



Review

A review: Fabrication of porous polyurethane scaffolds

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ABSTRACT

The aim of tissue engineering is the fabrication of three-dimensional scaffolds that can be used for the reconstruction and regeneration of damaged or deformed tissues and organs. A wide variety of techniques have been developed to create either fibrous or porous scaffolds from polymers, metals, composite materials and ceramics. However, the most promising materials are biodegradable polymers due to their comprehensive mechanical properties, ability to control the rate of degradation and similarities to natural tissue structures. Polyurethanes (PUs) are attractive candidates for scaffold fabrication, since they are biocompatible, and have excellent mechanical properties and mechanical flexibility. PU can be applied to various methods of porous scaffold fabrication, among which are solvent casting/particulate leaching, thermally induced phase separation, gas foaming, emulsion freeze-drying and melt moulding. Scaffold properties obtained by these techniques, including pore size, interconnectivity and total porosity, all depend on the thermal processing parameters, and the porogen agent and solvents used. In this review, various polyurethane systems for scaffolds are discussed, as well as methods of fabrication, including the latest developments, and their advantages and disadvantages.

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1. Introduction

The main aim of tissue engineering is the fabrication of functional replacements for damaged tissues or organs. Scaffolds play a crucial role in tissue engineering, because they represent an alternative to the conventional implantation of organs and tissues. The main goal of scaffolds is to provide appropriate base for tissue growth and cell proliferation [1]. Biomaterials play a critical role in tissue engineering. For the preparation of scaffolds a great number of different natural or synthetic materials have been studied and proposed [2]. The most frequently employed polymers of natural origin in biomedical applications are polysaccharides (alginate, chitosan, starch, cellulose) and proteins (collagen, silk fibroin), due to their bioresorbability, low toxicity, and low

manufacture and disposal costs [3,4]. Moreover, they offer a wide range of advantages for tissue engineering applications such as biological signalling, cell adhesion, cell responsive degradation and re-modelling [5]. However, the physical and mechanical properties of natural polymers do not always match to the properties of tissues, there is less control over the bioresorbability, the risk of immunorejection and disease transmission makes proper screening and purification necessary [6]. The most widely used synthetic polymers are polyesters, having FDA approval for various applications. Many are already clinically used as biomaterials for example poly(glycolic acid) (PGA), poly(lactic acid) (PLA), poly(ϵ -caprolactone) and their copolymers [7,8]. However, they degrade via a random, bulk hydrolysis of ester bonds in the polymer chain, releasing acidic degradation products, which can cause a strong inflammatory response [9,10]. Other drawback of polyesters is their hydrophobicity, which can be unfavourable in tissue regeneration applications due to the poor wetting and lack of cellular attachment

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and interaction [11]. Next to polyesters applied in tissue engineering there are synthetic polymers called polyurethanes. They have unique segmented structure, due to which more diverse properties can be obtained using relevant raw materials and additives. PU can have a wide range of mechanical and physical properties, from thermoplastic to thermosetting, from stable to degradable materials, from hydrophobic to hydrophilic depending on the composition and synthesis procedure applied [12,13]. PUs exhibit moderate compatibility with blood, and are characterised by biocompatibility, bioresorbability and excellent mechanical properties, which can be adjusted to specific tissue [14,15].

In the beginning of their application in medicine PUs were used as artificial skin [16], vascular grafts [17], neural connections [18], bone grafts [19] and materials for the repair of articular cartilage [20]. The recent literature describes many polyurethane systems that are suitable for scaffolds (Table 1). PU as a material for scaffold fabrication must be bioresorbable, thus polyester-urethanes are mainly synthesised from PCL, PLA or PGA, whilst polyether-urethanes are from polyols such as poly(ethylene glycol) (PEG) or poly(propylene oxide) (POP). Aliphatic or cyclic diisocyanate (hexamethylene diisocyanate HDI, 4,4'-methylenebis(cyclohexyl isocyanate) HMDI, isophorone diisocyanate IPDI) is used instead of aromatic diisocyanate, for example MDI (4,4'-methylenebis(phenyl isocyanate)) and TDI (tolylene-2,4-diisocyanate), because they can degrade into carcinogenic and mutagenic aromatic amines [21]. One can find in the literature the use of 1,4-diisocyanatobutane (BDI) and lysine methyl ester diisocyanate (LDI), as they potentially degrade in the body to the biological diamine putrescine and to the amino acid lysine, respectively, a biogenic amines, which play an important role in cell growth and differentiation [22,23]. Degradation products from segmented poly(ester-urethane)urea elastomers comprising BDI, lysine ethyl ester and putrescine chain extenders, and poly(ϵ -caprolactone) (PCL) diols demonstrated no toxic effects on human endothelial cells cultured in vitro [24]. However, the use of putrescine can be controversial, as some papers describe it as toxic substance [25].

