

# Macro, Micro, and Nano-Inspired Bioactive Polymeric Biomaterials in Therapeutic, and Regenerative Orofacial Applications

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**Abstract:** Introducing dental polymers has accelerated biotechnological research, advancing tissue engineering, biomaterials development, and drug delivery. Polymers have been utilized effectively in dentistry to build dentures and orthodontic equipment and are key components in the composition of numerous restorative materials. Furthermore, dental polymers have the potential to be employed for medication administration and tissue regeneration. To analyze the influence of polymer-based investigations on practical medical trials, it is required to evaluate the research undertaken in this sector. The present review aims to gather evidence on polymer applications in dental, oral, and maxillofacial reconstruction.

**Keywords:** polymers, regeneration, oral, dental, maxillofacial

## Introduction

Numerous conditions, including infections, genetic disorders, malignancies, and trauma, can lead to dental, oral, and maxillofacial tissue defects. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD 2017) demonstrated that oral problems had the most significant occurrence and frequency rates on a global scale.<sup>1</sup> In this context and thanks to recent advancements in biomaterials and production technologies, natural and synthetic polymeric biomaterials have been introduced as viable therapeutic alternatives for various defects and abnormalities in dental, oral, and maxillofacial structures.<sup>2</sup> The therapeutic application of polymeric scaffolds has been extensively studied in regenerative therapies for several tissues. Numerous tissue engineering methods and surgical interventions have been introduced with an emphasis

on comprehending the unique features of a biomaterial at cellular contact. Accordingly, this review provides an overview of the most important polymeric scaffolds utilized for therapeutic, and regenerative purposes in dental, oral and maxillofacial tissues, as well as information on their characteristics, formulations, manufacturing techniques, advantages, disadvantages, and clinical uses.

## Overview of Biomaterials in Dental Applications

Polymers are macromolecules made up of repeated monomeric subunits that have outstanding characteristics. Innovation in biomaterials research encompasses applications in tissue engineering, nanotechnology, and the administration of bioactive molecules for the healing and regeneration of diverse tissues. The new generation of polymers was eminently distinguished by the development of resorbable, biodegradable polymers that displayed controlled degradation of the polymer chain<sup>3</sup>. Various biomaterials have been implemented in the dental field (Table 1).<sup>4</sup> Naturally, materials (eg, collagen) attracted attention; synthetically derived polymeric biomaterials were later introduced. Chitosan and collagen are naturally occurring polymers with high biocompatibility, bone conductivity, and minimal immunological reactions.<sup>5</sup> Nevertheless, disadvantages include a slow degradation rate and inferior mechanical qualities.

Breakthroughs in the composition of synthetic biopolymers have paved the way for the development of further novel materials with excellent tissue responsiveness and integration, and capable of being degraded and removed from the system, permitting correct tissue integration as the material breaks down, without exerting any harmful influence on the biological systems.<sup>7</sup> Further investigations are underway to develop scaffold formulations appropriate for biological systems with little or no negative impact on living systems.

Polymers are macromolecules made up of repeated monomeric subunits that are covalently bound. They can be amorphous or crystalline, having linear, branching, or cross-linked chains. Their mechanical characteristics could be extremely well regulated, allowing for the acquisition of desirable features based on application requirements. Polymers have lately been used to construct microneedles (MNs), hydrogels, microcapsules, microspheres, and fibers. These frameworks can further be designed to be biocompatible and biodegradable, eliminating possible immune reactions and allowing for simple body disposal (Figure 1 shows the advantages of polymeric scaffolds).<sup>6</sup> Furthermore, their hydrophilicity may give them biologically advantageous properties, especially as reservoirs for biological compounds in various medical applications.<sup>6</sup>

## Biological Requirements

The essential component in applying biomaterial in situ tissue engineering frameworks is biocompatibility. The scaffold is biocompatible, does not elicit an immune response, generates no hazardous byproducts, and permits cells to attach, proliferate, reproduce, and survive on its surface.<sup>8,9</sup>

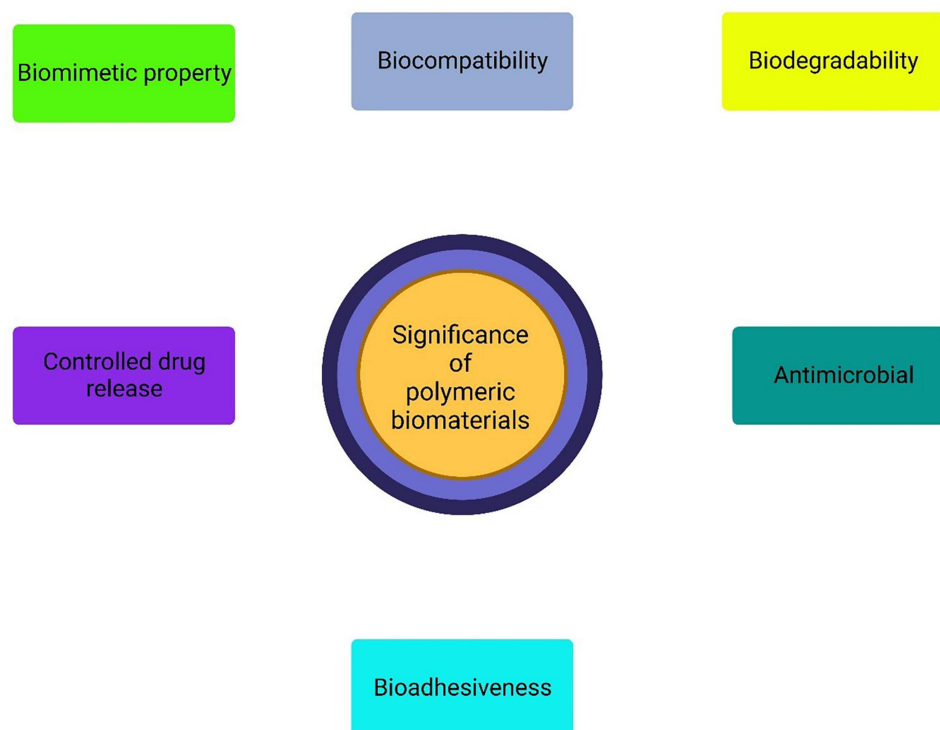
## Structural Features

Scaffolds must have high porosity to allow cell growth and movement, essential micronutrients, angiogenesis, and spatial layout. They should be customized to fit the regenerated tissue. They should be strong enough to endure biomechanical

**Table 1** Various Biomaterials Employed in the Dental Field

Biomaterials	Examples
Polymers	Chitosan, cellulose, hyaluronic acid etc.
Metals	Collagen, gelatin, albumin, etc.
Lipid-based	Polyethylene glycol (PEG), etc.
Ceramics	Chitosan/ hydroxyapatite scaffolds
Carbon-based biomaterials	Graphene, nanodiamonds, etc.

**Note:** Data from Sun et al<sup>8</sup> and Jin et al.<sup>9</sup>



**Figure 1** Advantages of polymeric scaffolds.

loads until restored tissue can withstand forces.<sup>10</sup> Another critical factor is architecture, which could be altered by adjusting artificial ECM and/or biomolecules to be administered in the microenvironment.<sup>11</sup>

## Biomaterial Composition

Depending on their architecture and intended use, they can be injectable or rigid.<sup>12</sup> Polymers may be both natural and synthetic. Chitosan and collagen are naturally occurring polymers with high biocompatibility, bone conductivity, and minimal immunological reactions. Nevertheless, disadvantages include a slow degradation rate and restricted mechanical qualities.<sup>5</sup>

## Polymeric-Based Biomaterials

Nowadays, polymer-based methods can be used as a tactic to enhance tissue regeneration. Examples of polymeric materials implemented in tissue engineering applications, as represented in Table 2.<sup>10,13–15</sup> Figure 2 represents natural and synthetic polymers in dental applications. Many polymeric formulations, including dendrimers, nano gels, micro-needles, and nanocapsules, have been studied as prospective approaches for dental applications.

## Natural Polymers

Natural polymers originate from natural substances and guaranteed natural restructure biomimetic character and biocompatibility. Table 3 shows the advantages, and disadvantages of some natural biopolymers.<sup>16</sup> Polysaccharide and protein-based polymers are roughly classified based on their monomeric units and structure.<sup>17</sup>

## Polysaccharide-Based Polymers

Thanks to their resemblance to the extracellular matrix, polysaccharides have great degradability, bioactivity, ease of chemical modification, and low manufacturing costs.<sup>25</sup> Even with their numerous advantages, natural polymers have some downfalls related to their branching, dispersion, pattern, and molecular mass, which results in the preparation of unreliable scaffolds, which harms biological recognition events and rheology.<sup>26</sup>

**Table 2** Polymeric Biomaterials, Benefits, and Limitations in Biomedical Applications

Types	Polymers	Advantages	Disadvantages	References
Natural polymer based scaffold	<ul style="list-style-type: none"> <li>• Natural polysaccharides:</li> <li>• Chitosan</li> <li>• Dextran</li> <li>• Hyaluronic acid</li> <li>• Heparin</li> <li>• Alginate</li> <li>• Pullulan</li> <li>• Carrageenan</li> <li>• Chondroitin Sulphate</li> <li>• Cellulose</li> <li>• Agar</li> <li>• Starch</li> <li>• Gum Tragacanth</li> <li>• Natural proteins:</li> <li>• Collagen</li> <li>• Fibronectin</li> <li>• Gelatin</li> <li>• Elastin</li> <li>• Keratin</li> <li>• Fibrin</li> <li>• Soy</li> <li>• Silk fibroin</li> <li>• Poly glutamic acid</li> <li>• Polydopamine (PDA)</li> <li>• Lignin (LIG)</li> </ul>	<ul style="list-style-type: none"> <li>• Biocompatibility</li> <li>• Non-toxicity</li> <li>• Easy availability</li> <li>• Cost-effective</li> </ul>	<ul style="list-style-type: none"> <li>• Poor mechanical properties</li> <li>• Low reproducibility due to variations in composition</li> </ul>	[10,13]
Synthetic polymer based Scaffold	<ul style="list-style-type: none"> <li>• Degradable polymers:</li> <li>• Polyethylene glycol (PEG)</li> <li>• Polyethylene oxide (PEO)</li> <li>• Poly-β-hydroxybutyrate (PHB)</li> <li>• Polypropylene fumarate (PPF)</li> <li>• Polycaprolactone (PCL)</li> <li>• Polyvinyl alcohol (PVA)</li> <li>• Poly (lactic-co-glycolic acid) (PLGA)</li> <li>• Polyethylenimine (PEI)</li> <li>• Poly (vinylpyrrolidone) (PVP)</li> <li>• Non-degradable polymers:</li> <li>• Polyurethane (PU)</li> <li>• Poly methyl methacrylate (PMMA)</li> <li>• Polystyrene (PS)</li> <li>• Polyethylene terephthalate (PET)</li> <li>• Polyether sulfone (PES)</li> <li>• Poly (di (ethylene glycol) methyl ether methacrylate) (PDEGMA)</li> <li>• Zwitterionic Polymers</li> <li>• Poly hydroxyortho esters</li> <li>• Polyvinyl alcohol (PVA).</li> </ul>	<ul style="list-style-type: none"> <li>• Mechanically stable</li> <li>• Ease of modification</li> <li>• Because of the homogenous chemical structure, repeatability is consistent.</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of cell adhesion sites</li> <li>• Less biocompatible</li> <li>• Expensive</li> </ul>	[14]

(Continued)

Table 2 (Continued).

