold, (d) cubic scaffold, (e, f) low and high magnified SEM image, (g, h) X-ray images of large bone defects before surgery and 24 weeks after implantation, and (i) histological section image after 24 weeks [19]. Reproduced with permission.

biomimetic gradient scaffold can better mimic the human natural cartilage and subchondral bone.

As for tissue engineering scaffolds fabricated via LTDM, their porosity, mechanical properties, biodegradability, biocompatibility, and osteogenic capability are of great importance for the successful tissue regeneration and repairment. Table 1 lists the porosity and mechanical properties of various scaffolds fabricated via LTDM. With this technology, the porosity can be tailored in a wide range (70%~90%) by designing the macroporous structures using CAD tools.

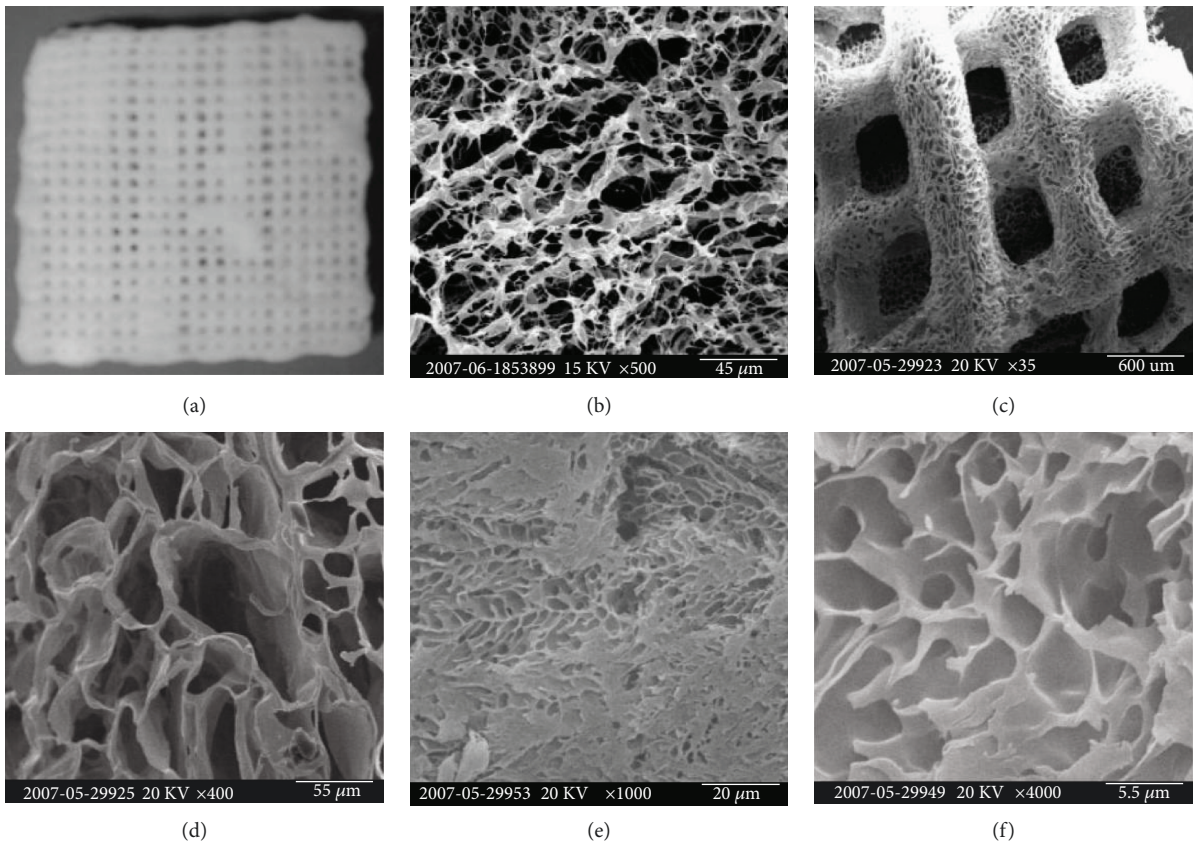

Figure 5: Natural-derived biomaterial scaffolds fabricated by LTDM. (a) Collagen scaffold, (b) microporous structures of collage scaffold, (c) chitosan scaffold, (d) microporous structures of chitosan scaffold, and (e, f) low and high magnified SEM image of gelatin scaffold [64]. Reproduced with permission.