One of the requirements imposed on scaffolds is a suitable, porous structure with uniformly distributed interconnected pores. Materials should be characterised by great porosity (above 90%) and proper pore dimension (from ten to hundreds of μm) depending on the application. According to the literature, scaffolds for liver regeneration should have a pore diameter of 20 μm to allow the growth of hepatocytes, for skin, the proper pore diameter should be within a range from 20 to 150 μm , whilst, for bone, the best pore size is from 200 to 400 μm [26]. Moreover, pores must be interconnected to allow cell and tissue ingrowth. All of the above-mentioned properties depend either on the polymer used or the method of fabrication.

The fabrication of 3-dimensional porous structures is based on transforming polymers from the solid to liquid state, mostly by melting or dissolving. Generally, those techniques can be divided into two groups: conventional and advanced. Advanced techniques include, among others, electrospinning [27], 3D printing [28] and rapid prototyping [29], whilst conventional techniques include solvent casting/particle leaching (SCPL) [30,31], thermally-induced phase separation [32,33], gas foaming [34,35] and melt moulding [36,37]. In this paper, we present an overview of the conventional techniques used for fabricating polyurethane scaffolds.

2. Solvent casting/particle leaching (SC/PL)

Solvent casting combined with particle leaching involves leaching out solid particles from the polymer solution. To the polymer solution, which is usually prepared at a concentration from 5 to 20% [38] (Table 1, 1–3, 7–10), specified diameter particles are added. After solvent evaporation by air-drying, vacuum-drying or freeze-drying, salt particles remain embedded throughout the polymer matrix. After immersion in water, salt particles are leached out, leaving a porous structure (Fig. 1).

According to Zhu et al. [39], highly porous scaffolds with porosity up to 93% and average pore sizes of up to 500 μm can be obtained. The structure of the formed scaffold depends on many factors. The shape and size of pores are directly determined by the shape and dimensions of the leachable particles used (Table 1, 1–3). The pores take over the shape of the particles, and therefore, by selecting the size of the particles, it is possible to control the pore size. Salt particles are mainly used, but the use of sugar, ammonium chloride, sucrose, starch particles and gelatine, paraffin microspheres is also known [40,41]. According to Draghi et al. microspheres are more effective than particles, because spherical pores improve fluid exchange and nutrient supply to cells. Moreover, the regular geometry obtained by microspheres leaching improved scaffolds mechanical performance. Another parameter which influences the structure is the amount of particles added. If the salt content is insufficient, the polymer solution will surround the particles and isolated pores will appear. On the other hand, if the amount of salt added is too high, a deficient structure with voids will be formed due to close geometric packing [42]. Another parameter which significantly affects the structure of the scaffold is the initial concentration of the polymer solution. The density of the polymer solution increases with increasing amounts of particles added; therefore, it is difficult to control the direct contact between the crystals and the polymer [43]. The effect of pore size on the mechanical properties of the scaffold should also be taken into account. According to Sin et al. [30]

Table 1
Techniques and systems used in scaffold fabrication.