Types	Polymers	Advantages	Disadvantages	References
Hybrid Scaffolds	<ul style="list-style-type: none"> <li>• PCL/Collagen</li> <li>• PCL/Collagen/Titanium oxide</li> <li>• PEO/Chitosan/Collagen</li> <li>• Silk/Gelatin/Alginate</li> <li>• AgNPs/Chitosan</li> <li>• Carboxyethyl chitosan/PVA</li> </ul>	<ul style="list-style-type: none"> <li>• Increased mechanical strength</li> <li>• Good tensile strength</li> <li>• Regulated biocompatibility, degradation rates, cytotoxicity and thermo stability</li> </ul>	<ul style="list-style-type: none"> <li>• Non-facile fabrication methods Often require sophisticated instruments</li> <li>• Expensive</li> </ul>	[15]

Chitosan

Chitosan is the world’s second most common natural polysaccharide, following cellulose. Several studies have investigated the biological applications of chitin and chitosan.<sup>27</sup> Chitosan is principally a chitin metabolite that has been

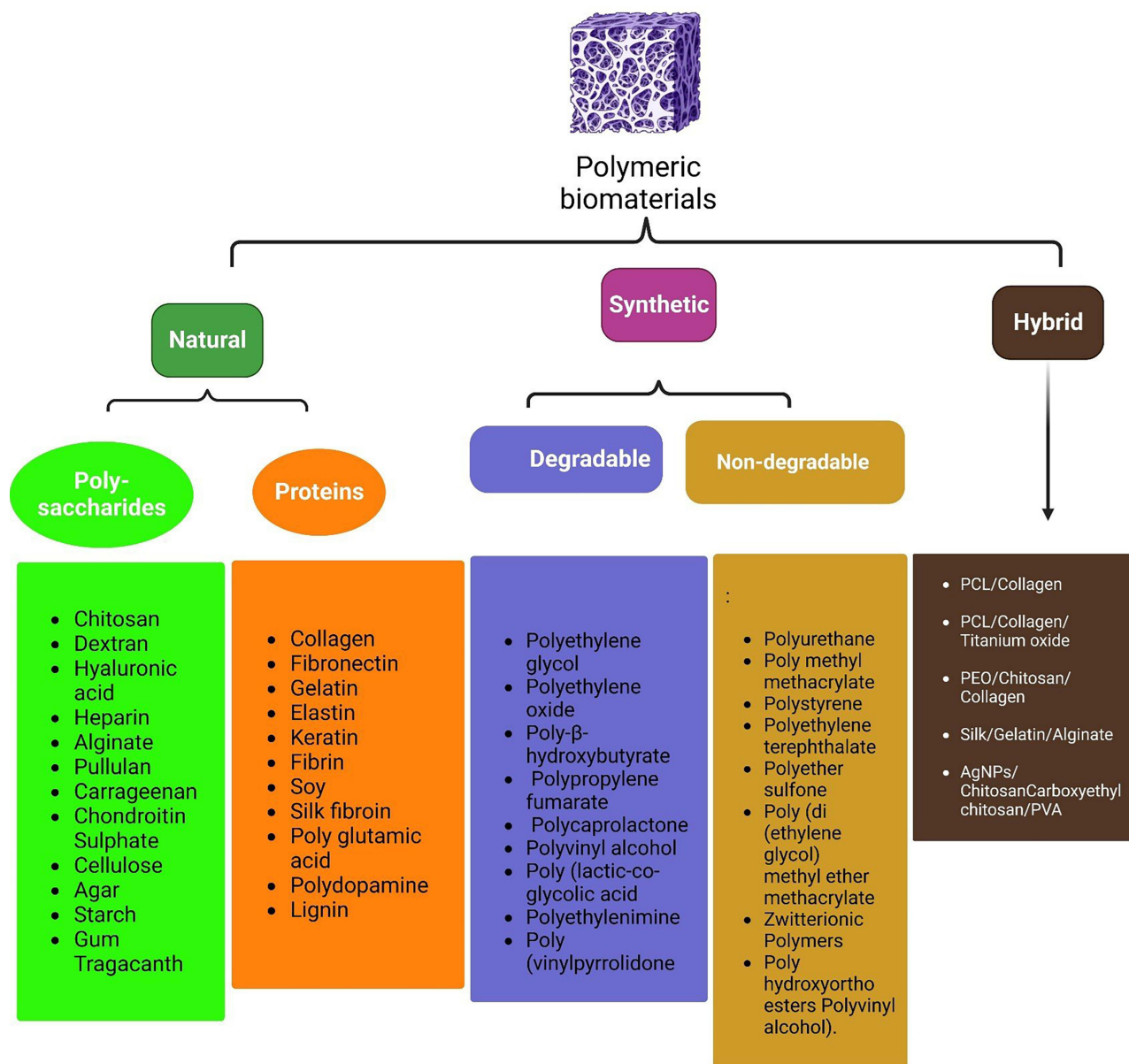


Figure 2 Natural and synthetic polymers in dental applications.

**Table 3** Advantages and Limitations of Some Natural Polymers

Polymer	Advantages	Limitations	References
Alginate	<ul style="list-style-type: none"> <li>• Biocompatible and biodegradable</li> <li>• Mechanical qualities that may be tuned</li> <li>• Low manufacturing costs</li> </ul>	<ul style="list-style-type: none"> <li>• Absence of therapeutic effects</li> <li>• Reduced mechanical properties.</li> <li>• Rapid decomposition</li> </ul>	[18]
Cellulose	<ul style="list-style-type: none"> <li>• Have a 3D high porosity.</li> <li>• Biocompatible</li> <li>• Hydrophilic shape improves cell attachment, multiplication, and mechanical characteristics</li> </ul>	<ul style="list-style-type: none"> <li>• Water insoluble</li> <li>• Not biodegradable in humans</li> </ul>	[19]
Chitosan	<ul style="list-style-type: none"> <li>• Hydrophilic architecture encourages cellular attachment, specialization, and multiplication</li> </ul>	<ul style="list-style-type: none"> <li>• Expensive manufacturing</li> <li>• Unpredictable characteristics</li> <li>• Harmful to the ecosystem</li> </ul>	[20]
Silk	<ul style="list-style-type: none"> <li>• Outstanding mechanical characteristics</li> <li>• Receives chemical modifications to be physiologically friendly</li> </ul>	<ul style="list-style-type: none"> <li>• Environmental concerns</li> </ul>	[21]
Protein-based polymers	<ul style="list-style-type: none"> <li>• Tissue regeneration capacity</li> </ul>	<ul style="list-style-type: none"> <li>• Immunogenic and allergic potential</li> </ul>	[22,23]
Hyaluronic acid	<ul style="list-style-type: none"> <li>• Bioactive and biodegradable</li> </ul>	<ul style="list-style-type: none"> <li>• Weak mechanical properties</li> <li>• Speedy degradation rate</li> </ul>	[34]

deacetylated.<sup>28</sup> Because of its unique features of bioactivity, good biocompatibility, and non-immunogenicity, chitosan has become increasingly popular in the biomedical field.<sup>20</sup> Chitosan-derived metabolites have been employed in several applications.<sup>24</sup>

### Dextran

Scheible in 1874 created the term Dextran.<sup>27</sup> It is an extracellular microbial carbohydrate derived from sucrose-derived bacterial lactic acid.<sup>29</sup> Because of their nontoxicity, hydration, bio-compatibility, and degradability, dextran polymers are frequently employed in the food sector, personal care products, wastewater treatment, and biomedical purposes.<sup>30,31</sup>

### Hyaluronic Acid

HA contributes significantly to the environment's extracellular matrix and synovial fluids.<sup>32</sup> The molecular weight of HA governs numerous biomedical actions. High molecular weight HA has been discovered to have anti-inflammatory and immune-modulatory properties.<sup>33</sup> A few high molecular weight HA metabolites have also been proven to show anti-angiogenic characteristics and the capability to suppress cell growth.<sup>34</sup> Low molecular weight HA promotes cell motility and vasculogenesis.<sup>35</sup> HA is classified as a naturally existing negatively charged polysaccharide because of a carboxyl group in its backbone.<sup>36</sup> This feature allows HA to maintain a substantial amount of water, leading to bulging behavior of HA up to 1000 times its solid dimensions, which several investigators have used to develop HA pharmacological carriers,<sup>37</sup> and numerous biological implementations.<sup>38,39</sup>

### Heparin

While researching cephalin in 1916, Jay McLean observed anticoagulant phosphatide fractions independent from it. Emmett Holt and William Henry Howell later called Heparin after another anti-coagulant molecule obtained from the liver.<sup>40</sup> Heparin is a natural glycosaminoglycan produced by mast cells in the Golgi apparatus and the endoplasmic reticulum. It is derived from various origins for pharmaceutical and industrial use.<sup>41</sup> Heparin has been employed as a transporter of growth factors.<sup>42</sup> Heparin is also anticoagulant since its penta saccharide specifically reacts with anti-thrombin.<sup>43</sup> These features emphasize the ubiquitous utilization of heparin-based carriers, like micelles and nano gels, as drug delivery vehicles.<sup>44</sup>

### Alginate

E. C. C. Stanford revealed alginic acid in 1881, detailing the isolation of alginate with sodium carbonate and its deposition in an acidic solution.<sup>45</sup> Species of brown seaweeds like *Laminaria* and *nereocystis*, along with bacterial strains like *Azotobacter* and *Pseudomonas*, are significant sources of alginates.<sup>46</sup> Because of its unique characteristics, alginate-based biomaterials are utilized in many biomedical applications.<sup>18</sup> The thickness of polymeric alginate impression materials should be reduced into minimal as it greatly influences the tear strength of the polymer after setting.<sup>47</sup>

### Pullulan

Pullulan is a structurally intermediate polysaccharide containing matotriose particles between amylose and dextran.<sup>48</sup> Pullulan is hydrophilic and moderately soluble in alkaline solutions, whereas inorganic solvents, including formamide and dimethyl sulphoxide, are completely insoluble (DMSO).<sup>49</sup> Pullulan is an intriguing material for the nutraceutical and pharmaceutical sectors, as well as medication delivery, biomedical engineering, gene therapy, and so on, due to its biodegradability, non-toxicity, and non-mutagenicity.<sup>50</sup>

### Carrageenan

Carrageenan is an anionic, sulfated polygalacton discovered in the cell walls of red algae that is comparable to ECM-derived glycosaminoglycans. Carrageenan's structure promotes osteoblastic growth and attachment.<sup>51</sup> It increases osteoblastic activity when combined with hydroxyapatite.<sup>52</sup> Carrageenan was mixed with other chemicals in bone regeneration tissue engineering investigations to generate hybridized bio-scaffolds.<sup>53</sup>

### Chondroitin Sulphate

Chondroitin Sulphate (CoS) is an essential cartilage component connected with compression resistance. CoS originated from chondrocytes and has a crucial influence in preserving the physiological functions of cartilages.<sup>54</sup> CoS absorbs water and has a cushion-like effect on cartilage.<sup>55</sup> CoS's polyanionic nature offers a foundation for electrostatic interactions with positively charged moieties, which could be employed to deliver medications and growth nutrients. CoS is anti-inflammatory, anti-apoptotic, antioxidant, and anti-cancer.<sup>56</sup>

### Cellulose

Cellulose is often recognized as the most widely recognized polysaccharide on the planet.<sup>57</sup> Cellulose derived from bacteria, termed bacterial cellulose (BC), is highly pure, but cellulose derived from plants is documented to include trace levels of contaminants such as lignin, pectin, and hemicellulose.<sup>58</sup> Because of its nontoxicity, degradability, biocompatibility, wide availability, and remarkable mechanical qualities, cellulose, and its variants are valuable materials for drug administration, wound healing, and other biological purposes.<sup>19</sup> Using oral thin film made from a blend of hydroxyethyl-cellulose (HEC) and cellulose nanofibers (CNF), loaded with nepheline fluorapatite glass powder as a remineralizing agent for prevention of carious lesion by remineralization was tested. Significant quantities of calcium and fluoride ions discharged and the pH values were practically neutral. The arrangement of glass powder particles was consistent, according to SEM. In comparison to the demineralized samples, the findings of enamel micro-hardness (VHN) and ultra-morphology showed a considerable rise in mean VHN following remineralization for 15 and 30 days.<sup>59</sup>

### Agar

Agar is another polysaccharide biopolymer that is commonly recognized for its strong bioactivity and biocompatibility.<sup>36</sup> It can generate a gel that resembles the physical properties of the ECM and tissues essential for transferring growth factors to wounds.<sup>60</sup> Previous studies proved its non-toxicity and successful cell proliferation. Consequently, it can be employed in healing and skin regeneration.<sup>61</sup>

### Starch

Due to starch's degradability, non-cytotoxicity, and processability, it is an excellent example of a storing polysaccharide.<sup>62</sup> Polymers made from starch have shown promise in a variety of biological applications. Starch

hydrogels fortified with zeolite NPs and chamomile preparations successfully treated chronic ulcers with no hypersensitivity reaction to the scaffold.<sup>61</sup>

### Gum Tragacanth

This is a polysaccharide originating from the *Astragalus* plant.<sup>63</sup> Gum Tragacanth is widely utilized in tissue engineering to create biodegradable frameworks and medicine administration mechanisms. This scaffold has demonstrated encouraging outcomes in terms of osseous regeneration.<sup>64</sup>

### Natural Proteins

#### Collagen

Collagen is one of the most widely utilized protein biopolymers. It possesses a significant conjunction effectiveness with other compounds, which may be changed to achieve improved biological and mechanical qualities.<sup>22</sup> Over 28 isomers of collagen have been extracted, each with a different helix length and the type and dimensions of the non-helical parts.<sup>65</sup> Type I collagen is the most prevalent kind that constitutes the ECM of several oral tissues, such as periodontal ligament, enamel, etc.<sup>66–70</sup> As an ECM structural element, it has strong biocompatibility, low immunogenicity, and significant mechanical integrity, and it assists in growth, differentiation, cell attachment, and ECM formation.<sup>71</sup> It is an attractive natural resource due to the ease with which it may be modified.<sup>72</sup> Tannic acid cross-linked collagen frameworks made by casting have been used to improve wound healing qualities.

