Microfluidic Biomaterials

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Abstract

Biomedical applications—prostheses, tissue engineering, drug delivery, and wound healing—demand increasingly sophisticated characteristics from the materials that come into contact with living systems in the laboratory and the clinic. With the development of microfluidics, there is an opportunity to create active biomaterials based on embedded microfluidic structures. These structures allow for control of the concentrations of soluble chemicals and hydrodynamic stresses within the material and at its interfaces, and thus allow one to tailor the environment experienced by the living tissue. In this article, we review initial efforts to develop these microfluidic biomaterials and present considerations regarding the required characteristics of the materials and of the microfluidic-mediated mass transfer. As specific examples, we present work toward microfluidic control of mass transfer in scaffolds for tissue engineering and in wound dressings.

Keywords: *biological, biomedical, fluidics, microscale, soft lithography, tissue.*

Introduction

Biomedical technologies such as prosthetics, scaffolds for tissue engineering, wound dressings, and vehicles for drug delivery require synthetic materials to interact with complex biological systems. Research in biomaterials has led to new chemistries and processing techniques that allow this interaction to be more sophisticated by, for example, tailoring rates of degradation,[1] adding cell-specific chemical moieties,[2] and tuning mechanical properties.[3] Despite these advances, most biomaterials function in a passive manner, as they lack a mechanism by which the user—scientist or clinician—can tune their properties after synthesis. Recent developments in microfluidic technology suggest a route to integrating function into synthetic biomaterials to control their internal and interfacial chemistry with high spatial and temporal resolution: microfluidic paths permeating the material and connected to external reservoirs could allow a user to control the exchange of solutes with the bulk and surfaces of the material.

Figure 1 illustrates the rudimentary concept of an embedded microfluidic network to serve this purpose; we refer to such a structure as a microfluidic biomaterial. In this conception, the microfluidic network is defined by interconnected voids within the biomaterial itself; flow of solutions through these channels mediates the exchange of solute with the interior of the material. The addition of this fluidic infrastructure is important when the material is host to chemically active processes such as living cells, when the material is a delivery vehicle of soluble species such as drugs, or when the material must regulate its chemical environment, as is the case in wound dressings. In this article, we begin with a presentation of general considerations regarding the choice of materials, methods of fabrication, and microfluidic design. We then turn to specific examples of microfluidic biomaterials developed in the contexts of tissue engineering and wound dressings. Our goal is to point out the ways in which this nascent effort presents interesting challenges and intriguing opportunities to the field of biomaterials.

Approach

The development of a microfluidic biomaterial must take into consideration the inherent *material properties* of the components; the *fabrication process* that allows for the integration of microfluidic structure, interconnects, and potentially living tissue; and the *modes of operation.* We will outline design considerations in these three categories with an eye toward applications in three-dimensional tissue culture and wound dressings.

Materials

The materials used to make up a microfluidic biomaterial ought to satisfy the constraints on conventional biomaterials for the application at hand. Important characteristics of materials for biological applications include lack of toxicity, lack of immunogenicity (the tendency to induce an immune response), biodegradability (fast, slow, or absent), adhesiveness (or lack thereof) to bio-macromolecules and cells, and appropriate mechanical properties (modulus and strength). Additional requirements of a material for use as microfluidic structures are the ability to reproduce and maintain microstructure, well-defined permeability to the motion of fluids by convection (convective permeability) and of solutes by diffusion (diffusive permeability), and the ability to form a pressure-tight seal with itself and other components such as tubing. As mentioned in the introduction, many materials have been developed over the past decades that satisfy the conventional constraints on biomaterials,[3] and a number of these are appropriate for transformation into microfluidic biomaterials. For ex-

