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Review

Design Parameters of Polymers for Tissue Engineering Applications

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Abstract: The loss or failure of an organ or tissue can occur because of accident or disease, for which tissue or organ transplantation is a generally accepted treatment. However, this approach is extremely limited due to donor shortage. Tissue engineering is a new and exciting strategy, in which patients who need a new organ or tissue are supplied with a synthetic organ or tissue. In this approach, tissues are engineered using a combination of the patient's own cells and a polymer scaffold. The polymer scaffold potentially mimics many roles of extracellular matrices in the body. Various polymers have been studied and utilized to date in tissue engineering approaches. However, no single polymer has been considered ideal for all types of tissues and approaches. This paper discusses the design parameters of those polymers potentially useful in tissue regeneration.

Keywords: tissue engineering, design parameters, cell-polymer interactions.

Introduction

Tissue engineering is one recent and exciting approach used to provide man-made tissues or organs to patients who suffer the loss or failure of an organ or tissue as a result of accident or disease.[1,2] In this approach, tissues or organs are typically engineered using a combination of a patient's own cells and polymer scaffolds. In brief, tissue-specific cells are isolated from a small biopsy from the patient and expanded *in vitro*. The cells are subsequently incorporated into three-dimensionally structured porous polymer scaffolds, and are transplanted back to the patient either by surgical implantation or in a minimally invasive manner using a syringe or endoscope.[3] The polymer used in this approach potentially mimics many roles of extracellular matrices of tissues in the body. It is generally expected that a polymer scaffold will bring cells together, control the tissue structure, regulate the function of the cells, and allow the diffusion of nutrients, metabolites, and soluble factors.[4,5] Many tissues, including skin, artery, bladder, cartilage, and bone, are being engineered using this approach, and several of them are already commercially available or are near clinical trials.[6]

One critical factor in this tissue engineering approach is the regulation of interactions between cells and polymer scaffolds. The interactions can be regulated by controlling biological interactions (e.g., specific ligand-receptor interactions), the physical properties of the polymer scaffolds (e.g., mechanical properties and degradation rate), and the release of soluble factors from the scaffolds (e.g., growth factor and DNA). All of these signals can alter the gene expression of the cells to be engineered, which is critical to achieve fully functional and clinically successful tissue for-

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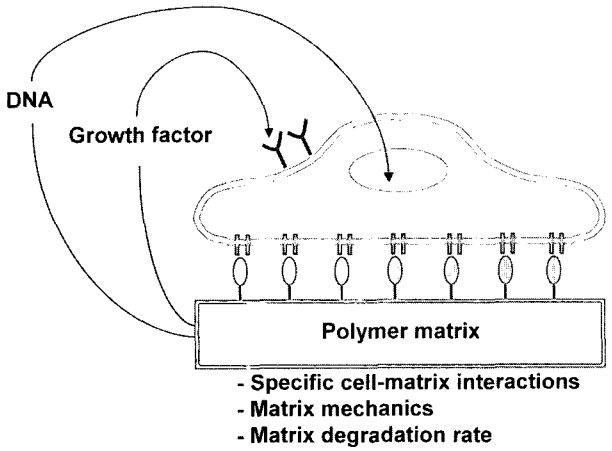

Figure 1. Cellular microenvironments affecting the gene expression of cells used in tissue engineering approaches.

mation (Figure 1). To date, a number of natural or synthetic polymers have been studied and used in tissue engineering approaches. However, no single polymer has been considered ideal for all types of tissues and approaches. In this review, several natural and synthetic polymers that can be used for tissue engineering applications will first be discussed. The role of biological (e.g., ligand-receptor interactions) and physical (e.g., mechanical properties of polymer scaffold) signals generated from polymer scaffolds in controlling the function and structure of engineered tissues will then be discussed for the design and tailoring of polymers for tissue engineering applications.