#### Fibronectin

Fibronectin is a glycoprotein with a high molecular mass that is extracted from plasma. Its major purpose as a scaffold is to facilitate cell attachment and motility, influencing cell division and growth.<sup>73</sup> Fibronectin nano fibers produced by rotary jet spinning demonstrated faster wound closure.<sup>74</sup>

#### Gelatin

Gelatin is an organic protein generated from collagen commonly employed in biomedicine thanks to its poor immunogenicity, bioactivity, and good biocompatibility.<sup>75</sup> Because of its gelation properties and simplicity of processing, it may be processed into numerous formulations such as injectable hydrogels, sponges, and microspheres.<sup>76</sup> Gelatin has also been combined with copper-activated faujasite to generate composites with high anti-microbial action using the freeze-drying process.<sup>77</sup> Li et al established a straightforward strategy for creating gelatin-based scaffolds with hollow alginate fibers to create a vascular network.<sup>78</sup>

#### Elastin

Elastin is a hydrophobic and insoluble extracellular matrix (ECM) protein. Collagen-elastin frameworks have been used to treat full-thickness skin abnormalities such as burn wounds as dermal replacement.<sup>79</sup>

#### Keratin

Keratin is a protein in the skin, fingernails, and hair.<sup>80</sup> This protein is found in the skin, nails, and hair. It is biocompatible and capable of building frameworks that coordinate cellular activities.<sup>61</sup> By lyophilization, Keratin has also been used with chitosan to create a porous keratin/chitosan scaffold. The antimicrobial activity and cell proliferation rates of keratin/-chitosan scaffolds used for wound dressings were increased.<sup>81</sup>

#### Fibrin

Fibrin is a naturally degradable matrix composed of fibrinogen, created soon after trauma.<sup>82</sup> The fibrin-based scaffolds promote growth by allowing the attachment of various biologically active biomolecules, promoting specific cell-matrix interactions and boosting tissue regeneration.<sup>83</sup> They allow enough time to form neo matrix and progressive re-assimilation via protease activity.<sup>84</sup> Fibrin can be employed as a biological framework with other elements to regenerate

primary cells, skin, bones, and so on.<sup>85</sup> Nevertheless, it has the disadvantage of quick degradation, which makes it unsuitable for creating particular scaffolds.<sup>86</sup>

### Soy

Soy protein extract is a sustainable and readily accessible protein with more than 90% polypeptide. It has a macromolecular structure equal to the naturally generated proteins in bone.<sup>23</sup> Wu et al employed a comparable bi-component scaffold for bone tissue creation in experiment.<sup>23</sup>

### Silk Fibroin

Silk fibroin is a significant constituent with a unique amino acid composition that encapsulates sericin obtained from *Bombyx mori* cocoons.<sup>87</sup> Because the protein resembles the stroma of bone, it is synthesized into frameworks for regenerating bone tissue.<sup>21</sup> The addition of fibroin enhances the hydrophilicity and mechanical properties of the scaffolds, allowing human osteoblast-like cells to survive.<sup>88</sup> A two-stage functionalization procedure generated silk fibroin nanofibers containing hydroxyapatite particles.<sup>89</sup>

### Poly Glutamic Acid

Polyglutamic acid is a biopolymer made up of carboxy-linked glutamate residues released by *Bacillus subtilis*.<sup>90</sup> This polymer is edible and has great biocompatibility, nontoxicity, and biodegradability. These characteristics make it a desirable material for tissue engineering,<sup>91</sup> biodegradable wrappers,<sup>92</sup> wound bandages,<sup>92</sup> and pharmaceutical administration.<sup>93</sup>

### Polydopamine (PDA)

PDA is a darkish, opaque polymer generated by dopamine autoxidation.<sup>94</sup> Thanks to its intriguing features and simplicity of manufacture, PDA has recently attracted significant attention in various biological applications, including medication delivery, photodynamic therapy, skeletal tissue engineering, cell attachment and imprinting, and antibacterial use.<sup>95</sup>

### Lignin (LIG)

LIG is a recyclable, sustainable, safe, economical, and natural biomaterial that has grabbed the spotlight of research scientists thanks to its distinctive characteristics and environmentally friendly nature.<sup>96</sup> LIG is antibacterial, antioxidant, and antiviral, with UV protection, biocompatibility, and minimal cytotoxicity.<sup>97</sup> LIG has been poorly investigated in the biomedical area until now, with just a few research reporting on its use in healthcare applications.<sup>98</sup>

## Synthetic Polymers

In the research laboratories, synthetic polymers are created using hydrocarbon-building components.<sup>99</sup> They have the benefit of infinite shapes and well-established structures. They are mechanically stable and free of contaminants.<sup>100</sup> They enable convenience and administration of manufacturing via polymerization, interlinkage, and productivity due to their molecular weight, molecular weight, and physicochemical characteristics. These polymers are classified according to their hydrophobicity and hydrophilicity<sup>101</sup> and can also be categorized according to degradability.<sup>102</sup> They are instrumental since their features may be easily modified for various and specialized purposes.<sup>14</sup> However, their fundamental drawback is the lack of cell attachment sites and the need for chemical functionalization for cellular growth.<sup>103</sup>

### Degradable Polymers

As the term indicates, biodegradable polymers may be rapidly decomposed or converted into simpler molecules or by-products.<sup>104</sup>

### Polyethylene Glycol

Polyethylene glycol (PEG) is a commercially important polyether among degradable polymers (PEG). It is an ethylene oxide polymer called polyethylene oxide (PEO) or polyoxyethylene.<sup>105</sup> It is non-ionic, biocompatible, and has excellent biological and physicochemical qualities. The cross-linking techniques used to create hydrophilic PEG hydrogels can

impact scaffolds' physicochemical characteristics and degradation rates.<sup>106</sup> Architecture's ease of manipulation and chemical makeup makes it an appealing scaffold material.<sup>107</sup>

### **Polyethylene Oxide (PEO)**

PEO is a hydrophilic polymer with minimal pathogenicity, cell attachment, immunogenicity, and the ability for protein binding.<sup>108</sup> PEG's smaller molecular structure became well-known when its ability to block protein absorption was discovered.<sup>109</sup> More research is needed to modify these gels to include places for cell attachment, which will help cells penetrate the scaffolds.<sup>110</sup> When combined with electro-spun scaffolds made from other biodegradable polymers, PEO microparticles generated utilizing electro spraying approach enhanced the porosity and cellular penetration of scaffolds.<sup>111</sup>

### **Poly- $\beta$ -Hydroxybutyrate (PHB)**

Poly- $\beta$ -hydroxybutyrate (PHB) is a linear biodegradable homopolymer of  $\beta$ -hydroxybutyric acid that is found in many bacteria as an energy storage molecule.<sup>112</sup>

### **PPF (Poly (Propylene) Fumarate)**

PPF (poly (propylene) fumarate) is a linear polyester with fumaric acid as the repeating unit. It is biodegradable, cross-linkable, and powerful.<sup>113</sup> Cross-linking of fumarate double bonds results in creating a polymeric network.<sup>114</sup> Because of its high mechanical strength, it is predominantly employed in orthopedic surgery.<sup>115</sup> It is also employed with other polymers<sup>116,117</sup> to improve their hydrophobicity. To study bone formation, pre-treated PPF scaffolds were placed into the craniums of rabbits with cranial abnormalities.<sup>118</sup> The PPF scaffold covered with rh TGF- (PPF-TGF-) performed better regarding bone area%, bone surface area, and gap-filling percentage.<sup>61</sup>

### **Polycaprolactone (PCL)**

Polycaprolactone (PCL) is a robust aliphatic polymer with good biocompatibility.<sup>119</sup> It is a polyester with remarkable elasticity, physical qualities, minimal breakdown levels, non-toxicity, and low price.<sup>120</sup> The capacity of PCL as a biologically friendly material has been demonstrated for several biomedical purposes.<sup>121</sup> The fundamental drawback of PCL is its weak bioactivity and excessive hydrophobicity, which leads to poorer cell adhesion and restricted tissue regeneration.<sup>122</sup> Polylactic acid is mixed with PCL to produce a less hydrophobic structure with increased processability and mechanical behavior.<sup>123</sup>

### **Polyglycolic Acid**

Sekiya et al used polyglycolic acid to build a nano-fiber with collagen and test its in vivo potential to induce neovascularization and granulation histology. The study's outcomes revealed strong cellular migration with excellent neovascularization.<sup>124</sup>

### **Polyvinyl Alcohol (PVA)**

Polyvinyl alcohol (PVA) is a commonly utilized polymer employed in numerous biomedical applications thanks to its favorable features such as biodegradability, biocompatibility, and non-toxicity.<sup>125</sup> It is frequently used with other polymers to create nano-fibers for wound healing and other tissue engineering applications.<sup>126</sup>

### **Poly (Lactic-Co-Glycolic Acid) (PLGA)**

PLGA is an artificial, biodegradable, and FDA-approved polymer.<sup>127</sup> Because of its degradability, simplicity of modification, superior mechanical properties, potential for continuous drug delivery, and sustained clinical applicability, PLGA has been extensively researched in the realm of nanomaterials for creating pharmaceutical delivery systems.<sup>128</sup>

### **Polyethylenimine (PEI)**

PEI is an artificial, water-soluble, positively charged, linear, or branching polymer amino group. PEI has been employed in various biomedical applications such as medicine administration, gene transfer, antimicrobials, and multimodal

imaging. Due to its amino groups, PEI has been extensively utilized to fabricate various organic/inorganic hybrid nano materials for various biological purposes.<sup>129</sup>

### Poly (Vinylpyrrolidone) (PVP)

PVP is an FDA-approved, artificial, neutral, water-soluble polymer widely used in biologics, personal care products, and nutritional supplements. Because of its advantageous properties, including bioactivity, biodegradability, and environmental friendliness, PVP is frequently employed as a protective coating.<sup>130</sup>

### Non-Degradable Polymers

Non-biodegradable polymers are generally utilized in wound dressings because they are neither destroyed nor dissolved into smaller molecules by biochemical processes.<sup>131</sup>

### Polyurethane (PU)

Polyurethane (PU) is characterized by its high flexibility and capacity to degrade into degradable forms such as poly (ester-urethane) urea.<sup>132</sup> It is used in various preparations, such as mixes with olive oil that contain antioxidant properties and a photoprotective mechanism.<sup>133</sup> Dextran fibers electro-spun with PU showed intense angiogenic activity and significant anti-inflammatory activity, accelerating dermatological lesion repair.<sup>134</sup>

### Poly Methyl Methacrylate (PMMA)

PMMA is a common biocompatible polymer that is used alone or in composites to produce frameworks for biomedical applications.<sup>135</sup>

### Polystyrene (PS)

Polystyrene (PS) is a crystalline, colorless polymer with excellent water vapor permeability and high electrical resistance.<sup>136</sup> In one study, combining PS with chamomile extract and poly (-caprolactone) expedited wound healing by increasing collagen fiber build-up, improving re-epithelialization, and increasing granulation tissue development.<sup>137</sup> Porous PS scaffolds were created to allow fibroblast cells to construct a network of indigenous extracellular proteins.<sup>138</sup> This enables the establishment of a sub-epithelial 3D microenvironment rich in chemical and mechanical signals, which promotes epithelial cell functionalization.<sup>139</sup>

### Polyethylene Terephthalate (PET)

PET is a robust synthetic fiber that is extensively utilized in biomedical engineering as an implanted biomaterial.<sup>140</sup> PET nano-fibers made with honey have shown astonishing outcomes as a functional wound dressing, with enhanced ability of the mats to absorb water, which is essential for wound healing.<sup>141</sup>

### Polyether Sulfone (PES)

PES is a polymer with high porosity and a large surface area.<sup>142</sup> The electro-spun nano-fibers generated from PES displayed enhanced adsorption efficiency, which is crucial for optimal wound healing.<sup>143</sup>

### Poly (Di (Ethylene Glycol) Methyl Ether Methacrylate) (PDEGMA)

Nanofibers composed of PDEGMA and poly (l-lactic acid-co-caprolactone (PLLA-CL) have been utilized for controlled drug delivery, specifically for the antimicrobial ciprofloxacin.<sup>144</sup> Because they are thermo-sensitive, they facilitate cell dissociation and ciprofloxacin distribution to wound-infected regions when the temperature is reduced. In vivo, testing on mice with excision wounds revealed that the composite scaffold had superior healing properties to commercial gauzes.<sup>145</sup>