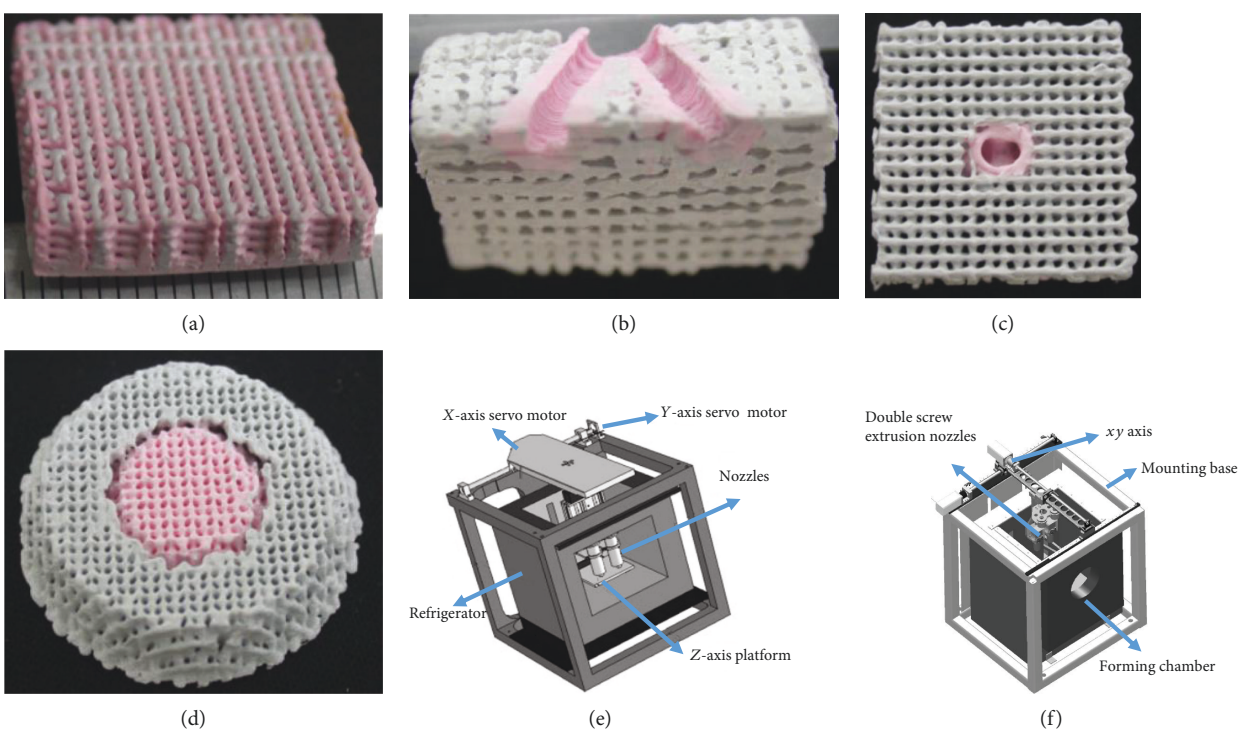

Figure 6: Multimaterial scaffolds fabricated via multinozzle LDTM. (a) Cubic multimaterial scaffold, (b, c) cubic scaffold with internal blood vessels (red), (d) cone-shaped multimaterial scaffold, (e) syringe-driven multinozzle system, and (f) screw extrusion-based multinozzle system [64]. Reproduced with permission.