Potential Polymers for Tissue Engineering

Naturally Derived Polymers. Proteins: Collagen is one of the main components of many tissues in the body, and has been used for many drug delivery and tissue engineering applications, due to its biocompatibility and ease of gelation via physical or chemical cross-linking reactions. A number of chemical modification methods have been reported to improve the poor mechanical properties of collagen matrices.[7]

Gelatin, a derivative of collagen, can be obtained by breaking the natural triple-helix structure of collagen into single-strand molecules, and can easily form gels by changing the temperature of its solution. Gelatin has also found numerous applications in drug delivery and tissue engineering approaches.[8]

Fibrin was originally developed as a sealant and an adhesive in surgery, as it is critical for natural wound healing. Fibrin gels can be prepared from the patient's own blood by the enzymatic polymerization of fibrinogen in the presence of thrombin at room temperature.[9] Fibrin gels can be degraded and remodeled by cell-associated enzymatic activity during cell migration and wound healing.[10] Fibrin gels have been used as an autologous scaffold to engineer tissues using skeletal muscle cells,[11] smooth muscle cells,[12] and chondrocytes.[13]

Polysaccharides: Alginate is a widely used natural polymer for drug delivery and tissue engineering applications due to its biocompatibility, low toxicity, and ease of gelation with divalent cations (Figure 2).[14] Many efforts have been devoted to controlling the properties of alginate gels via chemical and/or physical approaches, including the development of various cross-linking molecules, the introduction of cellular adhesion ligands, and controlling the size of cross-linking junction sites,[15-17] in order to regulate cell-polymer interactions.[18]

Chitosan is the second most plentiful natural polymer (next to cellulose), and has found many useful applications in tissue engineering (e.g., liver and neural tissue regeneration),[19,20] due to its biocompatibility, low toxicity, structural similarity to natural glycosaminoglycans, and ease of enzymatic degradation.[21] Many derivatives have been reported to enhance the solubility and processibility of chitosan.[22,23]

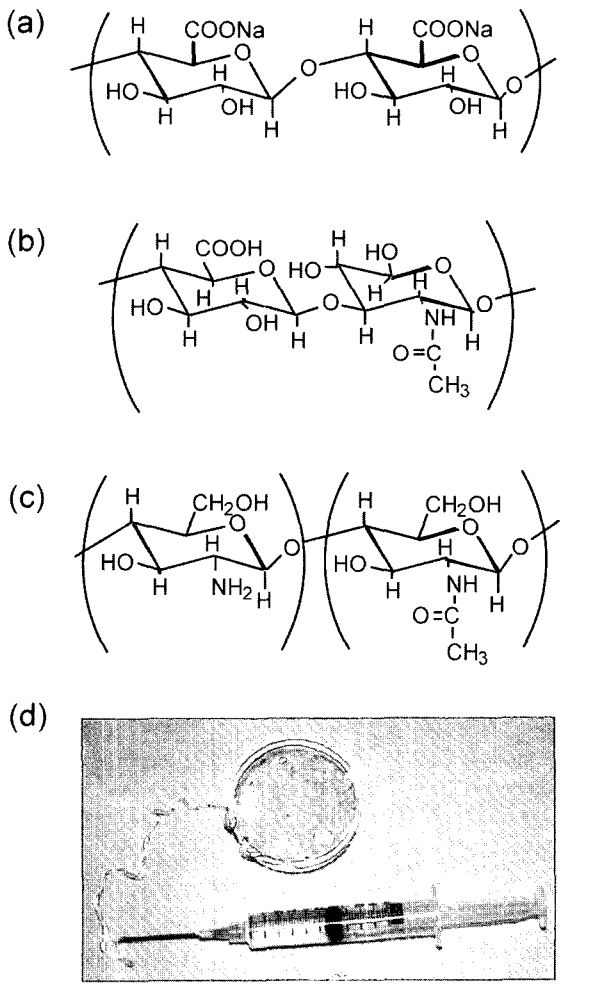

Figure 2. Chemical structures of (a) sodium alginate, (b) hyaluronic acid, and (c) single chitosan. (d) Example of injectable alginate gels cross-linked with calcium ions.