### Zwitterionic Polymers

Zwitterionic Polymers gained so much interest thanks to their remarkable features. Despite their excellent biocompatibility and stimulus reactivity, zwitterionic hydrogels need mechanical properties to be suitable tissue-promoting material

in direct blood contact. This issue was overcome in a 2020 study by adding Electro spun fiber scaffold to zwitterionic hydrogels for biocompatibility and mechanical strength, allowing long-term blood contact devices to be developed.<sup>146</sup> Over the past ten years, the combination of zwitterionic polymers' increased hemocompatibility, outstanding non-fouling characteristics, charge-switching qualities, and resistance to protein adsorption has made them appealing in biomedical applications, particularly in tissue engineering.<sup>146</sup> Other zwitterion therapeutic applications include implantable medical devices, tissue repair bandages and tissue frameworks, drug delivery vehicles, and biosensors.<sup>147</sup>

## Hybrid Scaffolds

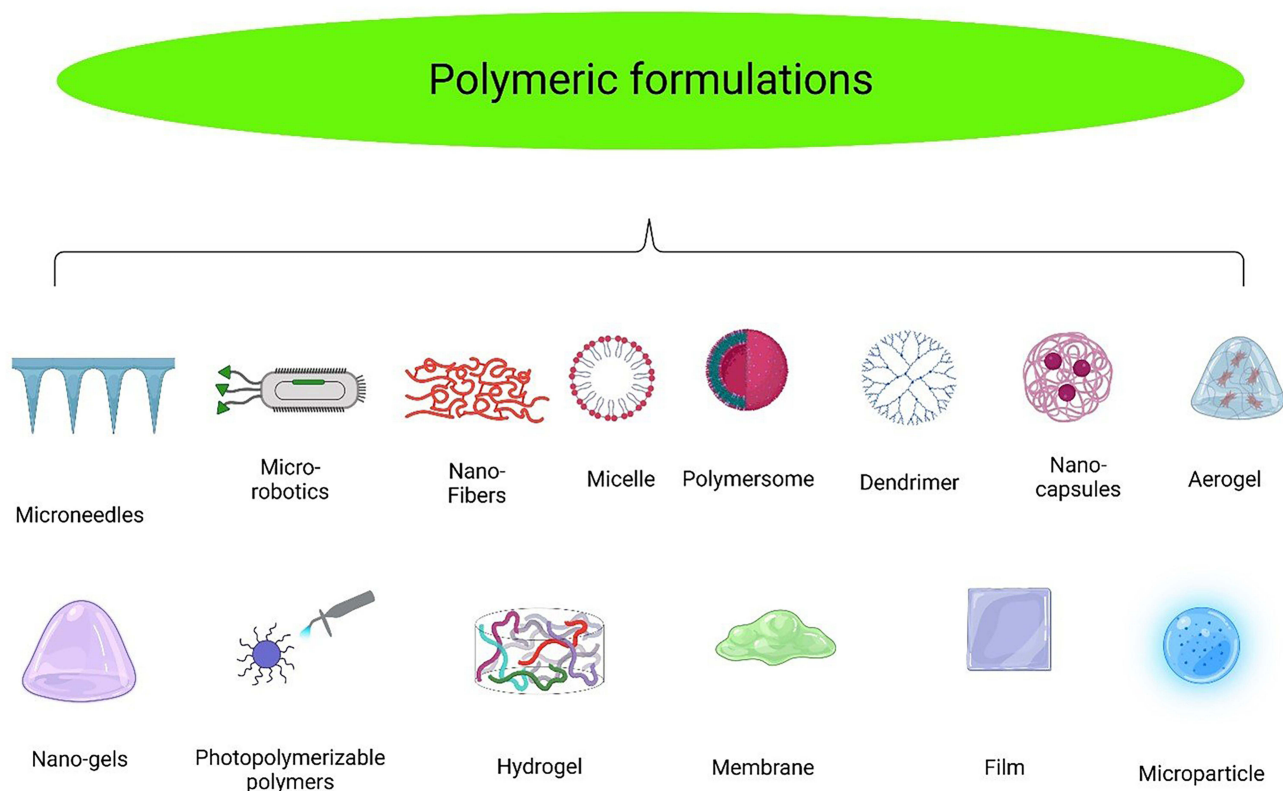
Hybrid scaffolds are one of the most exciting topics of study due to improved characteristics that are more acceptable for diverse tissue engineering applications resulting from combining numerous materials.<sup>15</sup>

## Different Polymeric Formulations

Different formulations of polymeric biomaterials are currently employed in different biomedical applications, as shown in Figure 3.

### Micro Needles

MNs are collections of tiny needles up to 1 mm in length that enable medicinal materials to pass through without triggering tissue injury or patient pain.<sup>148</sup> Cells are among the therapeutic materials given through MN-based medication carriers,<sup>149</sup> tiny substances,<sup>150</sup> and macromolecules.<sup>151–153</sup> MNs might be hard, disintegrating, porous, covered, or hydrogel-forming.<sup>154</sup> Although no MN-based medicines are commercially available, various clinical studies using MN-based pharmaceutical delivery methods have already been accomplished.<sup>155</sup> Moreover, MN-based drug delivery systems are feasible for meeting the demands of vulnerable groups receiving biological therapy, including older people and children.<sup>156</sup> Due to favorable characteristics, including improved bioactivity, better drug loading potential, a divalent



**Figure 3** Different polymeric formulations.

affinity for their specialized biochemical implementations, versatility, wettability, and low cost of production, polymer-based MN materials are the most notable topic for researchers in drug delivery systems.<sup>157</sup>

## Microrobots

Micro robots have shown enormous promise for doing micro-scale activities such as medicine delivery, cell handling, micro construction, and bio detection<sup>158–160</sup> using manual control. Microrobots might be employed for minimally invasive procedures as well.<sup>161</sup> A micro-robot may perform surgical procedures such as vein or channel opening, electrocautery, hyperthermia treatments, diagnostics, electrotherapy, chopping, drilling, or biomaterial elimination.<sup>162</sup>

## Nano Fibers

Nanofibers have sizes ranging from 1 to 1000 nm and give advantages, including a large surface area, permeability that provides effective mechanical action, pore connectivity, and flow properties.<sup>163,164</sup> Nanofibers are used in medical services such as inserts for longer drug release, pharmaceutical items, healing dressings, and tissue engineering scaffolding.<sup>165</sup> Table 4 shows the characteristics of the various production processes of nanofibers.

## Micelles

They are amphiphathic particles with a hydrophobic tail that faces the core and an external hydrophilic spike that links to the fluids. An amphoteric chemical can also form an inverted micelle in a neutral medium, with the spike towards the core and the tail pointing outward. Two copolymers mix with chemicals in some solvents to form polymeric micelles. The solvent dissolves one copolymer but not the others. The inner component comprises insoluble copolymers, whereas the outside part comprises soluble copolymers, from which the micellar assembly is made. This polymeric micelle is helpful in a variety of applications.<sup>166</sup>

## Polymersome

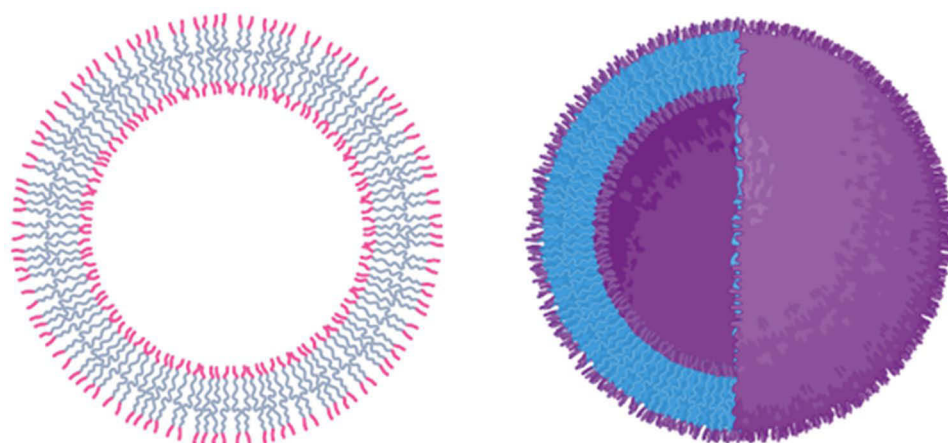
Polymersomes are synthetic vesicles with an aqueous cavity formed by amphiphilic copolymer self-assembly, as shown in Figure 4.<sup>167</sup> Furthermore, vesicular membrane improvement can aid in the adaptation of polymersomes for several purposes, such as drug delivery systems<sup>168</sup> or artificial organelles.<sup>169</sup> Polymersomes are excellent antibiotic delivery vehicles for drugs that do not ordinarily enter host cells.<sup>170</sup>

## Dendrimers

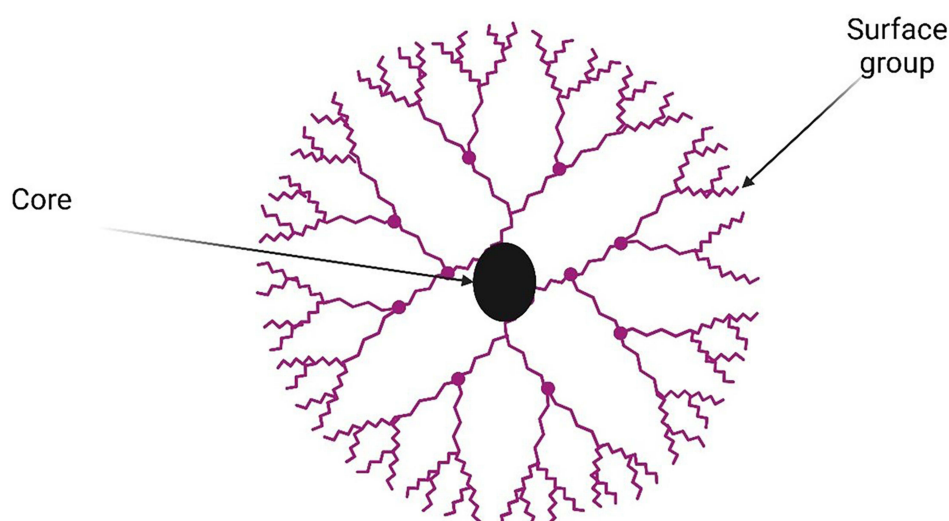
D.A.Tomalia coined the name Dendrimer from two Greek words: dendrons (trees) denotes their morphology, and meros (parts) indicate their chemical structure, which is made up of continuous monomers, as represented in Figure 5. Even though dendrimers are not polymerized, they are classified as polymers due to their repetitive pattern.<sup>171</sup> Dendrimers can function as biomimetic materials because of their globular design with less than 10nm dimensions. This results in

**Table 4** Features of Nanofiber Manufacturing Strategies

Strategy	Self-Assembly	Phase Separation	Electrospinning
Status	Semi-solid	Solid	Solid
Physical shape	Hydrogel	Scaffold	Scaffold
Size (nm)	5–20	50–500	50–2000
Benefits	<ul style="list-style-type: none"> <li>• Absence of biohazardous solvents</li> <li>• 3D structure</li> </ul>	<ul style="list-style-type: none"> <li>• Simple process</li> <li>• Better control of pore size</li> <li>• 3D Shape</li> </ul>	<ul style="list-style-type: none"> <li>• Single manufacturing process</li> <li>• Ability to control the pores</li> </ul>
Limitations	<ul style="list-style-type: none"> <li>• Complex process</li> <li>• Expensive</li> </ul>	<ul style="list-style-type: none"> <li>• Absence of control over the internal structure</li> </ul>	<ul style="list-style-type: none"> <li>• Inability to conform the 3D architecture.</li> </ul>



**Figure 4** Polymersome.

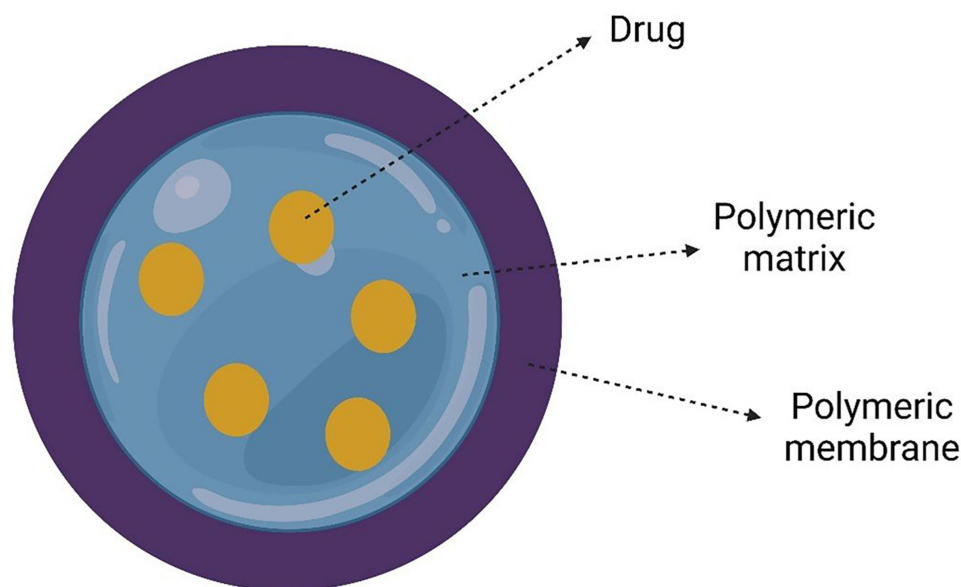


**Figure 5** Structure of Dendrimer.

constant dimensions and morphologies that can be changed to develop new dendrimer populations. When employed as scaffolding, their low polydispersity ensures polymeric agent cellular absorption repeatability.<sup>172</sup> Dendrimers can be utilized for several functions, including target-specific medication delivery, neovascularization, and gene delivery.<sup>173–175</sup>