Technique	No.	PU system	Solvent	PU concentration [%]	Porosity [%]	Pore size [μm]
SC/PL	1	Zytar® Z1A1 (thermoplastic polyether-urethane) [30]	DMF/THF	15	>91	~250
	2	PCL/HMDI/EG [31]	1-Methylo-2-pirolidone	20	>70	100–400
	3	PCL/HMDI/isosorbide diol [38]	DMF		90	200 \pm 16
TIPS	4	PHB-PCL/TMDI [32]	1,4-Dioxane	5		100–150
	5	PCL-PEG/BDI/Putrescyna [55]	DMSO	10	94	76–387
TIPS/PL	6	PCL/BDI/BDO [55]	DMSO	10	>80	36–203
	7	PCL/BDI/BDO [33]	1,4-Dioxane	17		150–300
	8	PCL/BDI/BDO [59]	DMSO	35	80	Different
	9	PCL/HDI/isosorbide diol [61]	DMF/THF	9,5	90	200 \pm 45
	10	Poly(ethylene adipate) diol/IPDI/hexamethylene diamine [60]			87	50–400
Freeze-drying	11	PCL/BDI [86]	1,4-Dioxane/water		>80%	150–300
	12	PCL-PEG/IPDI/BDO/L-lysine [88]	Water	16		10–172
	13	PCL-PEBA-PLA/IPDI [89]	–	5	97%	
Melt moulding	14	Texin (thermoplastic polyether-urethane) [73]	–	–	64	30–450
	15	PCL-PEG/HDI/benzoic acid [37]	–	–	88	153 \pm 70
Gas foaming	16	PEG-PPG/TDI [77]	–	–	85	300–800
	17	POP/TDI [80]	–	–	–	95 \pm 40
	18	PCL-PEG/HMDI [78]	–	–	>75	50–2000

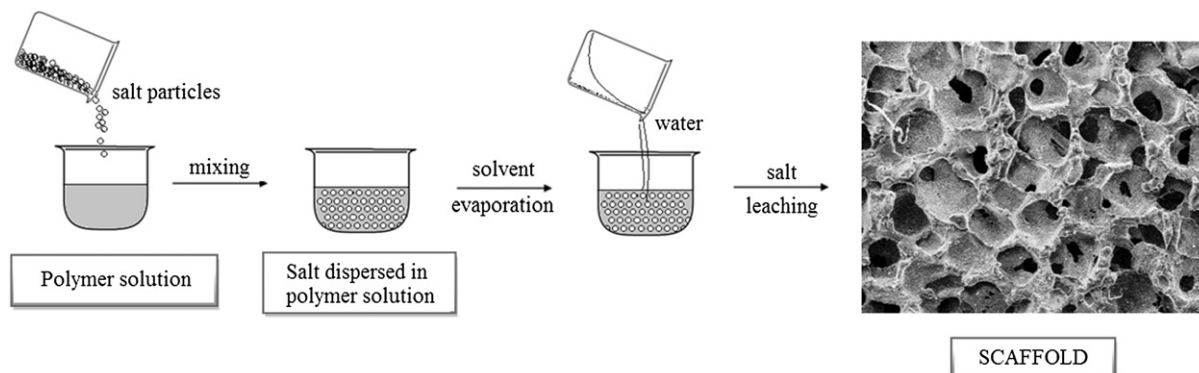


Fig. 1. Scaffold preparation using solvent casting combined with the salt leaching technique.

(Table 1, 1), mechanical strength properties increase with increasing average pore diameters. Pores with greater diameters will have a lower total porosity and higher mechanical strength.

The main advantage of this method is the ease of fabrication without the need of specialized equipment. The disadvantage of this method is the difficulty in selecting the size of the particles needed to obtain a material with high porosity, whilst maintaining adequate mechanical properties and preparing a thick material, since it is difficult to leach out the particles from a large volume. According to Mikos et al. [44], it is possible to produce only thin materials, up to 3 mm thick. Another drawback is the use of organic solvents. Residual solvents can be toxic, thus they must be removed to avoid any possible damage to the cells seeded and to the proteins or other active molecules incorporated in the scaffolds [45,46]. Polyurethane scaffolds prepared by the SCPL method are mainly used in soft-tissue engineering [47], for example for the repair of coronary arteries [48] and bone [49]. The use of SCPL for fabricating memory polyurethane scaffolds has also been reported [50,51].

3. Thermally-induced phase separation (TIPS)

Thermally-induced phase separation (TIPS) is based on quenching the polymer solution below the solvent's freezing point (T_k) and inducing liquid–liquid separation (Fig. 2). Two phases are formed: a polymer-rich phase and a polymer-poor phase. The polymer-rich phase solidifies, whilst the polymer-poor phase crystallises. The formed crystals are removed, leaving a highly porous structure (more than 90%) [52,53].