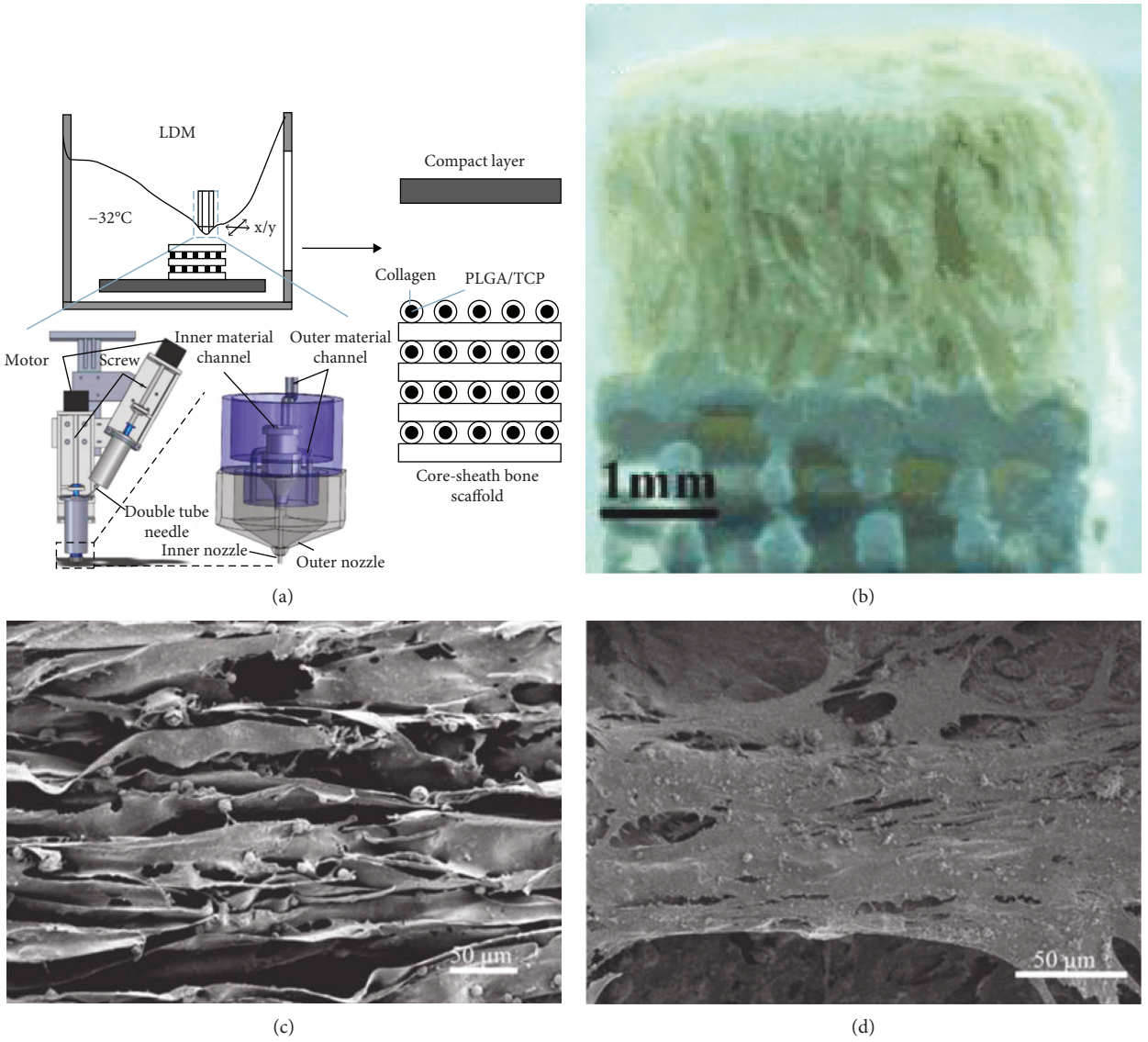

Figure 7: Core-shell structures fabricated via LTDM. (a) Core-shell nozzle, (b) fabricated gradient scaffolds, and (c, d) cell morphology on the biomimetic scaffold [70]. Reproduced with permission.

Correspondingly, the compressive modulus and compressive strength can also be customized through tailored macroporous/microporous/nanoporous structures. These values are able to well match human bone mechanical properties, thereby offering excellent mechanical support during the regeneration process [19]. Cell culture experiments were also performed by seeding bone marrow stem cells or bone mesenchymal stem cells onto various composite PLGA scaffolds [65, 69–71]. Results showed that these scaffolds provided good templates for cell adhesion and proliferation. With the addition of TCP, HA, pearl, Mg, phytomolecule icariin, etc., the biocompatibility and degradation rate can also be improved. Successful implantation experiments have been carried out for repairing large bone defects [19, 69, 70, 72]. Therefore, these scaffolds fabricated via LTDM have very promising applications in bone tissue engineering.