## Nano Capsules

Polymeric nanocapsules have recently received much attention as a possible medication delivery mechanism. They are nanoparticles with a distinct architecture comprising a liquid/solid core surrounded by a polymeric shell, as represented in [Figure 6](#). They can increase payload bioavailability and provide prolonged and localized distribution as medication delivery devices. Similarly, they can substantially decrease the adverse effects of payload and tissue conditions. By encapsulating the medicine in them, it is possible to protect the drug against breakdown or disintegration induced by the biological microenvironment. Furthermore, it can help lessen drugs' adverse effects on healthy tissue.<sup>176</sup>



**Figure 6** Structure of drug loaded nano capsule.

## Aerogels

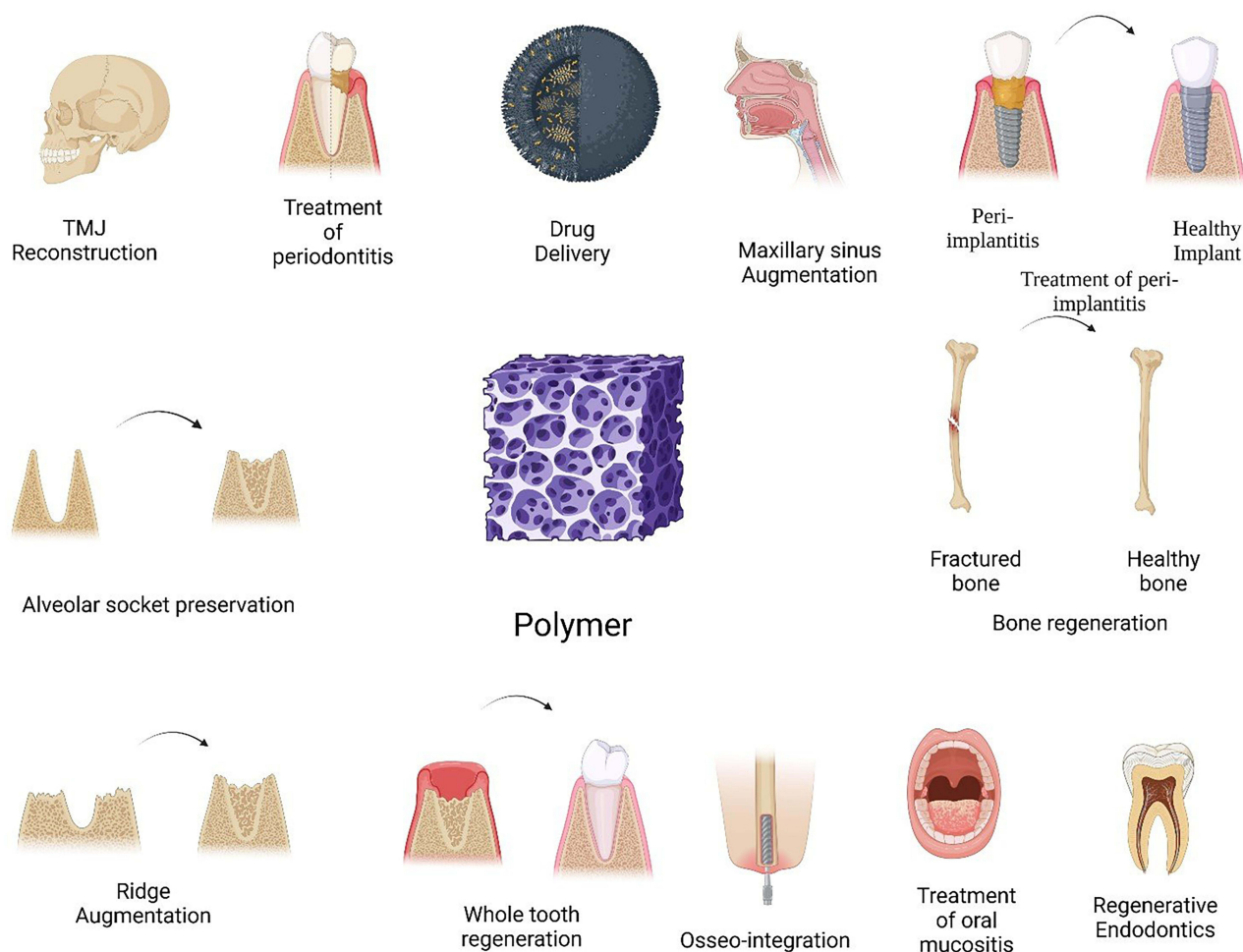
Aerogels are polymeric materials with high porosity, large surface area, a large pore volume, and varied chemical structures. They are frequently used in aircraft, chemical engineering, building, electronics, and bioengineering.<sup>177</sup> In the past few years, there has been a significant increase in the production of innovative aerogels with unique physicochemical features and functionalities. However, native aerogels with a single element typically suffer from substantial issues like poor structural rigidity and a shortage of functionalities. Building hybrid aerogels is one solution to the challenges. The initial aerogel was produced by Kistler in 1931, and he characterized aerogels as “gels where the liquid has been substituted by air, with the modest shrinking of the solid network”. There is, nevertheless, no commonly recognized description of porous materials. The most widely recognized report is that “aerogels are materials in which the usual pore patterns and connections are amazingly preserved when the liquid of a gel is displaced by air”, as stated by Hüsing and Schubert.<sup>178</sup>

## Nano Gels

Nano gels are created by cross-linkers with hydrophilic or amphiphilic groups, resulting in a three-dimensional architecture with particle sizes ranging from 1–200 nm, shared by hydrogels and nanoparticles.<sup>179</sup> Nano gels are now recognized as a new class of sophisticated delivery vehicles. This unique capacity also allows Nano gels can absorb bioactive compounds into their network, reducing bioactive component degradation due to external factors.<sup>180</sup> Furthermore, nano gels have smaller particle sizes and a larger specific surface area, allowing for greater bio-coupling. Nano gels have the potential to significantly increase the beneficial in vivo content of bioactive compounds, making clinical or daily usage of a wide range of bioactive substances more convenient.<sup>181</sup> Moreover, it is reported that addition of nanogel reduce the polymerization shrinkage.<sup>182</sup>

## Photopolymerizable Polymers

Photopolymerizable and biodegradable polymers are increasingly used in dental applications, as shown in Figure 7. Photo-triggered polymerization technique has enabled the development of injectable photopolymerizable biomaterials for dentistry and other purposes.<sup>183</sup> Consequently, the procedure leads to the formation of cells and a conducive microenvironment for development, which aids the manufacture of scaffold materials and, thus, the formation of complex systems. The ingredients produced by this technique vary from totally synthetic goods like polyethylene glycol to those formed entirely of natural



**Figure 7** Polymeric biomaterials in oral, dental, and maxillofacial reconstruction.

polymers like hyaluronic acid.<sup>184</sup> Photopolymerizable biomaterials are utilized to create injectable biomaterials that may be utilized to create multifunctional scaffolding and distribute growth factors, cells, chemicals and pharmaceuticals.

## Hydrogels

Hydrogels are three-dimensional frameworks of different polymers, such as chitosan, alginate, casein, and others, with increased wettability and excellent permeability for several molecules. They have features that are pretty useful for a variety of purposes. Furthermore, the hydrogel architecture and characteristics may be dramatically altered by a reversible sol-gel phase transformation induced by temperature variations or the existence of certain chemicals reacting with the polymer network and causing their collapse or swelling.<sup>185,186</sup>

## Membranes

Barrier membranes are utilised in dentistry to enhance the chances of successful periodontal tissue regeneration, particularly in the bifurcation area and during implant therapy.<sup>187</sup> The treatment of periodontal and peri-implant abnormalities has been made possible by the development of a number of resorbable membranes that have proven clinically successful. The resorbable nature of these membranes eliminates the need for additional surgery. Patients favour them over non-resorbable membranes as a result. Depending on the epithelial exclusion concept, commercially accessible resorbable membranes have been employed over the past ten years to address periodontal and peri-implant abnormalities by GTR.<sup>188</sup>

## Films

Thanks to their simple manufacturing process, polymer-based films were originally brought to the field of tissue engineering. In the realm of wound treatment, the polymeric films have gradually proven to be effective for application as occlusive wound dressings. Wound dressing materials made of natural and synthetic polymer-based films have been widely researched.<sup>189</sup> Natural polymer-based films have been demonstrated for possessing lower durability and more readily degradable characteristics. Chemical cross-linkers like glutaraldehyde were first utilised to enhance their physical qualities. Researchers have begun to look towards non-cytotoxic cross-linkers since chemical cross-linkers have shown to be toxic to growing cells in recent years.<sup>190</sup> A polymeric film was prepared for biological purposes using several cross-linking techniques, including physical cross-linking and ionic cross-linking.<sup>191</sup> There have been reports of increased antibacterial and healing characteristics in polymeric films loaded with bioactive molecules.<sup>192–194</sup>

## Micro-Particles

Microspheres and are other names for microparticles. They are tiny, irregularly shaped polymeric particles having a range of sizes. Micrometres, generally between 1 and 1000, are the range in which microparticle sizes vary. Typically, a polymer matrix where a lower quantity of an active ingredient may be immobilised forms polymeric microparticles.<sup>195</sup> Natural or synthetic polymers, that might be biodegradable or nondegradable, can be used to create micro-spheres. Emulsification-solvent evaporation, coacervation, spray drying, electrospraying, and phase separation are a few techniques for producing the micro-particles.<sup>196</sup> Interleukin-1 receptor antagonist (IL-1ra) was added to dextran/poly (d,l-lactide-co-glycolide) microspheres in an experiment conducted by Lu et al, and the system was then tested for its physicochemical and anti-inflammatory capabilities.<sup>197</sup>

## Methods of Scaffold Fabrication

Common approaches for creating polymeric scaffolds involve solvent casting/salt leaching, phase separation, gel casting, precipitation, and emulsion freeze-drying.<sup>198,199</sup> Despite the idea that traditional fabrication methods can integrate pores of the necessitated surface topography by influencing numerous variables, the frameworks generated from these strategies can be made from a single polymer. They could result in inaccurate and unexpected amorphous morphological features.<sup>200</sup> Furthermore, these procedures need an organic solvent purification phase, which is time-consuming and difficult for quick adoption.

## Electro Spinning

The electrospinning technology was utilized to develop 3D nanofibrous scaffolds. This technology is essential to build a supporting scaffold for cell proliferation by mimicking the precise nanoarchitecture of an extracellular matrix. Electrospun scaffolds have a controlled fiber diameter and are ideal for constructions constructed in sheets and layers.<sup>201</sup> Despite the small number of in vivo uses, multiple research has demonstrated the bioactivity of electrospun scaffolds in regenerative endodontics, demonstrating the diversity of scaffold synthesis for pulpal regeneration.<sup>202,203</sup>

## Supercritical Fluid-Gassing

Maspero et al proposed a unique approach for rapidly fabricating a net-shaped porous scaffold.<sup>200</sup> This method, which comprised the rapid centralization of PLGA particles in a mould using sub-critical CO<sub>2</sub>, enabled the rapid manufacture of a precise porous copy of a tooth root without chemicals. In this method, a mould was created using sterile polyvinylsiloxane, recreating the meticulous architecture of the tooth by inserting the dental root into the polyvinylsiloxane polymer. After the imprint had been set, the root was drained, and the mould was filled with sterile PLGA particles ranging in size from 700 to 1400 m, resulting in an indiscernible structure. Open porous scaffolds with the required form were made using the demonstrated moulding procedure.<sup>200</sup> Tai et al found limitations and improvement information.<sup>204</sup> They revealed that PLGA structures are brittle and that their pore size decreases as glycolic acid concentration increases. A nonporous layer may emerge when the depressurization phase is finished too quickly. They pushed for a lesser speed of

pressure loss to develop more uniform and broader pores. This technique is slower; it may take an hour or more instead of a few minutes, but it may provide better outcomes.