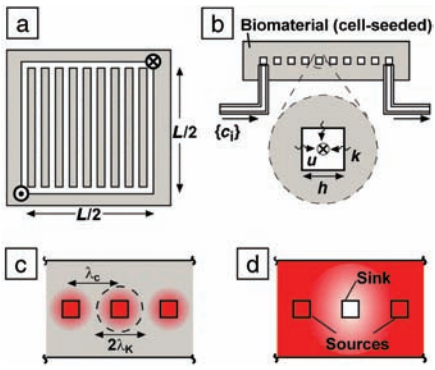

Figure 1. (a)–(b) Schematic diagram of a rudimentary microfluidic material in top (a) and cross-sectional (b) views. (c)–(d) Characteristic modes of operation for solutes that are consumed in the bulk material (c), and solutes that are not consumed (d), where the degree of saturation of the color indicates the concentration of the solute. Parameters: axial dimensions of a channel, L *(m); concentrations of solutes in flow,{c_i} (mol/m^3); flow speed in microchannel,* u *(m/s); mass transfer coefficient,* k *(m/s); channel dimension,* h *(m); interchannel spacing, λ_c (m); penetration depth of a consumed solute, λ_K (m).*

ample, acrylate-based biomaterials such as poly(hydroxyethyl methacrylate) (pHEMA) and poly(ethyleneglycol diacrylate) have been use to used to form microstructures via *in situ* photopolymerization.[2,4,5] As we will see in later sections, polymers of metabolites such as poly(L-lactic glycolic acid) (PLGA) and poly(saccharides) such as alginate are also good candidates.

Fabrication

The detailed constraints on the fabrication process used to create a microfluidic biomaterial will depend on the particular materials and geometries that are required, but a few general considerations can be identified. The process should be mild enough to avoid damaging the material; in particular, for cases in which living tissues (e.g., dispersed cells) are present during the fabrication, the process must not involve significant deviations from physiological temperature, pH, and osmolarity. Furthermore, the process should not compromise the biocompatibility of the material by introducing persistent toxins or infectious agents; either the fabrication process must be entirely sterile or the final system must be compatible with a chemical or thermal sterilization.

Soft lithographic methods, which were pioneered by the laboratory of Whitesides in poly(dimethylsiloxane) (PDMS),[6] are well suited for the manipulation of biomaterials, as demonstrated by a number of recent efforts.[5,7–9] In the context of the formation of microstructure, this strategy employs photolithography to define a microstructured master in conventional microfabrication materials such as a negative photoresist (SU-8) or silicon; the material of choice is then molded on this master. Grooves molded into the surface of a material can then be formed into microchannels by sealing the grooved surface to a flat surface of an identical or distinct material. The quality of this seal frequently defines the maximum pressures that can be applied to drive fluids in the microfluidic structure. An example of the soft lithographic approach to forming a microfluidic biomaterial is shown schematically in Figures 2a and 2b, from the work of Borenstein and collaborators.[10]

Soft lithography is attractive for its simplicity, its adaptability to the specific constraints of biomaterials mentioned earlier, and its parallel nature (i.e., all features are generated simultaneously during the molding step). Nonetheless, it generates structures one layer at a time, rendering the creation of complicated 3D structures difficult. The creation of generalized microfluidic structures will be simplified by the development of methods to build 3D networks within biomaterials. Direct-write methods, such as that of Lewis' group, are good candidates for this advance.[11]