Hyaluronic acid is one of the glycosaminoglycan components in natural extracellular matrices, and it can be degraded by hyaluronidase that exists in cells and serum.[24] Hyaluronic acid has shown excellent potential for tissue regeneration such as artificial skin,[25] facial intradermal implants,[26] wound healing,[27] and soft tissue augmentation.[28] However, hyaluronic acid requires a thorough purification process to remove impurities,[29] and hyaluronic acid scaffolds typically possess poor mechanical properties.

Synthetic Polymers. Aliphatic Polyesters: Limitations in the properties of naturally occurring polymers have been the motivation behind the development of various synthetic polymers. One of the most frequently used synthetic polymers in biomedical applications is aliphatic polyesters, such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymers (PLGA). PGA has a high crystallinity and low solubility in organic solvents, while PLA has better solubility in organic solvents, due to the methyl group in PLA. However, PLA is less labile to hydrolysis due to steric hindrance of the methyl group, resulting in a slower degradation rate. PLGA can be readily synthesized, and their physical properties and degradation rates can be controlled by the ratio of glycolic acid to lactic acid.[30] Various methods such as phase separation,[31] emulsion freeze-drying,[32] fiber extrusion and fabric formation,[33] and gas foaming/particulate leaching[34] have been reported to fabricate scaffolds using these polymers (Figure 3). Non-woven fabrics of PGA have been stabilized by physically bonding them with PLA to increase the resistance to compressive forces, and these have been used to successfully engineer smooth muscle tissues.[35] Polycaprolactone (PCL) is also one of the widely used aliphatic polyesters, and is a semi-crystalline polymer with high solubility in organic solvents and a low melting temperature. The degradation rate of PCL is much slower than that of PGA or PLA, and it can be controlled by copolymerization with lactic acid.[36]

Polyacrylates: Many different types of molecules and cells have been encapsulated into hydrolytically stable cross-linked poly(2-hydroxyethyl methacrylate) (HEMA), which has been widely used in many drug delivery and tissue engineering applications.[37,38] Degradable dextran-modified poly (HEMA) gels have also been synthesized, and are reported to be degradable by enzymes.[39] In addition, enantiomeric oligo (L-lactide) and oligo(D-lactide) were grafted to poly(HEMA) to form gels without using any toxic chemical reagent as a cross-linker.[40]

Poly(*N*-isopropylacrylamide) (NIPAAm) is very attractive for tissue engineering applications including cartilage and pancreas engineering,[41,42] due to its phase transition behavior in an aqueous solution above the lower critical solution temperature (LCST). The LCST of poly(NIPAAm) in water is approximately 32 °C, and approaches body temperature with copolymerization.[43] Thus, the use of poly(NIPAAm) and its copolymers in tissue engineering would be very beneficial, as one can easily prepare a mixed cell/polymer solution at room temperature, or even at a lower temperature, and inject it into the desired site in the body. This will result in the formation of a solid cell/polymer construct when the mixed solution warms to the body temperature. The unique temperature-responsive nature of these polymers is also leading to a variety of biomedical applications. For example, the culturing of cells on poly(NIPAAm)-grafted matrices enables one to easily recover intact cell sheets by simply decreasing the temperature without using proteases such as trypsin.[44] Dextran-grafted poly(NIPAAm) copolymers have been synthesized to overcome the limited degradability of poly(NIPAAm) gels, and it has been reported that these copolymers might modulate degradation in synchronization with temperature.[45]