### Three-Dimensional Bio Printing

The most recent advancement in tissue engineering methodologies is the incremental pouring of a cell-containing hydrogel using inkjet equipment and CAD/CAM technology.<sup>205</sup> The exact placement of various cells in 3D printing is useful, like the implantation of odontoblasts in the scaffold's perimeter and angiogenic fibroblasts in the core, which will preserve a fundamental matrix of blood vessels and nerves in the substituted pulp tissue.<sup>206</sup> Bioprinting techniques can result in readily customizable cell orientation inside a scaffold, improving cell adhesion and regeneration. It can also generate functioning small-diameter blood arteries local to the pulp chamber.<sup>207</sup> Nevertheless, in vivo, models continue to have constraints.

### Self-Assembling

Moreover, innovative regenerative approaches were developed using a tissue regeneration technique that utilized a hydrogel scaffold implanted with SHED and DPSCs in addition to peptide-amphiphile (PA). Cell-matrix relationships can then be carried out by including the cell adhesion sequence, RGD, and an enzyme-cleavable region. SHED and DPSCs implanted in PA hydrogels were grown for four weeks under varied osteogenic induction settings. With the hydrogel scaffolds, these cells differentiated and proliferated typically. This technology might also be used to create 3D PAs self-assembly structures of Nanofibers and tissues. Moreover, due to the hydrogels' physicochemical qualities, they may be inserted into microscopic and randomized faults. The suggested approach is ideal for creating soft and hard mineralized dental/pulp tissue regeneration frameworks.<sup>208</sup>

### Clinical Applications

Polymeric biomaterials are extensively utilized in oral, dental, and maxillofacial reconstruction,<sup>209</sup> as depicted in Figure 7.

### Alveolar Ridge Preservation

The goal of alveolar ridge maintenance following tooth extraction is to prevent or eliminate resorptive bone remodeling and to optimize tissue distribution before fitting the final prosthetic replacement; Table 5 represents the application of biopolymers in alveolar ridge preservation.<sup>210–213</sup> Socket preservation treatments employ biomaterials and barrier materials to refill the socket. Salamanca et al found that hydroxyapatite/b-TCP ceramic combined with homogeneous

**Table 5** Implementation of Polymeric Materials in Ridge Preservation

Scaffold	Outcome	Reference
N-carboxyethyl chitosan (CEC) hydrogel loaded with nano-hydroxyapatite	<ul style="list-style-type: none"> <li>• Preservation of dimensions of alveolar ridge and soft tissue healing.</li> </ul>	[210]
BMP-2 loaded PLGA microspheres with gelatin/hydroxyapatite/b-tricalcium phosphate cryogel	<ul style="list-style-type: none"> <li>• The scaffold was very porous, allowing for the prolonged release of BMP-2.</li> <li>• The composite's osteogenic potential was increased, and supra-alveolar ridge augmentation was enhanced in vivo.</li> </ul>	[211]
Chitosan (CS) gel loaded with berberine (BBR)	<ul style="list-style-type: none"> <li>• The hydrogel was thermo-responsive, shapeable, and self-healing. Antimicrobial properties and extended-release for 20 days. Capability for osteogenic differentiation.</li> </ul>	[212]
Polyphosphate-cross-linked collagen scaffolds	<ul style="list-style-type: none"> <li>• Enhanced hemostatic properties in both a healthy and an anticoagulant-treated rat model.</li> <li>• In a rat alveolar bone lesion model, local bone regeneration was observed.</li> </ul>	[213]

collagen solution had slightly greater effectiveness in osteogenesis and similar osteoconductivity to bovine-derived bone (Bio-Oss<sup>®</sup>) with collagen membrane in a canine investigation.<sup>214</sup>

## Vertical and Horizontal Ridge Augmentation

Guided bone regeneration (GBR) utilizing a membrane is the most often used surgical approach to regenerate atrophic residual ridges. GBR depends on three primary criteria: (1) cell occlusivity, (2) wound integrity, and (3) space formation and preservation. Resorbable polymeric membranes are preferred because they can regenerate noncritical-size defects continuously, promote the healing process and economical price, and reduce surgical discomfort and consequences.

Membrane permeability impacts vasculature and bone progenitor cell growth over competitive soft tissue cells.<sup>215</sup> Composite grafts of bone allografts or xenografts with a resorbable membrane provided clinical outcomes comparable to autologous bone transplants.<sup>216</sup> These findings support that composite grafts might be a viable alternative to autogenous bone harvesting, overcoming key obstacles such as donor site complications. Differences in surgical procedures and operator skills should be addressed when estimating clinical outcomes of various combinations.

## Maxillary Sinus Augmentation

Maxillary sinus augmentation can be accomplished using the lateral window method or the transrectal approach to create a gap between the sinus floor and the Schneiderian membrane to fill with biomaterials that encourage the creation of new osseous tissue.<sup>217</sup> Several bone fillers have demonstrated effectiveness in increasing vertical bone height for future implant implantation. Table 6 depicts the implementation of polymers in sinus lifting.<sup>218–220</sup> A comprehensive review discovered no statistically significant variations in implant longevity between bone auto grafts and bone replacement materials.<sup>221</sup>

## Temporomandibular Joint Reconstruction

The TMJ's two interacting structural constituents are the temporal bone and the mandibular condyle. TMJ deterioration can damage the disc, the surrounding fibrous tissue, the proliferative and hypertrophic fibrocartilage layers, or the condylar bone. Regenerative TMJ therapies have been offered to enhance clinical outcomes, long-term ossification, and adherence prevention. To reconstruct the TMJ, biphasic cartilage and bone engineering employing ex-vivo cell seeding and bioactive chemicals on an acellular scaffold is being employed. Among the several multipotent cell types studied for condylar cartilage regeneration, DPSCs have been extensively researched for their high reliability and multi-lineage development into chondrogenic cells, osteoblasts, and other important cell forms.<sup>222,223</sup>

Natural materials have been widely employed for TMJ disc regeneration. They have mechanical characteristics comparable to those of the natural disc, like cell adherence and penetration, cell growth, and proteoglycan accumulation.<sup>224</sup>

Synthetic polymers have been presented to produce synthetic ECM for TMJ fibrocartilage regeneration that outperforms natural materials in terms of mechanical strength and biodegradability.<sup>225</sup> Poly-L-lactic-glycolic acid is one

**Table 6** Various Polymeric Scaffolds in Sinus Lifting

Scaffolds	Outcome	Reference
Vancomycin/deferaxamine/dexamethasone (Van/DFO/Dex) liposome–alginate hydrogel composite	<ul style="list-style-type: none"> <li>Improved antibacterial and cytocompatibility properties against <i>Staphylococcus aureus</i>.</li> <li>Angiogenesis enhanced osteogenic differentiation of MC3T3-E1 cells.</li> <li>Injectability that is suitable for the least invasive technique</li> </ul>	[218]
Thermo-reversible poloxamers gel	<ul style="list-style-type: none"> <li>Poloxamers are non-toxic.</li> <li>New bone formation</li> </ul>	[219]
Injectable thermo-sensitive (CS/GP/GA) hydrogel loaded with erythropoietin (EPO)	<ul style="list-style-type: none"> <li>Enhancing intramembranous ossification.</li> <li>The EPO-CS/GP/GA hydrogel offers a unique, less invasive therapy for MSFA.</li> </ul>	[220]

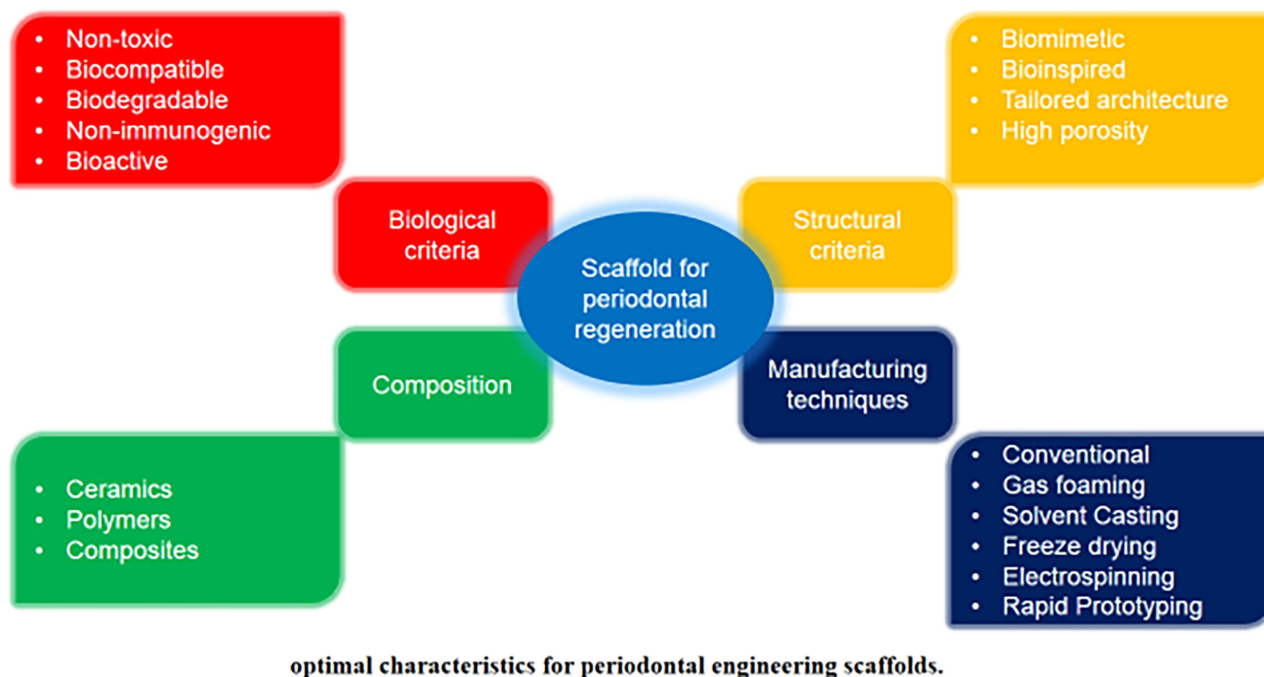
example the FDA has authorized for clinical use (PLGA). PLGA promotes mesenchymal stem cell colonization and proliferation while interacting with chondrocytes and other TMJ discal cells.<sup>226</sup> PCL fibers are a form of pro-regenerative biomimetic nanofiber that the FDA has cleared for clinical use.<sup>227</sup>

## Periodontal Tissue Regeneration, and Engineering

Periodontal regeneration attempts to heal the alveolar bone, periodontal ligament, and cementum that have been damaged by periodontitis. Scaling and root planning, curettage, and open flap cleaning are current therapy techniques with minimal success. Periodontal regeneration using GTR permits bone cells, fibroblasts, and PDL cells to be chosen to fill the periodontal defect. Melcher was the first to utilize a barrier membrane to control the natural wound-healing process in 1976. Bioactive substances and nanoparticles recently incorporated into polymeric scaffolds in order to create a smart scaffold that respond to internal signals.<sup>228</sup> The use of regenerating biomaterials in GTR is widely established.<sup>229</sup> A systematic review of GTR results with a collagen membrane revealed that pocket depth reduction is predictable with or without a bone replacement.<sup>230</sup> Scaffolding materials, in addition to membranes, are commonly used in fault areas. On the other hand, polymeric scaffold materials are often osteoconductive, maintaining room for cells to migrate into the defect location; [Figure 8](#) represents optimal characteristics for periodontal engineering scaffolds.

Different polymer matrices and scaffolds have been employed for periodontal regeneration of intraosseous abnormalities since the 1980s, as shown in [Table 7](#).<sup>231–246</sup> Likewise, 3D-printed scaffolds have recently been designed to improve on current supporting matrices. In contrast to traditional grafts' brittleness, poorly processed porosities, and generic shapes, 3D scaffolds may be adapted to the unique demands of patients. To regenerate each periodontium tissue type ideally, compartmentalization, internal topographies, and pore diameters and angulations can be precisely engineered.<sup>13</sup>

A case study proved the effectiveness of using a 3D-printed PCL scaffold for periodontal regeneration. The graft failed because of the slow breakdown rate of PCL in comparison to surrounding tissue, resulting in graft exposure.<sup>34</sup> Recent advancements in additive manufacturing technology enable the creation of nanoscale scaffolds with adjustable parameters such as fiber diameter, porosity, shape, and surface properties.