The structure of the scaffold obtained depends on the polymer solution concentration, the quenching temperature and the quenching rate [54]. The temperature and quenching rate affect the process of solvent crystallisation. At lower temperatures, solvent nuclei are formed faster, but crystal growth is limited, which results in the formation of a large amount of small crystals, and a small pore diameter. At higher temperatures, the nucleation rate is limited and the crystal growth is increased, which leads to the formation of larger crystals and a larger pore

diameter. Guan et al. [55] (Table 1, 5–6) compared the influence of the quenching temperature of the polymer solution on pore diameter size obtained by this technique. The average pore size of the resulting scaffold when using liquid nitrogen ($-196\text{ }^\circ\text{C}$) was much smaller (3 to $19\text{ }\mu\text{m}$) than that of the resulting scaffold at a temperature of $-80\text{ }^\circ\text{C}$ (23 – $154\text{ }\mu\text{m}$) and at $-20\text{ }^\circ\text{C}$ (36 – $203\text{ }\mu\text{m}$). The structure and porosity of the scaffold also change with the polymer concentration. The higher the concentration, the less solvent is in the system, which leads to the formation of a lower amount of crystals, and thus a smaller porosity. Furthermore, as the concentration increases, the viscosity of the solution increases. In more viscous solutions, the formation of large crystals is hampered. During quenching, the porous structure is mainly formed by a large amount of small crystals, and thus a microporous structure can be obtained.

It is also possible to control the shape of the pores by modifying the TIPS method, using a technique known as directional thermally-induced phase separation (dTIPS). Phase separation was carried out using a uniaxial temperature gradient. The mould, which contained the polymer solution, was wrapped with a layer of heat-insulating material to reduce heat transfer through the side walls and increase the thermal conductivity along the entire volume. In the case of the classical phase separation, when the temperature gradient is not uniaxial, pore architecture is oriented randomly. In contrast, when the temperature gradient is maintained uniaxially, an array of parallel microtubules and microchannels [56] or an array of straight parallel channels with side tubular branches of comparable diameters is formed [57]. However, using the TIPS technique, it is difficult to obtain pores with a diameter above $200\text{ }\mu\text{m}$, a limited range of pore size is generally achieved and it is difficult to control the micro- and macro-structure of the scaffold [58], which limits its use in tissue engineering. To solve this problem, the phase separation technique has been combined with particulate leaching (TIPS/PL) [33,59] (Table 1, 7–10). In this case, the porous structure is formed either by leaching the solid particles out or by using a polymer-poor phase [60,61].

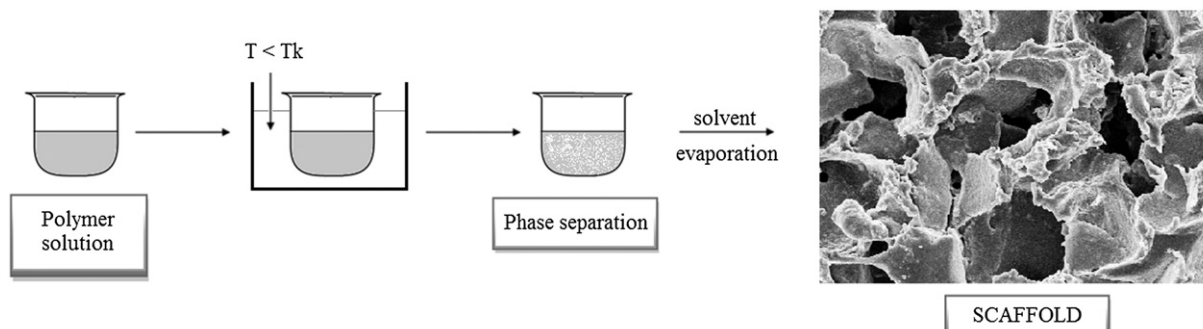


Fig. 2. Scaffold preparation using thermally induced phase separation technique.

Polyurethanes obtained from thermally-induced phase separation are mainly used as cardiovascular [55,62] and bone [63,64] scaffolds, but have also been used in regeneration of the meniscus [65,66], nerves [67] and the hypopharynx [68].