3.2. Porous Electrodes for Electrochemical Energy Storage. Electrochemical energy storage devices including batteries and supercapacitors play an important role in modern society. To satisfy the urgent need for devices with improved energy density and power density, a lot of efforts have been made in this area [75–77]. A big challenge for conventional energy storage devices is that good performance was achieved only in very thin electrodes with low mass loading ($\leq 1\ mg{\cdot}cm^{-2}$) [78]. When other passive components including metal current collectors, separators, electrolytes, and encapsulation are taken into account, the actual electrode-specific capacity is only ~10% of the material capacity with thin electrodes at a low mass loading level. As a result, it is highly desirable that the electrode mass loading increases from $\sim 1\ mg{\cdot}cm^{-2}$ to $\sim 10\ mg{\cdot}cm^{-2}$ with thick electrodes and sufficient charges (ions and electrons) can be delivered to fully utilize the charge storage capacity of thick electrodes

Table 1: Porosity and mechanical properties of tissue engineering scaffolds fabricated via LTDM.

No.	Scaffold materials	Porosity	Mechanical properties (MPa)	Ref.
1	PLLA/TCP	89.6%	$E = 60.11$, $\sigma_y = 4.71$	[19]
2	PLLA/TCP	86.0%	$E = 24.0$, $\sigma_y = 1.40$	[73]
	PDLLA/TCP	83.2%	$E = 19.0$, $\sigma_y = 1.25$	
	PLGA/TCP	82.9%	$E = 17.5$, $\sigma_y = 0.70$	
3	Cartilage layer: PLGA	$(90.2 \pm 0.2)\%$	Not reported	[72]
	Separate layer: PLGA/TCP	$(75.2 \pm 0.98)\%$		
	Bone layer: PLGA/TCP	$(88.7 \pm 0.55)\%$		
4	Pearl/PLGA	74.1%	$E = 26.58$, $\sigma_y = 1.46$	[65]
		85.2%	$E = 12.35$ MPa, $\sigma_y = 0.53$ MPa	
5	PLLA/nano-HA	Not reported	$E = 28.5$ (PLLA : HA = 100 : 0, wt%)	[74]
			$E = 31.5$ (PLLA : HA = 70 : 30, wt%)	
			$E = 47.0$ (PLLA : HA = 50 : 50, wt%)	

at the same time. To address this challenge, conventional electrodes with flat metal current collectors and two-dimensional (2D) planar electrodes are facing fundamental challenges. Therefore, 3D porous thick electrodes with a 3D electrically conductive network as a 3D current collector and a 3D porous network for efficient ion transport have been developed [5, 79–81]. By combining 3D printing and TIPS, LTDM is an ideal technology for fabricating porous structures. Therefore, we speculate that LTDM can be used to fabricate thick electrodes with effective 3D carbon conductive network and porous network to achieve efficient ion and electron transport simultaneously. Liu et al. developed an ink composed of $LiFePO_4$ (LFP) as cathode materials, super-p as conductive agent, carboxymethyl cellulose (CMC) as binder, and dioxane/water as solvent and fabricated porous 3D LFP electrodes (as shown in Figures 8(a) and 8(b)) [63]. Pore size and distribution measured by mercury porosimetry indicated that hierarchically porous structures were obtained with the porosity of over 60%. The porous electrodes exhibited improved rate performance (~82 $mAh \cdot g^{-1}$ @ 10C rate) in comparison with conventional roller coated 2D planar electrodes. Figure 8(d) shows the charge/discharge curves of LFP electrodes fabricated via LTDM, and Figure 8(e) shows the comparison of rate capacities of LFP electrodes (ink solid content: 0.467 g/mL) fabricated by LTDM, direct ink writing, and roller coating. It can be seen that LFP electrodes had the best performance among the three types of fabrication technologies [82]. We anticipate that LTDM would find more applications in energy storage applications.