**Figure 8** Optimal characteristics for periodontal engineering scaffolds.

**Table 7** Different Polymeric Biomaterials in Periodontal Tissue Regeneration and Engineering

Scaffold	Target Tissue	Outcome	Reference
Guanidine appended polydiacetylene (G-PDA)		Cultivating human primary periodontal ligament (hPDL) cells was shown to be non-cytotoxic and cytocompatible. In vitro osteogenic differentiation	[231]
PCL fibers		Over 21 days, increased transcription of osteogenic marker (Runx2) overexpression of M1 signals	[232]
Cellulose acetate (CA) and hydroxyapatite (HA) films		Improved cell attachment Increased cell survival	[233]
Dimethyloxalylglycine (DMOG) and nano silicate (nSi)/poly (lactic-co-glycolic acid) (PLGA) fibers		Increased osteogenesis and angiogenesis	[234]
Bilayered (polycaprolactone (PCL)/ gelatin membrane		Improved osteogenesis and the regeneration of bone defects.	[235]
Collagen	PDL	The most prevalent protein in the alveolar bone, PDL, and cementum ECMs. Biocompatible Mechanical characteristics are low. Safety issues include pathogen spread and immunological response.	[236]
Gelatin	PDL; alveolar bone; cementum	Collagen hydrolysis byproduct There is no pathogen spread and no immunological response. Simple to modify for chemical and light crosslinking	[237]
Chitosan	Alveolar bone; PDL; cementum	Biocompatible and antimicrobial characteristics resulting from chitin	[238]
Poly (lactic-co-glycolic acid) (PLGA)	Alveolar bone; PDL	Biocompatible Controllable rate of deterioration There is no cell recognition pattern.	[239]
Polycaprolactone (PCL)	Alveolar bone; PDL	Non - immunogenic The slow pace of deterioration	[240]
PLGA + CaP	Alveolar bone	Made up of two layers (smooth outer layer and rough microporous inner layer)	[241]
Collagen + HA	Alveolar bone	Produced by freezing both collagen and HA or converting HA to collagen	[242]
Chitosan+β-TCP	Alveolar bone	Made by freezing and frying. HPDLC was sown into the scaffold to attract host cells and stimulate osteoblast development.	[243]
PCL+ β-TCP + CaP coating	PDL; Alveolar bone	As the PDL layer, a PCL electro-spun scaffold was created. To increase the osteogenic potential of the PCL —TCP scaffold, a thin coating of CaP was placed on the surface. CaP coating increased bone development.	[244]

(Continued)

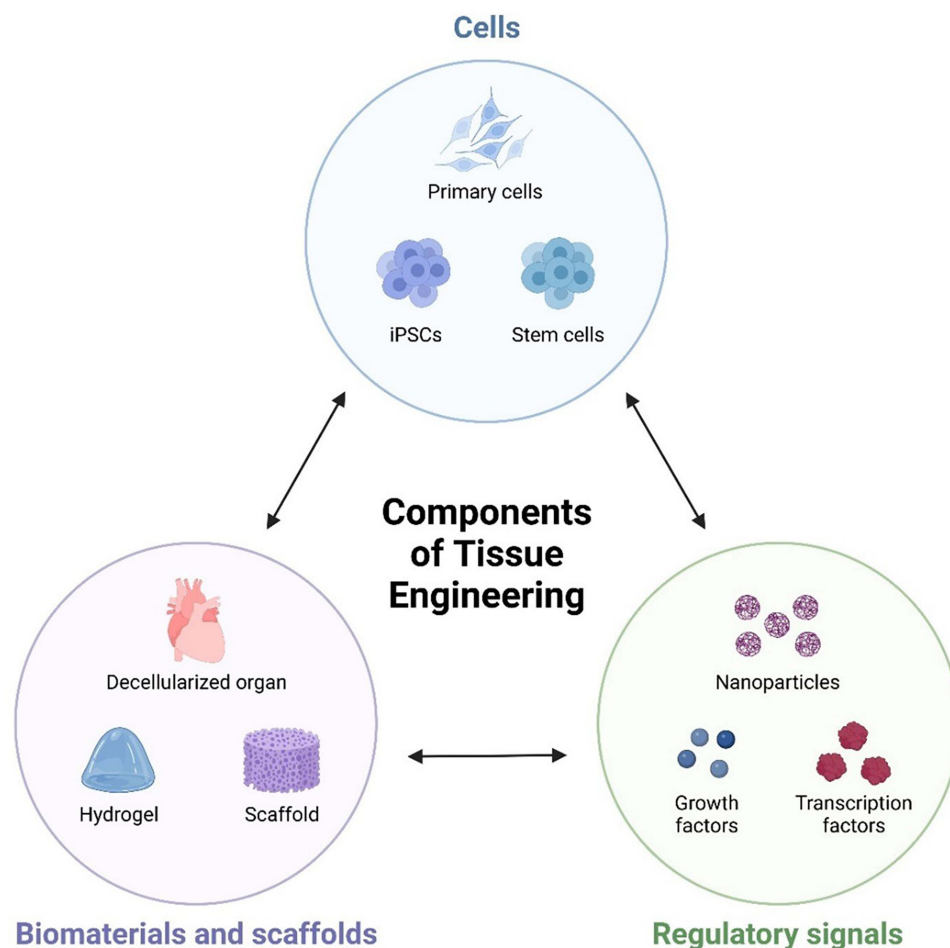
**Table 7** (Continued).

Scaffold	Target Tissue	Outcome	Reference
Chitin + PLGA + BCG	Alveolar bone; cementum; PDL	PLGA was included to enhance structural performance and extend degradation time. BCG increased bone and cementum layer osteogenic ability.	[245]
PCL + HA	Alveolar bone; PDL; cementum	Three layers of scaffolding were employed to simulate the architecture of the periodontium. There was no organized fiber insertion in the PDL or bone interface.	[246]

Growth factors, proteins, and medications can also be added to these polymeric matrices to regulate cellular responses and adjust the local inflammatory milieu to enhance periodontal tissue engineering, as seen in [Figure 9](#).

## Implant Coating

Dental implants are often used to replace missing teeth, restore function, and enhance patients' life satisfaction.<sup>247,248</sup> The long-term durability of dental implants may malfunction because of biological peri-implantitis (20%) caused by microbial infections and mechanical issues, including stress shielding, which may cause osteopenia and clenching-

**Figure 9** Requirements of tissue engineering.

bruxism.<sup>249</sup> Several investigators<sup>156,234,250–253</sup> have assessed the effectiveness of these biopolymer-based hydrogels as coating materials for enhancing the characteristics of dental implants. In addition to surface changes, the coating of dental implants with various materials and biomolecules to accomplish particular advantages has been studied in the past few years.<sup>254,255</sup>

Ansari et al used the in-situ sol-gel approach to create polycaprolactone (PCL) and PCL/fluoride substituted HA (PCL-FHA) composites as a coating material for alkali-treated Ti6Al4V platform to increase protection against corrosion and in vitro biocompatibility.<sup>250</sup> Joo et al<sup>251</sup> synthesized and employed a hydrogel generated from hyaluronic acid and gelatin for the surface modification of polydimethylsiloxane (PDMS), frequently employed as an implant-supported covering material. In another study, Yang et al used carboxymethyl cellulose-dopamine (CMC-DA) hydrogel as a stimulator to cover the surface of magnesium alloys with HA.

The surface-modified alloys' corrosion resistance and biocompatibility were then assessed. The outcomes showed that corrosion resistance of CMC-DA/HA coated AZ31 alloy (AZ31/CMC-DA/HA) enhanced 18.9-fold compared to naked AZ31 alloy. Furthermore, biocompatibility experiments revealed that AZ31/CMC-DA/HA induced a 21% boost in the multiplication of MC3T3-E1 cells following 5-day incubation compared to the raw AZ31 alloy, showing the coating's superior cytocompatibility.<sup>153</sup> Table 8 shows polymers as coating materials around implants<sup>210,250,251,256–260</sup>.

**Table 8** Polymeric Coating Materials Around Implants

Coating	Type of Implant	Outcome	Reference
PCL/fluoride substituted HA (PCL-FHA) nanocomposite	Alkali-treated Ti6Al4V	Reduce the corrosion of the Ti6Al4V substrate. More viable human osteoblast-like MG63 cells Increased the proliferation and dissemination of these cells.	[250]
Hyaluronic acid /gelatin/polydimethylsiloxane (PDMS)	Ti6Al4V	Bacterial adhesion inhibitor. Bacterial adhesion inhibitor ( <i>Pseudomonas aeruginosa</i> ; <i>P. aeruginosa</i> ) Biocompatible hydrogel Improvement in coated implant biomedical applications	[251]
Dopamine (DA)-loaded alginate-arginine-glycine-aspartic acid (RGD) (AlgR) hydrogel	Vaterite (CaCO <sub>3</sub> )-modified Ti implant (SLA/CaCO <sub>3</sub> Ti)	Enhance bone regeneration and raise the Ti implants' protection against bone destruction Following 14 days, there was a 2.3-fold elevation in ALP activity in human bone marrow stem cells (hBMSCs). Enhanced bioactivity and Osseo integration.	[256]
Multifunctional hydrogel using sodium tetraborate (Na <sub>2</sub> B <sub>4</sub> O <sub>7</sub> ), polyvinyl alcohol (PVA), silver nanoparticles (AgNPs), and tetraethyl orthosilicate (TEOS as a bone induction factor	Porous Ti (pTi)	Biocompatible three-dimensional (3D) composite devices boosted bone marrow mesenchymal stem cell proliferation and differentiation potential while inhibiting bacterial growth.	[210,257]
BMP2/PLGA/vancomycin/CS hydrogel		Rapid release of vancomycin for the first two days, followed by continuous release of rhBMP-2 for roughly 12 days Promotes Osseo integration as a coating around dental implants.	[258]
Keratin hydrogel	Dental Ti implants	Enhanced Osseo integration.	[259]
Photo-cross linkable gelatin methacryloyl (GelMA)/dopamine hydrochloride/antimicrobial peptide (AMP) / silicate nanoparticles (SNs)	Ti implants.	Significant decrease in bacterial CFU levels Increased expression of pathogenic markers. Enhanced Osseo integration capability	[260]

## Oral Mucositis

Oral mucositis (OM) is a classic side event in oncological patients. It results from pathogenesis is a direct and indirect effect of tumor therapeutics that suppress physiologic cellular pathways and results in epithelial apoptosis.<sup>261</sup> In vivo testing revealed that benzydamine hydrochloride-loaded lyophilized mucoadhesive displayed consistent structural, mechanical, and biological properties. It might be effective carrier for drug distribution for OM<sup>262</sup> —carboxymethyl cellulose is functionalized with N-(2-aminoethyl) maleimide.

Through the interaction of the maleimide moiety and mucin, the polymer demonstrated outstanding mucoadhesive potential compared to carboxymethyl cellulose. The functionalized polymer may also regulate the release of benzydamine using Higuchi's release model, proving it to be a reliable solution in bio-adhesive drug delivery.<sup>263</sup>

Liquid oral gel based on polyacrylate silver salt/polyvinylpyrrolidone Clinical OM and oral function were examined weekly after four weeks, until 5e10 days after radiation was completed. Standard Terminology Criteria for Adverse Events (CTCAE) v3.0 was used to evaluate the data of OM grade.<sup>264</sup>

## Regenerative Endodontics

In regenerative endodontics, polymeric scaffolds have been utilized to produce an appropriate microenvironment for dentin-pulp system regeneration. Various scaffolds have shown clinical effectiveness in multiple applications, as shown in Table 9.<sup>265–269</sup>

PRF scaffolds revealed apical closure, elimination of apical radiolucency, continued root extension, and dentinal wall thickening in permanent adolescent teeth with necrotic pulps.<sup>268</sup>

Bio-Gide collagen membranes (Geistlich, Wolhusen, Switzerland) have been found to enhance dentinal wall formation in the middle third of the root, strengthening the root and preventing cervical root fractures.<sup>270</sup>

## Whole Tooth Regeneration

Whether treated or not, dental disorders such as tooth decay or periodontitis ultimately lead to tooth loss. Bioengineered edentulism management is a viable alternative to the advancement of tissue engineering.