4. Melt moulding

Melt moulding is commonly used for the preparation of porous ceramics and metals [69]. However, it can also be applied to polymeric materials [70], including polyurethanes [37]. Moulds filled with porogen compounds and granulated or powdered polymers are heated above the polymer's glass transition temperature (T_g) at an elevated pressure [71] and raw materials join together to form a scaffold in the shape of the mould. After removal from the mould, the porogen is leached out, as in the case of the solvent casting technique combined with the particulate leaching (Fig. 3) [50].

From an industrial point of view, the preparation of porous structures by melt moulding is the most convenient and economical, since it allows the rapid production of polymer scaffolds of various shapes and sizes [72]. However, it is limited by the complexity in the design and construction of the mould. The shape and size of pores can be controlled by the selection of a porogen (Table 1, 14–15). In contrast to methods described previously, melt moulding does not require the use of organic solvents to create scaffolds [73].

The disadvantages of this method include the presence of a non-porous layer on the surface, the difficulty of leaching out the porogen compound, and thus the possibility of its remaining in the scaffold, and the unfavourable, high temperature of the process, which excludes versatile application [74,75]. The melt moulding technique allows the ceramics hydroxyapatite and polyurethane to be combined, and is therefore mostly used for the preparation of bone scaffolds [37,76].

5. Gas foaming

Gas foaming of polymers is a process that is widely used in industry for the preparation of e.g. expanded polystyrene, polyvinyl chloride foams, but it can also be applied for the preparation of scaffolds. Foaming can be carried out by reacting the components or releasing the gas which is a product of the thermal degradation of the gas-foaming agent. An example of this is the preparation of polyurethane foams. Water, added to the reaction mixture, reacts with an isocyanate group and forms a carbamic acid derivative, which transforms into carbon dioxide after decarboxylation. This technique is rarely used for the fabrication of scaffolds, because it is hard to control pore diameter and the average pore diameter is too large to allow adequate cell proliferation [77]. Consequently, the polyurethane scaffolds formed by gas foaming are mainly used for bone regeneration [78,79]. Another method of foaming PU is introducing gas into the melted polymer. The melted polymer is pressurised at high pressure with gases such as

carbon dioxide, fluoform, and nitrogen [80,81]. This creates a scaffold with a pore diameter ranging from 500 to 2000 μm (Table 1, 16–18).

Gas foaming does not require the use of organic solvents, which is a huge advantage. The main disadvantage is the difficulty in controlling the size and interconnection of pores, because large, closed pores can be created inside the polymer structure during the foaming process [82].

6. Emulsion freeze-drying

By emulsion freeze-drying, it is possible to obtain a porous material with a pore size from 20 to 200 μm and porosity above 90% [83]. This technique requires the preparation of an emulsion created by homogenisation of two immiscible phases, where the continuous phase contains the polymer-rich solvent and the dispersed phase is water (Fig. 4). A homogeneous emulsion is quickly frozen e.g. in liquid nitrogen (temp. -196°C) to maintain the structure of the liquid state, and is then freeze-dried to create a porous scaffold with a pore size and interconnectivity that is dependent on the processing parameters.

In the structure of the scaffold obtained by emulsion freeze-drying, there are two types of pores: macro and micro. Micropores are formed by removing the aqueous solvent, whilst macropores are formed by coalescence of the micropores during homogenisation [84]. The porosity and pore size are affected by the concentration and viscosity of the polymer solution and the amount of aqueous phase dispersed in the system. The volume of the aqueous phase in the emulsion affects the pore size; with a decrease in the amount of water, the average pore size also decreases [85]. However, with an increase in the polymer concentration in the continuous phase, the dispersed aqueous phase is exposed to higher shear forces, which reduce the size of the small water domains and a material with lower porosity and smaller pores is formed as a result (Table 1, 11). More uniform porous scaffolds can be manufactured using a constant cooling rate freezing technique. A rapid, uncontrolled quench freezing process leads to non-uniform nucleation and growth of ice crystals and consequently to scaffold morphological heterogeneity caused by space and time variable heat transfer through the system [5].

Emulsion freeze-drying is mainly used for the fabrication of soft-tissue scaffolds [86,87]. The advantages of this technique are the reduction of toxic solvents use and the elimination of time-consuming drying and leaching processes of porogen components. The problem that appears in the preparation of scaffolds by this method is the instability of the emulsion, which requires the addition of suitable surfactants [85]. To solve this problem, waterborne polyurethane (WBPU) can be applied [88]. The synthesis of WBPU is more complicated than PU. However, subsequent fabrication of scaffolds is more convenient and less difficult. Synthesised WBPU dispersion is freeze-dried and highly porous structure can be obtained (Table 1, 12–13). Hsu SH et al. [89] fabricated polyurethane foam with total porosity equal 97%. This scaffold fabrication method avoids the possible toxicity from the residual organic solvent.