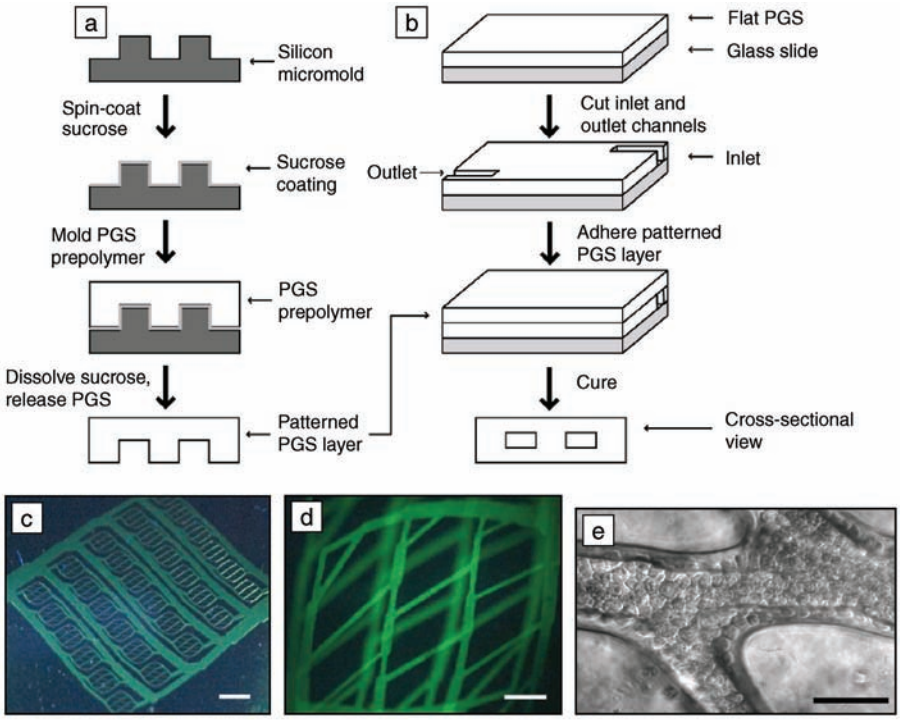

Figure 2. (a)–(b) Soft lithographic fabrication of microfluidic structures in poly(glycerol sebacate) (PGS), a biodegradable, elastomeric material.[20] Fluorescence micrographs of (c) a single-layer (scale marker, ~2.5 mm) and (d) a two-layer (scale marker, ~300 μm) microfluidic network in PLGA perfused with fluorescent solutions.[10] (e) Optical micrograph of a section of microchannel in PGS in which endothelial cells have reached confluence after 14 days of culture (scale marker, ~100 μm). Adapted from References 10 and 20.

A mundane but crucially important consideration in the fabrication of any microfluidic system is the formation of connections between external fluid handling systems—reservoirs and pumps—and the microfluidic network. This step is complicated in work in biomaterials due to their low moduli ($<10^5$ Pa) and strengths. The use of supports made from a distinct, hard material such as a glass slide that can stabilize the junction can resolve this difficulty, as illustrated in Figures 3c and 3d.

Design and Operation

The design considerations for the chemical composition and geometry of a microfluidic biomaterial must account for the dynamic function—convective mass transfer—that it will mediate. We stress that this design problem ought to be treated as an exercise in chemical engineering, rather than direct biomimicry. In general, the constraints that have driven the evolution of physiology are not identical to those we face in designing artificial environments for biology. An example of how design principles from biology may be misleading (while not necessarily incorrect) is found by considering the long-standing principle of vascular architecture known as Murray's principle. This principle correctly predicts the branching ratios of the tubes in the vascular networks of many animals based on the minimization of an energetic cost function with respect to the radius of the tube; this cost function is the sum of the power consumed by viscous dissipation in flow through the tube and the metabolic power expended to sustain the volume of blood in the tube.[12] The difficulty of importing this conceptual tool into synthetic systems is that the relevance of Murray's cost function must be translated, as it is not clear that either the cost of pumping power or the volumetric cost of the working fluid (e.g., growth medium) will be dominant constraints on the design of biomedical technology.

Where then should one begin in designing a microfluidic biomaterial? To provide an example, we will consider a hypothetical case of 3D tissue culture where the microfluidic network permeates a material in which living cells are embedded