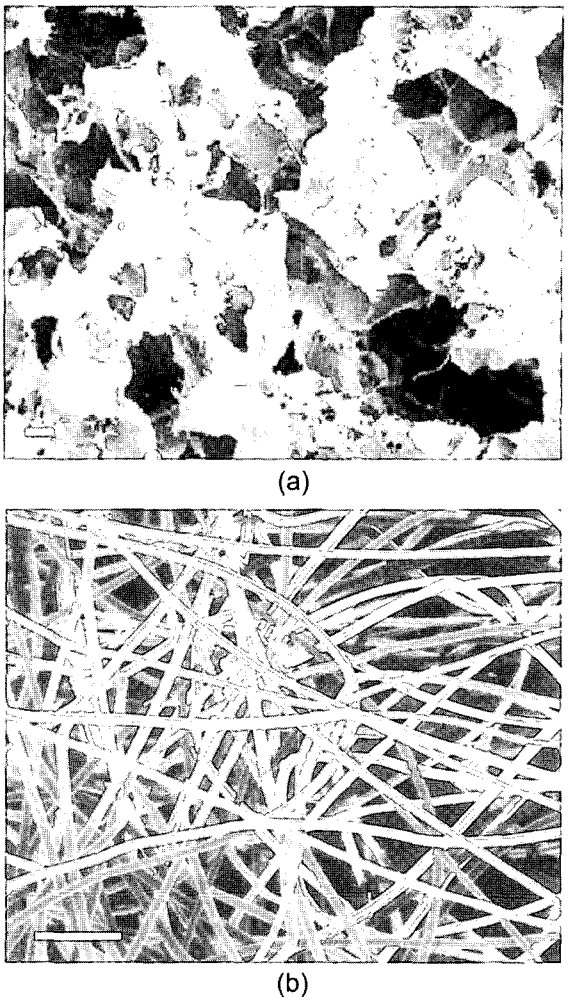

Figure 3. Scanning electron micrographs of (a) a porous scaffold of poly(lactic acid-*co*-glycolic acid) prepared by gas foaming/particulate leaching method and (b) non-woven fabric of poly(glycolic acid) (scale bar, 100 μm).

Poly(ethylene oxide): Poly(ethylene oxide) (PEO) and its derivatives have been extensively studied for biomedical

uses, including the preparation of biologically relevant conjugates,[46] surface modification of biomaterials,[47] and induction of cell membrane fusion.[48] PEO has been approved by the FDA for several medical applications, owing to its biocompatibility and low toxicity. Various PEO-based copolymers have been reported and utilized, especially in drug delivery applications.[49-51] One interesting copolymer is a triblock copolymer of PEO and poly(propylene oxide) (e.g., PEO-*b*-PPO-*b*-PEO), which is known by the trade name of Pluronics or Poloxamers, and is commercially available in various lengths and compositions. These polymers form thermally reversible gels without using any permanent cross-links, unlike poly(NIPAAm) and its copolymer gels. A variety of biodegradable di- or triblock copolymers of PEO and poly(lactic acid) (PLA) have also been synthesized and used to form gels for tissue engineering applications, as they can easily be formulated with protein drugs and/or cells and subsequently delivered to the desired site in the body in a minimally invasive manner.[52,53]

Poly(vinyl alcohol): Poly(vinyl alcohol) (PVA) can generally be obtained from poly(vinyl acetate) by alcoholysis, hydrolysis, or aminolysis.[54] PVA forms hydrogels either by chemical cross-linking with glutaraldehyde[55] and epichlorohydrin,[56] or by physical cross-linking using a repeated freezing/thawing method.[57] These gels are useful as a long-term or permanent scaffold. PVA has been frequently utilized for the regeneration of artificial articular cartilage,[58] hybrid-type artificial pancreas,[59] and bone-like apatite formation.[60] It was reported that oligopeptide sequences introduced onto the surface of PVA gels enhanced cellular interactions.[61]

Polyphosphazenes: Polyphosphazene is an organometallic polymer containing alternating phosphorous and nitrogen atoms with two side groups attached to each phosphorous atom. The degradation kinetics of polyphosphazenes can be controlled by changes in the side-chain structure rather than the polymer backbone, unlike aliphatic polyesters.[62] Non-ionic and ionic hydrogels can be prepared from polyphosphazenes. Non-ionic polyphosphazene gels are based on water-soluble polyphosphazenes containing glucosyl or glyceryl side groups.[63] Ionic polyphosphazene hydrogels, formed with divalent ions or ^{60}Co gamma irradiation, have been extensively studied for the delivery of protein drugs, due to their ability to respond to environmental changes such as pH and ionic strength.[64,65] It was also reported that these polymers might be useful for skeletal tissue regeneration.[66]