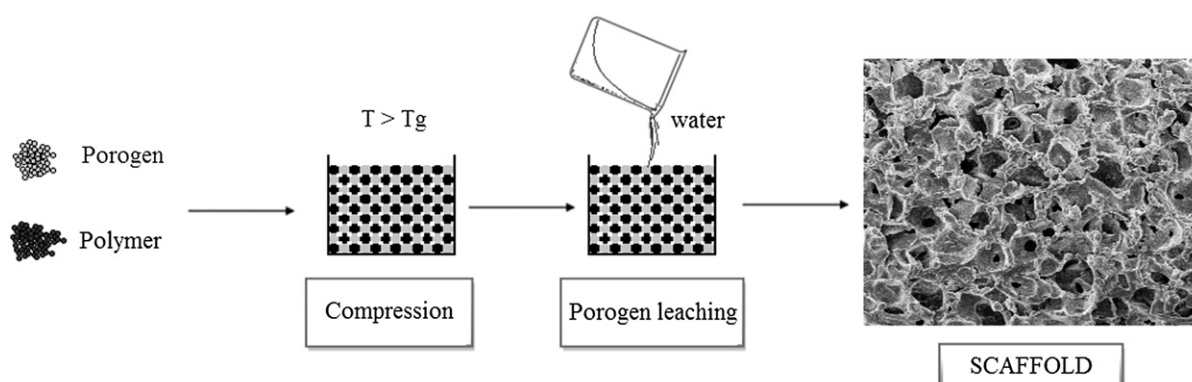


Fig. 3. Scaffold preparation using melt moulding technique.

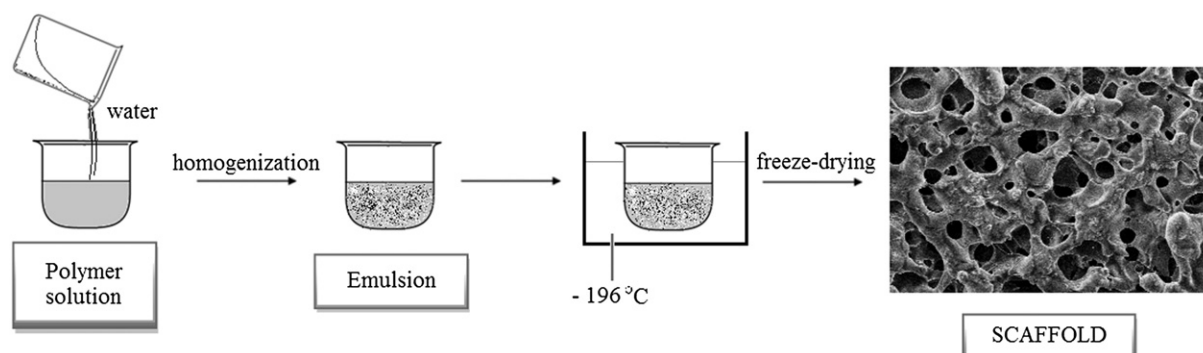


Fig. 4. Scaffold preparation using emulsion freeze-drying technique.

7. Conclusions

Techniques for fabricating polyurethane foams provide various scaffolds; depending on the application, it is possible to obtain scaffolds with different diameters and pore shapes. In methods involving the leaching of solid particles, the porosity can be effectively controlled by varying the amount and size of the pore former. In the phase separation technique, the different porosity occurs due to temperature changes and the concentration of polymer in the solution. In the case of emulsion freeze-drying, porosity is controlled by the concentration and viscosity of the polymer solution and the amount of dispersed aqueous phase in the emulsion. The melt moulding technique does not require organic solvents, as with gas foaming, and it is possible to produce scaffolds of various shapes and sizes. However, each of the conventional techniques has a number of disadvantages. At present, the main goal is to improve conventional methods or combine them with other techniques to eliminate their limitations and disadvantages.

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