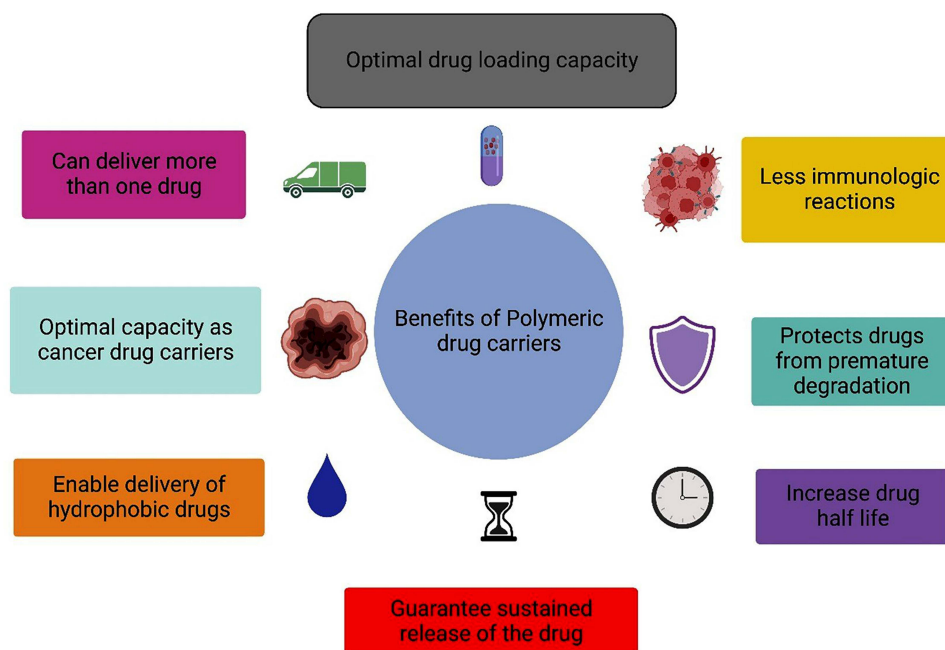
Yang et al<sup>271</sup> showed the reliability of incorporating fibrin glue with PRF as a matrix cultured with dental bud cells for dental regeneration purposes. PRF contains high amounts of tissue growth factor- $\beta$  (TGF- $\beta$ ) and platelets-derived growth factor (PDGF), significantly affecting angiogenesis and complex tissue regeneration. Additionally, dental bud cells seeded on PRF/PRP frameworks were observed to regenerate an entire tooth structure.

## Oral Drug Delivery Systems

Administering medicinal substances into the oral cavity is an established way of treating local inflammation, discomfort, and illnesses of the mucosa and dentition. Polymeric drug carriers have astonishing characteristics that make them widely utilized as drug delivery carriers, as shown in Figure 10.

**Table 9** Different Polymeric Scaffolds Utilized in Regenerative Endodontics

Scaffold	Outcome	Reference
Granular 3-D chitosan scaffolds	It improved cell viability. Enhanced cellular differentiation. Hydrogel is highly conductive. Neural differentiation of dental pulp stem cells (DPSCs)	[271]
Collagen/calcium phosphate bioceramic	Pulpal regeneration	[272]
Gelatin hydrogel loaded with fibroblast GF-2	Regeneration of dentin-pulp system	[273]
PRF	Successful revitalization	[274]
PRF	Improved multiplication of pulpal cells. Increased levels of osteoprotegerin (OPG) expression. Enhanced alkaline phosphate (ALP) activity.	[276]



**Figure 10** Benefits of polymeric biomaterials as drug delivery systems.

An injectable chitosan sponge could be utilized for this objective because it promotes biomineralization in major-sized osseous deformities and is less expensive than growth factors such as BMPs.<sup>272,273</sup> Bacterial cellulose is another substance that is very good for antibiotic dissemination.<sup>274</sup> Nanoparticles or comparable technical solutions should be noted among unique formulations of different films, fibers, biodegradable matrices, local gels, or microspheres.<sup>276</sup> Semi-solid gel preparations with antimicrobial, anti-inflammatory, and aseptic qualities commonly apply active compounds.

For the management of oral illnesses, several formulations have been developed, as represented in Table 10.<sup>275,277–281</sup> In therapeutic strategies for oral cancer, they are frequently distinguished by bio-adhesive characteristics or response to stimuli.

They could also be employed with photodynamic treatment to administer photosensitizers.<sup>276</sup> The ability to selectively destroy neoplastic cells while reducing cytotoxicity towards non-cancerous tissues and bactericidal action against bacteria building oral biofilm are further advantages of nanocarriers in oral cancer therapy.<sup>282</sup>

**Table 10** Advantages of Polymeric Drug Carriers

Bioactive	Characteristics	Function	Applications	References
Statins: Simvastatin (SMV): Atorvastatin (ATV)	Suppressors of 3-hydroxy-2-methyl-glutaryl coenzyme A (HMG-CoA) reductase, frequently utilized for arteriosclerosis and hyperlipidemia	Inhibition of osteoclastic actions. Up-regulation of BMP-2 levels	Improved CAL levels Increased osteogenesis	[275]
Metformin	Biguanide, an anti-hyperglycemic agent, is used to treat type II diabetes.	Enhances osteogenesis through LKB1/AMPK pathway	More Greater PD decline and CAL increase	[278]
Platelet-derived growth factor	Four isomers	Chemotaxis. Improved cellular multiplication. And development. Enhanced vascularity.	Increased bone regeneration, the concentration of 0.3 mg/mL	[279]

(Continued)

**Table 10** (Continued).

Bioactive	Characteristics	Function	Applications	References
Fibroblast growth factor	22 subfamily proteins activate tyrosine kinase action.	Promotion of the healing process. Improved angiogenesis.	Promotion of bone regeneration in periodontal defects.	[280]
Bone morphogenic protein	Belongs to the TGF- $\beta$ superfamily	Stimulation of osteogenesis and chondrogenesis. Improved angiogenesis.	BMP-2: Confirmation of bone regeneration capacity, but could result in root resorption and ankylosis BMP-6: Induction of bone, PDL, and cementum regeneration in periodontitis models in rats and dogs BMP-7: Enhances osteogenesis, and cementogenesis in Class III furcation defects in dogs	[281]
Amoxicillin	Broad spectrum antibiotic	Amoxicillin causes microorganism disintegration, while HAP NPs cause periodontal healing.		[282]

## Bone Tissue Engineering

Despite the endogenous reparative capacity of bone, polymeric scaffolds have a critical role in enhancing the recovery process, shortening the healing period, and thus limiting postoperative complications and maximizing treatment success, as shown in [Table 11](#).<sup>283–291</sup> It is critical to achieving the goals of regenerative medicine by generating specific releases of biomolecules at the specific receptors. This was associated with the balance of biological signaling pathways in tissues, particularly bone.<sup>292</sup>

Polyurethane foam/nano-hydroxyapatite composite was fabricated and potentially functioned as an extracellular environment in creating osteoblasts tissues.<sup>293</sup> PLA membrane was adjusted by incorporating HAP NWs to exert barrier/osteogenesis dual roles in a rat mandibular deformity.<sup>294</sup>

**Table 11** Numerous Polymeric Materials in Bone Tissue Engineering

Framework	Strategy	Results	Purpose	Reference
Oxidized (Alg)/Gel including NCDs	Chemical cross-linked (NHS and EDC) and freeze-dried	Improved mechanical characteristics and proper pore size.	Osseous tissue engineering	[284]
CS hydrogel/3D-printed PCL/ encapsulated BMMSCs and BMP-2	Injection and lyophilization, 3D printing	Greater osteogenesis, mineralization, and improved cellular maturation.	Bone tissue engineering	[283]
$\kappa$ -Carrageenan/ PDGF-BB	Hydrogel beads	Improved loading and sustained release of the pharmaceutical agent.	Angiogenesis property for bone tissue engineering	[285]
Ch-LA /BMP-2	Photocrosslinkable hydrogel	Greater compressive strength, elongation of crosslinking, better ALP function.	Bone tissue engineering	[286]

(Continued)

Table 11 (Continued).

Framework	Strategy	Results	Purpose	Reference
Polyacrylamide/ PVA/BG/ HNT	Nanocomposite and freeze-thawing technique	Increased mineralization and better cellular attachment.	Bone regeneration	[287]
Desferrioxamine (DFO) – loaded SF-HAP	Nanocomposite and freeze-dried	Improved angiogenesis and osteogenesis.	Bone development	[288]
$\gamma$ -Fe <sub>2</sub> O <sub>3</sub> /nano HAP/PVA	Nanocomposite and cyclic freeze-thawing technique	Better mechanical features and decline in porosity.	Bone tissue engineering	[289]
Type I Col- and CS–agarose hydrogel	3D printing	Higher replicability, osteogenic activity, and angiogenesis.	Osteogenesis and adipogenesis	[290]
CMC/Gel/ nHAP	Cross-linked with tyrosinase	Greater mechanical strength enhancement of osteoblastic activity, differentiation, and proliferation	Osteoinduction	[291]

## Conclusions

It is necessary to acknowledge that this review can hardly avoid bias and errors to some extent, as there is no uniform evaluation of the scientific validity of the design, methodology, and results of the original literature such as a systematic review. However, it is still informative to learn about the application and research progress of hydrogels in maxillofacial and oral drug delivery. Compared with other materials such as nanoparticles, nanofibers, and thin films, many hydrogels have biocompatibility and unique stimulusresponsive properties that make them suitable as carriers or platforms for transporting drugs, cells, and others to target locations, which have unique advantages in local therapies and are therefore well suited for topical applications in the oral environment. This paper describes the application and research progress of hydrogels in maxillofacial and oral drug delivery. Different types of hydrogels have a wide range of applications in oral soft and hard tissue regeneration, antibacterial, and local drug targeting delivery due to their injectability, temperature sensitivity, pH sensitivity, biodegradability, and other properties. Many hydrogels do not have the function of repairing tissue defects themselves, but can be used as carriers for different drugs, growth factors, and even stem cells to achieve higher concentrations maintained over a long period of time. Some hydrogel systems are able to respond to stimuli such as temperature, pH, and light irradiation, which can modulate the drug release from the hydrogel on demand. In the future, how to obtain hydrogel systems with greater biocompatibility through smaller cost and simpler synthesis methods to achieve superior sustained local drug delivery efficacy are still important issues for researchers to focus on. There are many hydrogel drug delivery systems made with different materials and synthesis methods for complex oral and maxillofacial environments, but the high costs, complex synthesis steps, and toxic biodegradation by-products may be the key challenges affecting their further clinical applications.<sup>295,296</sup> Meanwhile, *in vivo* studies and animal studies are relatively scarce, and the exploration of relevant hydrogels for clinical applications is even rarer. The stability of topical drug delivery and the biocompatibility of hydrogels need to be further investigated, and their use in the clinic requires more rigorous testing. It is expected that more clinical studies will be conducted in the future to verify the therapeutic effects of hydrogels as drug release platforms in different oral diseases, especially in the treatment of periodontal diseases, which currently have a relatively large number of clinical studies.

## Abbreviations

AgNPs, Silver nanoparticles; AMP, Antimicrobial peptide; ATV, Atorvastatin; BBR, Berberine; BC, Bacterial cellulose; BMP, Bone morphogenetic protein; CA, Cellulose acetate; CAD/CAM, Computer-Aided Design And Manufacturing; CEC, N-carboxyethyl chitosan; CMC-DA, Carboxymethyl cellulose-dopamine; COAs, Clear overlay appliances; CoS, Chondroitin sulphate; CS, Chitosan; CTCAE, Common Terminology Criteria for Adverse Events; DFO, deferoxamine; DMOG, Dimethylloxalylglycine; DMSO, Dimethyl sulfoxide; DPSCs, Dental pulp stem cells; ECM, Extracellular matrix; EPO,

Erythropoietin; FDA, Food and Drug Administration; GA, Gelatin; GBD, Global Burden of Diseases; GBR, Guided bone regeneration; GP, Glycerophosphate; G-PDA, Guanidine appended polydiacetylene; GTR, Guided tissue regeneration; HA, Hyaluronic acid; HA, hydroxyapatite; HBMSCs, human bone marrow stem cells; LIG, Lignin; MC3T3-E1 cells, Osteoblast precursor cell line derived from *Mus musculus* (mouse) calvaria; MNs, micro needles; nSi, nano silicate; OM, Oral mucositis; PA, peptide-amphiphile; PAA, Polyacrylic acid; PCL, Polycaprolactone; PCL-FHA, fluoride substituted HA; PDA, Polydopamine; PDEGMA, Poly di ethylene glycol methyl ether methacrylate; PDGF, Platelets derived growth factor; PDL, Periodontal ligament; PEEK, Polyether ether ketone; PEG, Poly ethylene glycol; PEI, Polyethylenimine; PEO, Polyethylene oxide; PES, Polyether sulfone; PET, Polyethylene terephthalate; PETG, Poly (ethylene terephthalate)-glycol; PHB, Poly- $\beta$ -hydroxybutyrate; PLGA, Poly (lactic-co-glycolic acid); PLLA-CL, Poly l-lactic acid-co-caprolactone; PMMA, Poly methyl methacrylate; PPF, Poly propylene fumarate; PRF, Platelet rich fibrin; PRP, Platelet rich plasma; PS, Polystyrene; PU, Polyurethane; PVA, Poly vinyl alcohol; PVP, Poly vinyl pyrrolidone; RGD, Arginyl-glycyl-aspartic acid; rh TGF, Recombinant Human Transforming Growth Factor; SHED, Stem cells from human exfoliated deciduous teeth; SMV, Simvastatin; SNs, Silicate nanoparticles; TGF- $\beta$ , tissue growth factor- $\beta$ ; TMJ, Temporomandibular Joint Reconstruction; Van, Vancomycin;  $\beta$ -TCP,  $\beta$ -tricalcium phosphate.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest.

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