Synthetic Polypeptides: There has been wide interest in synthesizing polypeptides to mimic naturally existing proteins, as they are major components of extracellular matrices of tissues in the body. However, it is generally very difficult to precisely control the sequence of amino acids of polypeptides, in addition to their poor solubility in common organic solvents. New polymerization strategies to synthesize polypeptides with well-defined amino acid sequences and a wide range of molecular weights were recently reported, which involve using various organonickel initiators[67] or synthesizing genetically engineered polypeptides.[68,69] Silk-like polypeptides have been prepared by this method,[70] and a Gly-Ala-rich sequence has been introduced into these artificial proteins to form reversible gels in response to environmental changes of pH and temperature.[71] Elastin-mimetic polypeptides, comprised of a Gly-Val-Pro-Gly-any amino acid sequence, have been also studied and considered to have potential for tissue regeneration.[72-74] However, this method is neither appropriate for economical large-scale production of polymers at the current time, nor for easy modification of the polymer products, because any change requires re-engineering of the entire system.

Design Parameters of Polymers for Tissue Engineering

Biocompatibility. One critical parameter of polymers for tissue engineering applications is biocompatibility. Biocompatibility relates to a material's ability to exist within the body without damaging adjacent cells or leading to significant scarring, and to perform appropriate host responses in specific applications. Inappropriate biocompatibility of materials may be especially problematic in tissue engineering, as the inflammatory response to a polymer can affect the immune response towards the transplanted cells.[75,76] Biocompatibility can result from the inherent features of a polymer or it can be improved by thorough purification procedures. Naturally derived polymers often demonstrate adequate biocompatibility, while synthetic polymers may elicit significant negative responses from the body.

Specific Interactions with Cells. Adhesive interactions of cells with polymers may significantly affect the proliferation, migration, and differentiation of the cells to be engineered. The adhesion of cells to polymer scaffolds may be cell-type specific, and is dependent on the interaction of specific cell receptors that recognize adhesion molecules (i.e., ligands) at the surface of materials.[77] The ligand molecules can either be inherent components of materials or be artificially introduced into the materials. A small peptide containing the RGD sequence (Arginine-Glycine-Aspartic acid) was introduced into an alginate backbone, in order to increase the survival of many cell types in alginate scaffolds.[78] In brief, alginate was modified with the G_4RGDY peptide in the presence of water-soluble carbodiimide (EDC) and *N*-hydroxysulfosuccinimide (sulfo-NHS). The optimum reaction condition was found to be slightly acidic (pH 6.0-7.5, 0.1 M MES buffer). Carboxyl groups of alginate offer potential reaction sites for covalent bonding with RGD-containing peptides. Mouse skeletal myoblasts adhered to the RGD-modified alginate gels, proliferated, fused into multinucleated myofibrils, and expressed heavy-chain myosin that is a differentiation marker for skeletal muscle.[79] The