4. Other Forms of LTDM

Another possible strategy to combine 3D printing and TIPS is to extrude materials onto a low-temperature building plate to freeze the extruded solution and maintain the geometry of printed objects (as shown in Figure 9). Using this strategy, porous gelatin/poly(vinyl alcohol) (PVA) composite scaffolds and collagen/decellularized extracellular matrix (dECM)/silk-fibroin composite scaffolds have been fabricated [83, 84]. The temperature of the building plate can be adjusted within a certain range from -5°C to -40°C. In comparison with the low-temperature chamber method, LTDM with a low temperature has some advantages such as more convenient transformation from desktop 3D printer and low cost. However, there exists obvious shortcomings with this method. Firstly, the height of printable objects is limited due to heat accumulation with the increase of sample height. As the sample grows, the layers far from the low-temperature building plate become more difficult to freeze, thereby limiting the achievable total height of the sample. Another disadvantage is that printable materials are limited due to the relative low cooling capacity of the low-temperature building plate.

5. Conclusions and Outlook

The idea of combining 3D printing and TIPS has endowed LTDM with the unique capability of fabricating macroporous/microporous/nanoporous combined materials and structures. The above sections described its current applications in tissue engineering scaffolds and porous electrodes for electrochemical storage. Although its current applications have been primarily limited to tissue engineering scaffolds, we forecast that this technology can be extended to many other fields. Porous electrodes for electrochemical energy storage are a promising field. LTDM might be a feasible technology for fabricating thick electrodes with hierarchically porous structures to facilitate ion and electron transport and ultimately improving the mass loading level from ~1 $mg \cdot cm^{-2}$ to ~10 $mg \cdot cm^{-2}$. Other fields such as porous membranes for water treatment, purification, and filtering may also be the potential applications of LTDM. The reason why LTDM is not as widely known as other 3D printing technologies such as FDM, SLA, and SLS/SLM might be the absence of commercially available machines on market. The transformation from conventional material extrusion-based 3D printer to a LTDM machine is a technology barrier. In addition, commercially available printable inks for LTDM