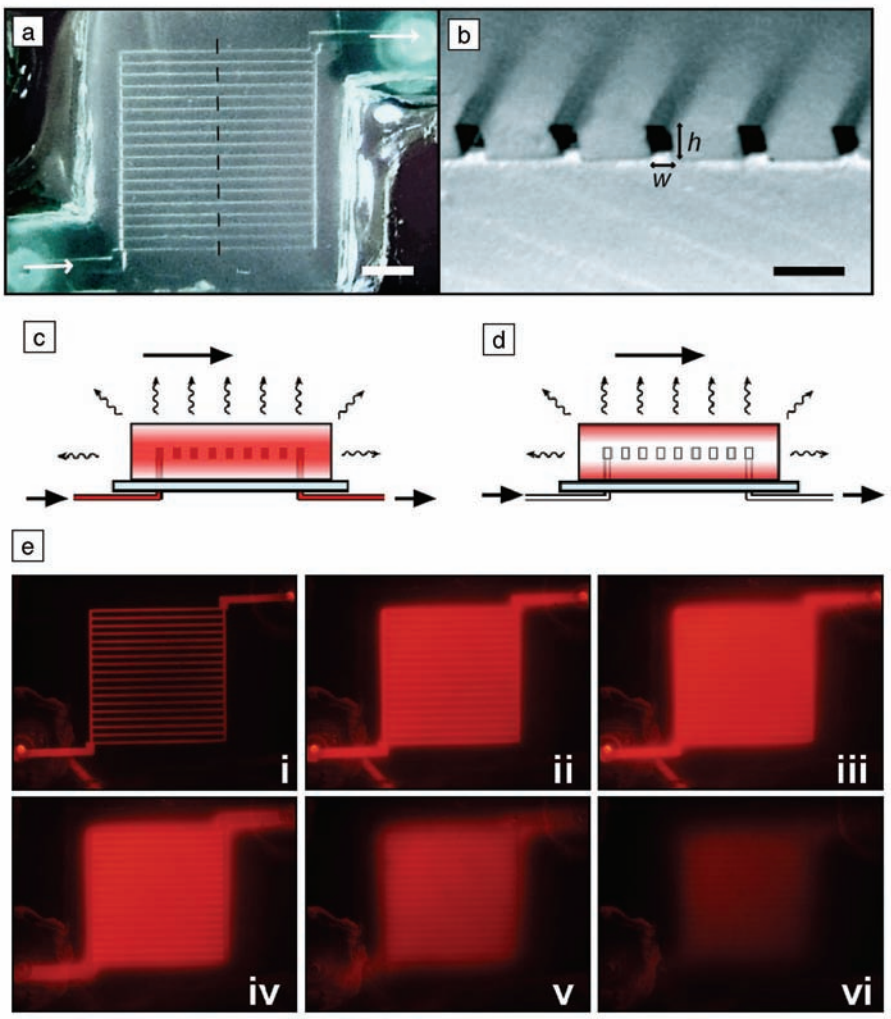

Figure 3. Microfluidic alginate gel. (a)–(b) Optical micrographs of (a) top view and (b) cross-sectional view of a sealed microfluidic network in calcium alginate. The scale bars are (a) 250 μm and (b) 500 μm. (c)–(d) Schematic depictions of operation of a microfluidic gel submerged in a well-stirred bath. The microfluidic network either (c) delivers solute (red) to the gel or (d) extracts solute from the gel. Straight arrows indicate flow through the channels and in the reservoir surrounding the material. Serpentine arrows indicate diffusion. (e) Time series of fluorescence micrographs of delivery (i)–(iii) and extraction (iv)–(vi) of rhodamine-coupled dextran (MW 70 kDa) from gel via microfluidic network. The square network of parallel channels is 1 cm across. Adapted from Reference 16.

(Figures 1a and 1b). The essential roles of the vascular structure could be to (1) maintain adequate concentrations of vital metabolites (e.g., oxygen) to the cells and (2) maintain a spatially varying concentration of a signaling molecule (e.g., a growth factor to define distinct cellular behavior). Given these desired functions, we are interested in defining the spacing between channels. For the supply of metabolites, we can follow a well-established result from theoretical biology (Krogh, ca. 1917)[13] and chemical engineering:[14] all cells should be within a distance of less than λ_K of the wall of a delivery channel (Figure 1c), where

$$\lambda_K \sim \sqrt{D_{s/m}\left(\frac{c_0}{\nu_{max}}\right)}. \quad (1)$$

In Equation 1, $D_{s/m}$ (m^2/s) is the diffusivity of the solute within the matrix, c_0 (mol/m^3) is the concentration of the solute at the channel walls, and v_{max} (mol/m^3 s) is the rate of consumption (or production) of the solute within the volume (the chemistry is assumed to be 0th order, as is commonly the case for enzymatically controlled biochemical processes such as respiration).[13] For muscle cells at physiological densities, λ_K could be as small as 50 μm; for chondrocytes, the cells in cartilage, λ_K could be as large as 1 mm.*

In order to define gradients of a signaling molecule, we must incorporate both sources *and* sinks of the solute of interest; otherwise, its concentration at steady state will be uniform (assuming its rate of degradation is negligible). As illustrated in Figure 1d, this source–sink strategy can be implemented in a microfluidic biomaterial by running streams of the solute through certain channels and solutions with none (or less) of the solute through others. The relative positions of the sources and sinks is set by the desired distribution of concentration of the species.

We have provided two simple examples—for metabolites and signaling molecules—of design rules for the geometry of a microfluidic material. How, though, should we define the desired operating conditions? In particular, at what speed should we run solutions through the device?