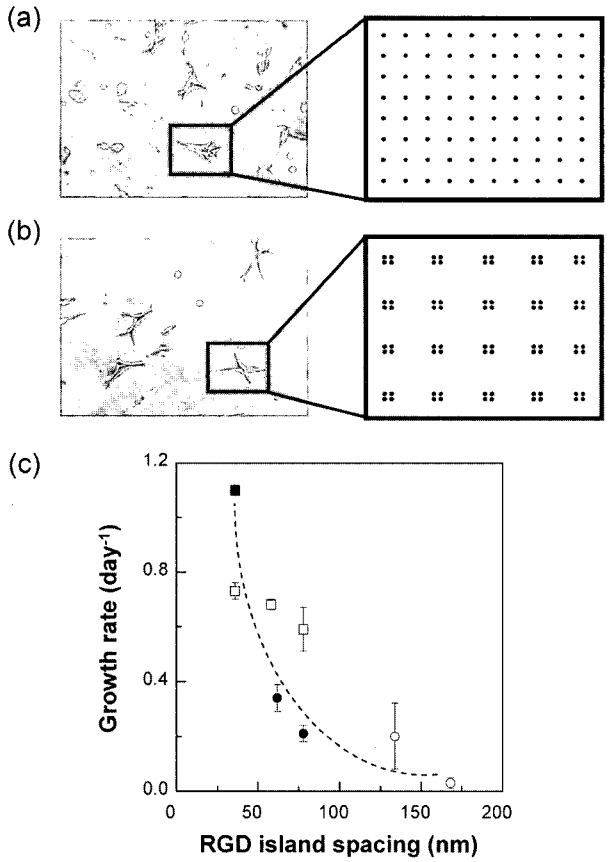

Figure 4. Photomicrographs of MC3T3-E1 cells adhered onto alginate gels with RGD island spacing of (a) 62 and (b) 78 nm. (c) Growth rates of MC3T3-E1 cells adherent to alginate gels with varying RGD island spacings (○, 0.125; ●, 1.25; □, 6.25; ■, 12.5 μg/mg polymer) (Adapted from reference 81).

adhesion, proliferation, and differentiation of mouse pre-osteoblasts was also significantly influenced by the existence of RGD peptides in the alginate scaffolds.[80] One recent finding is that nanoscale organization of RGD peptides in alginate scaffolds is critical to regulate the growth rate and differentiation of mouse pre-osteoblasts. A decrease in the RGD island spacing from 78 to 36 nm upregulated the growth rate of MC3T3-E1 cells from 0.59±0.08 to 0.73± 0.03 day^{-1}, and resulted in a four-fold increase in osteocalcin secretion levels, which is a typical marker of osteoblast differentiation (Figure 4).[81]

Mechanical Properties. Controlling the mechanical properties of polymer scaffolds is also an important design parameter, as the adhesion and gene expression of interacting cells may be related to the mechanical properties of the polymer scaffolds.[82] The mechanical properties of polymer scaffolds mainly depend on the inherent physical characteristics of the polymer chains, as well as on the processing technique used to form a three-dimensional scaffold. Useful polymer scaffolds with appropriate mechanical properties may arise from the synthesis of new types of polymers, or from the modification of conventional polymers that have an established history of biocompatibility. Alginate was covalently cross-linked with various cross-linking molecules, including adipic acid dihydrazide, L-lysine, and amino-poly(ethylene glycol), to control the mechanical properties of the scaffolds.[83] The mechanical properties of alginate scaffolds are mainly controlled by the cross-linking density, but are also moderately dependent on the type of cross-linking molecule (Figure 5). The introduction of hydrophilic cross-linking molecules as a second macromolecule (e.g., PEG) can compensate for the loss of the hydrophilic character of the gels resulting from the consumption of carboxyl groups of alginate chains during cross-linking.[15]

Biodegradation. Controlled degradation of polymer scaffolds is critical in many tissue engineering applications, as it is desirable to coordinate the degradation rate of the scaffolds with the rate of new tissue formation. Typical strategies to control the degradation rate of polymer scaffolds include either the use of degradable polymers (e.g., PLGA)[84] or the introduction of degradable cross-links using non-degradable polymers.[85] In the latter case, the polymer should be of sufficiently low molecular weight to be readily solubilized, released from the transplanted site, and subsequently be cleared from the body. The commercially available alginate is not degradable under physiological conditions, and its molecular weight is typically above the renal clearance threshold of the kidney.[86] To overcome these limitations, commercially available high molecular weight alginate was partially oxidized using sodium periodate, and proved to be degradable under physiological conditions (as in the first approach described above). The partially oxidized alginates