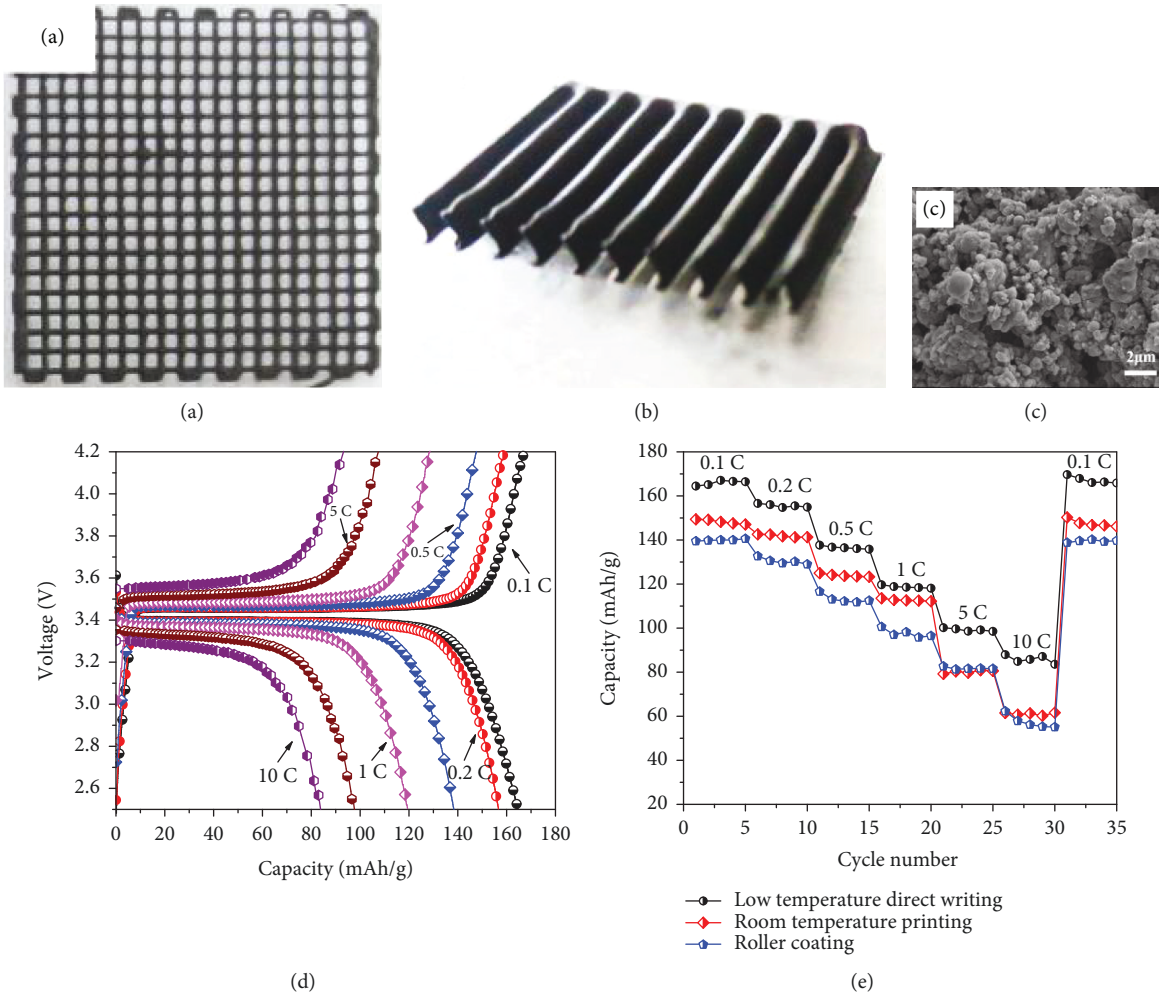

Figure 8: Porous $LiFePO_4$ electrodes fabricated via LTDM. (a) Grid structures, (b) comb-like electrodes, (c) porous microstructures, (d) charge/discharge curves of LFP electrodes fabricated via LTDM, and (e) comparison of rate capacities for LFP electrodes fabricated by LTDM, DIW, and roller coating (solid content: 0.467 g/mL) [63].

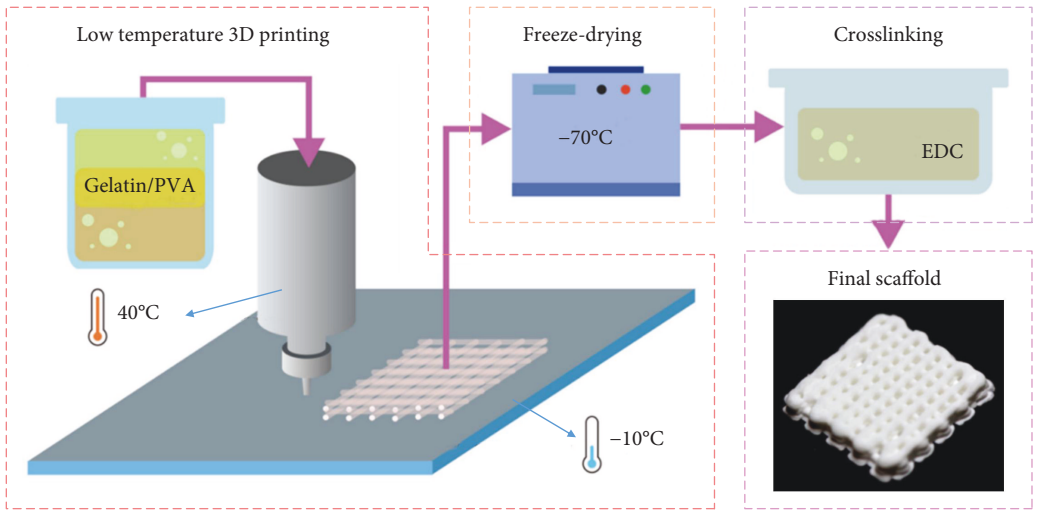

Figure 9: LTDM process by extruding materials onto a low-temperature building plate [83]. Reproduced with permission.

technology are quite limited. These factors have been the major obstacles for the promotion of LTDM.

As one of the very few technologies that are able to fabricate macroporous/microporous/nanoporous combined 3D objects, other merits of this technology include a wide range of printable materials, gradient multimaterial structures via multinozzle technology, and core-shell structures via core-shell nozzles. These advanced features make LTDM a competent tool for fabricating complex 3D objects with tailorable hierarchically porous structures. With the further development of this technology, we anticipate that LTDM will be applied in more fields.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

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