In either of the scenarios considered—delivery of metabolites or of signaling molecules—the design and operation of the microfluidic material is simplified if the solutions flow fast enough through the channels such that the concentration at the channel walls is maintained near to that of the bulk solution. In this case, the distribution of concentration within the material will be independent of the flow speed and defined exclusively by the reaction–diffusion (or simply diffusion) process in the bulk; the convective mass transfer through the network of microchannels will simply impose a set of externally controlled boundary conditions—that is, the concentrations $\{c_i\}$ in the solution—on this process (Figure 1b). This minimum flow speed, u_{min}, is identified by satisfying two conditions: (1) the resistance to convective mass transfer in the flow is small compared with the purely diffusive transfer in the material [high Biot number,† $B = k_{i,min}\lambda_c/D_{i/m} >> 1$, where $k_{i,min}$ (m/s) is the mass transfer for the ith solute at a flow speed u_{min}, $D_{i/m}$ is the diffusivity of the ith solute in the material,

*These numbers are relevant for oxygen: $D_{s/m} = 1.5 \times 10^{-5}$ cm^2/s, $c_0 = 100$ μM, and $v_{max} = 3 \times 10^{-8}$ mol/cm^3 s for muscle or $v_{max} = 2 \times 10^{-11}$ mol/cm^3 s for chondrocytes.[13,15]

†The Biot number is the ratio of the rate of transfer of solute between the flowing solution and the wall of the channel to the rate of purely diffusive transfer of solute within the material.

and λ_c is the interchannel spacing]; and (2) the solution is not depleted of the solute before it exits the material (high Péclet number,‡ $Pe_i = u_{min}h/D_{i/s} >> L/h$, where $D_{i/s}$ is the diffusivity of the ith solute in the solution, and h and L are the cross-sectional and axial dimensions of the channel, respectively. See Figures 1a and 1b).[16]

These simple design considerations certainly do not represent a complete conceptual foundation for the development of microfluidic materials, but we believe they illustrate the possibility and importance of applying basic engineering principles to the design of this technology.

Examples

We now turn to a review of some initial efforts to develop microfluidic biomaterials. These examples illustrate efforts to address challenges in two very distinct applications—tissue engineering and active wound dressings—that illustrate distinct design considerations.

Tissue Engineering

The ambitious, and largely unrealized, goal of tissue engineering is to grow physiologically appropriate human tissues—muscle, cartilage, bone, and others—for implantation into patients or for use as sophisticated models for pharmacological studies or basic research.[17] A dominant strategy in this pursuit is to template the growth process by seeding cells into a biomaterial; this scaffold can help define the geometry of the tissue as well as the chemical environment of the evolving cells during the growth process either *in vitro* or *in vivo* (e.g., within a laboratory animal acting as temporary host, or in the target patient). Important progress has been made in the past two decades on the chemical character of the materials that serve as scaffolds[3] and methods of controlling the growth process.[18] Despite this progress, significant limitations still exist on the size and complexity of engineered tissues. These limitations are in part due to the lack of infrastructure for solute exchange within existing scaffolds; as illustrated in the design examples in the "Design and Operation" subsection of "Approach" (Figures 2a and 2b), infrastructure in the form of microfluidic structure could serve to both supply the tissue with adequate fluxes of metabolites and define spatially and temporally varying chemical signals with which to influence the behavior—phenotype, metabolic activity, movement—of the embedded cells.

The effort to develop microfluidic materials for tissue engineering has been led by Borenstein, Vacanti, Langer, and Wang.[10,19,20] Their strategy has focused on embedding microfluidic networks within biodegradable materials [PLGA[10] and poly(glycerol sebacate)[20]] such that channels serve to guide the growth of a living vascular system of endothelial cell-lined tubes. The goal of pre-vascularizing the material is to employ the new vascular structure as a supply network for growth *in vitro*, and then form connections with the host's vascular system upon implantation. Their strategy, as illustrated in Figure 2, involves the following steps: (1) Definition of a microfluidic network by soft lithography within a biologically compatible material (Figures 2a and 2b), (2) plating (attachment) of endothelial cells onto the walls of the preformed microchannels by flowing a dispersion of cells through the network (not shown), and (3) culture of these cells within the microchannels until a confluent layer is grown over the entire inner surface of the microfluidic network (Figure 2e). A potential next step in this process would be the seeding of a distinct cell type in the bulk of this pre-vascularized biomaterial. Within the materials reported to date by this group [10,19,20], this step could be achieved by employing a porous form of the material; the use of a macroporous (~10–100 μm) structure is a common strategy used with dense materials to provide interstitial spaces to allow attachment of cells and adequate exchange of solute. A potential challenge with this method is that the porous structure could fail to maintain well-defined microfluidic paths for convection through the scaffold. Another proposed application of the pre-vascularized scaffolds would involve stacking them in an alternating fashion with cell-seeded layers such that the layers with vascular networks would provide mass transfer to the layers of living material.