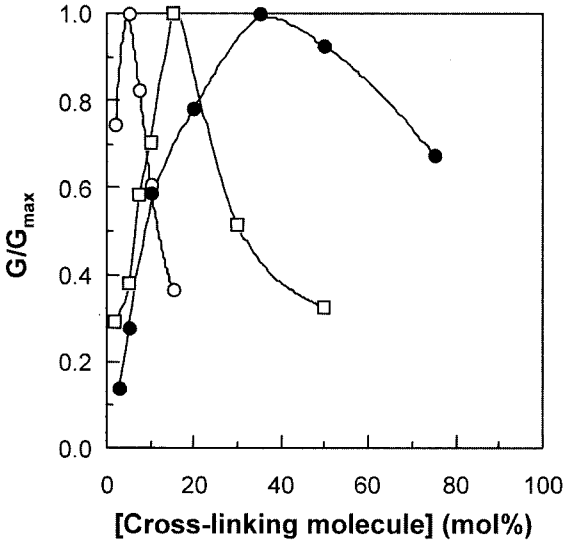

Figure 5. Shear modulus (G/G_{max}) vs concentration of cross-linking molecules for alginate gels cross-linked with adipic acid dihydrazide (●), PEG_{1000} (□), and PEG_{3400} (○) (Adapted from reference 83).

have been successfully used to engineer cartilage-like tissues *in vivo*, suggesting that these materials may have potential as a cell transplantation vehicle.[87] Degradable alginate-derived gels were also prepared by covalently cross-linking low molecular weight alginate derivatives (the second approach described above). Polyguluronate (M_w=6,000) was isolated from alginate, oxidized, and cross-linked with adipic acid dihydrazide to form gels, and these gels were degradable by hydrolysis.[88] The mechanical properties and degradation rates of the resultant gels were regulated by the extent of cross-linking.[85] These gels have found potential applications in engineering bone-like tissues with osteoblast transplantation (Figure 6).[89]

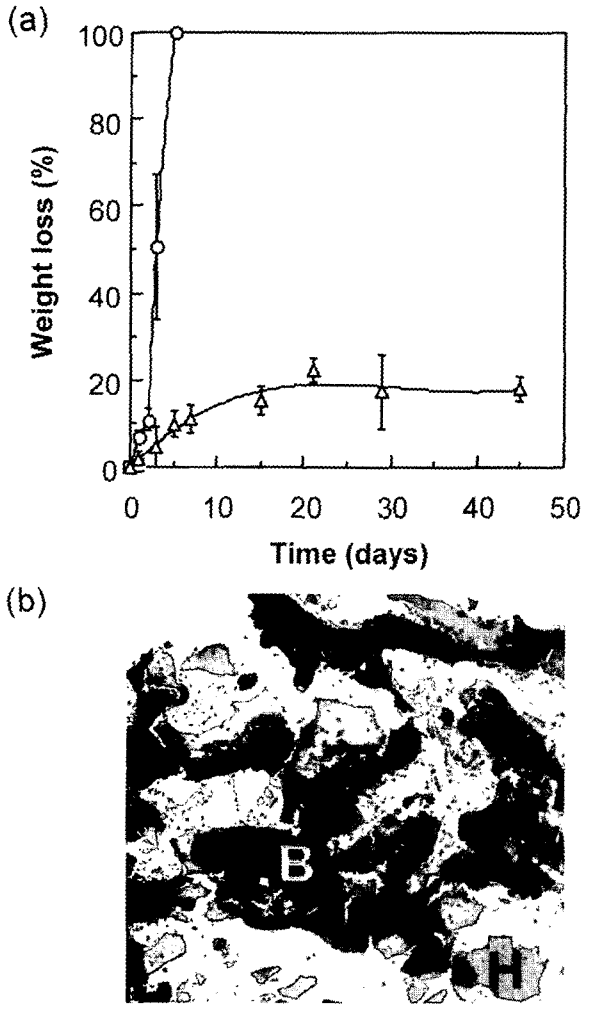

Figure 6. (a) Weight loss of poly(aldehyde guluronate) gels cross-linked with 100 (○) and 200 mM (△) adipic acid dihydrazide. Hydrogels were incubated in DMEM (pH 7.4) at 37°C (Adapted from reference 85). (b) Photomicrograph of representative tissue sections of osteoblasts transplanted in poly(aldehyde guluronate) gels cross-linked with 200 mM adipic acid dihydrazide. Tissue sections were taken after nine weeks and stained by the von Kossa method. Photomicrograph has labels for the remaining hydrogel (H) and newly formed bone tissues (B) (Adapted from reference 89).

The Release of Bioactive Molecules. One critical element in engineering large tissues is the development of new vascular network structures, which enable the delivery of sufficient oxygen and other nutrients to the engineered tissues. This vascular network should be formed in a timely manner during the process of tissue development. One recent and exciting approach to promote angiogenesis in engineered tissues is the delivery of angiogenic molecules and/or blood vessel-forming cells (e.g., endothelial cells) to the site at which the tissue is being engineered.[90,91] In the next section, the delivery of angiogenic promoters (e.g., growth factors, DNA) will be discussed as one design parameter of polymers for tissue engineering.

Protein Delivery: Localized and sustained release of angiogenic factors from polymer scaffolds may prevent them from degradation in the body and to optimize the vascularization process. It has been reported that various growth factors, including the vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF), can be incorporated into polymer scaffolds and released in a controlled and sustained manner for extended time periods (Figure 7).[92-94] However, the conventional delivery systems for angiogenic factors and/or cells have been designed to operate under static conditions, and the effect of mechanical stimuli on the release of the factors has not yet been systemically exploited. It has been demonstrated that mechanical signals can be exploited to modulate the release of angiogenic factors from polymer scaffolds, and to provide a novel approach for guiding tissue formation in mechanically stressed environments *in vivo*.[95,96]

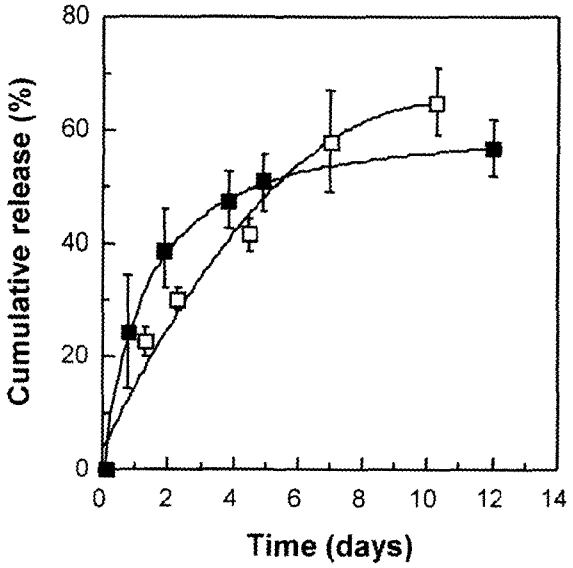

Figure 7. Cumulative release of VEGF (□) and bFGF (■) from alginate hydrogels cross-linked with calcium ions. The gels were incubated in DMEM at 37°C (n=3) (Adapted from reference 94).

DNA Delivery: The delivery of plasmid DNA encoding angiogenic proteins may provide an alternative approach for generating new vascular network structures in engineered tissues. Difficulties of protein stabilization have led to the development of polymer systems for DNA delivery.[97] Porous PLGA scaffolds containing a plasmid encoding for PDGF, a potent angiogenesis promoter, were prepared by the gas foaming/particulate leaching method, and proved to be useful in promoting blood vessel formation. This delivery vehicle greatly increased the number of blood vessels and granulation tissues formed in animals, compared to the direct injection of the plasmid.[34] Since transfection is transient, the sustained release provides high levels of expression over controlled time scales.

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