In collaboration with the laboratory of Bonassar, we recently created a microfluidic biomaterial entirely within a biocompatible hydrogel, calcium alginate (Figure 3). We adapted an injection molding technique that Bonassar developed to form macroscopic scaffolds;[21] we used the molding technique as part of a soft lithographic strategy.[16] Briefly, we flowed a solution of sodium alginate onto a microstructured master and cross-linked it *in situ* by adding calcium ions. We sprayed the resulting calcium alginate gel (with microfeatures) with a sodium citrate solution to dissolve a thin surface layer, and placed it in contact with another alginate gel containing fluidic connections; the tubing connections were supported by a glass substrate. We re-gelled the interface to produce a sealed bilayer with an enclosed microfluidic network.[16]

The development of a microfluidic structure in alginate is important in two ways: First, microfluidic structure can be formed in calcium alginate gels of low solid fraction (4 wt% in Figure 3). Due to this low solid fraction, the gel is permeable to diffusion of small and large molecules. As illustrated by the experiment shown in Figures 3c–3e, this property allows the flows through the microfluidic structure to exchange solute with the 3D volume defined by the gel; this exchange is crucial to the function of the microfluidic structure as a supply network of the material. Second, the entire fabrication process is performed under conditions that are mild enough to allow pre-seeding of the alginate with cells. By pre-seeding the cells, they end up uniformly dispersed in the gel that defines the channels. The viability of chondrocytes (cartilage cells) through the key steps in this fabrication process is well established.[21,22] Our plan is to use this microfluidic biomaterial to direct the development of cells growing in the 3D volume defined by the gel. In this application, the channels can act either as an entirely synthetic vascular system or with endothelial cells plated on their inner walls, as pioneered by Borenstein and his collaborators.

Active Wound Dressings

We now pass to the consideration of wound healing as an application of microfluidic biomaterials. Chronic wounds are a significant medical problem for the growing populations of the elderly and patients with diabetes in the United States. These wounds often fail to heal for weeks or months when treated with conventional wound dressings; the cause of this impairment of healing is not fully understood but is associated with biochemical imbalances, such as an excess of proteases (enzymes that cleave proteins), in the wound bed. In recent years, clinicians have been interested in the development of dressings that could be used to treat difficult wounds in a mechanically and chemically active manner; such active dressings could be used to inhibit infection by clearing pathogens and delivering antibiotics, providing diagnostic information on the wound in real time, and stimulating healthy healing responses.

In the past decade, a new dressing, called vacuum-assisted closure (VAC®) therapy, has become widely relied upon

‡The Péclet number is the ratio of the rate of motion of solute with the flow to the rate of diffusive motion within the flowing solution.

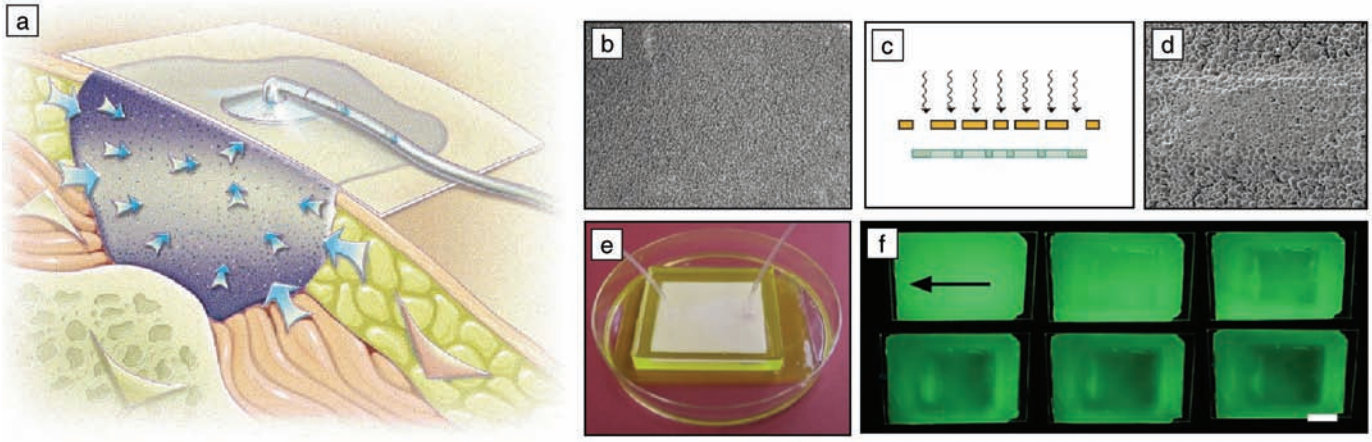

Figure 4. Active wound dressings. (a) Schematic diagram of the vacuum-assisted closure (VAC®) therapy commercialized by KCI. (b) Scanning electron microscopy (SEM) image of a microporous sponge in pHEMA, a biocompatible hydrogel (~20-μm pore diameter). (c) A strategy to photopattern the permeability of pHEMA. (d) SEM image showing a photopatterned pHEMA sponge with 1-mm-wide nonporous photopatterned channel. (e) Assembled microfluidic dressing on a model wound bed of sodium alginate saturated with fluorescein dye. (f) Fluorescence micrographs of a model wound bed after 0, 10, 20, 30, 40, and 50 minutes of application of the microfluidic dressing. Arrow in first frame indicates direction of flow driven through dressing during extraction (scale marker, 1 mm). Adapted from Reference 26.

for the treatment of chronic wounds.[23] The VAC treatment was developed by Morykwas[24] and is commercialized by Kinetic Concepts Inc. As shown in Figure 4a, at the heart of the VAC system is a soft foam formed of polyurethane or poly(vinyl alcohol). The application of the VAC is achieved by placing the sponge in the wound bed, covering it with a plastic sheet, and pulling a vacuum (down to ~635 torr) on the volume defined by the sponge. The foam is thus compressed beneath the plastic, distributing mechanical stresses onto the tissue in the wound bed and mediating the perfusion of wound fluids through the tissue and into the outlet. The mechanism by which the VAC aids the healing process is not well established, but it is hypothesized to be the result of a combination of mechanical stimulation of tissue activity (via deformation and fluid stresses) and of regulation of the chemistry in the wound via motion of the fluid.[23,25] The important characteristic of the sponge material for this application (beyond its biocompatibility) is its ability to distribute forces and flows within the wound bed; this characteristic is defined by the microstructure of the pores and the compressive modulus, as this defines the degree of compression. KCI's foam dressing material has a low modulus (~10^3–10^4 Pa) and large pores (~0.5 mm uncompressed), such that it conforms well to the complex morphology of wounds. The current sponge designs do not provide the possibility of spatially tailored treatment within the wound bed.

In order to provide finer control of fluid motion within an active wound dressing, we are developing an alternative strategy to the VAC in our laboratory.[26] Our approach, illustrated in Figures 4b–4e, focuses on the creation of a porous material for contact with the wound bed that has two key characteristics: (1) a well-defined geometry and (2) the potential to be patterned on the micrometer scale. We create a sponge of fixed micro- and macrogeometry (~20-μm pores in a 500-μm-thick layer) via phase-separation polymerization of hydroxyethyl methacrylate, following the methods of the Mikos group.[27] The scanning electron microscopy (SEM) image in Figure 4b shows the porous structure that is formed. The sponge material, poly(hydroxyethyl methacrylate), is a well-established biomaterial. Furthermore, this material is compatible with UV photopatterning, as indicated in Figure 4c. Figure 4d presents a scanning electron microscopy image of a porous pHEMA layer in which we created a 1-mm-wide line of nonporous pHEMA by saturating the preformed sponge with monomer, cross-linker, and initiator, and exposing it to UV through a photomask. This pattern influences the permeability of the sponge and can be used to direct the perfusion through the dressing. To form a complete dressing, we bond the sponge covalently to a silicone backing (PDMS) via acrylate-terminated silanes (Figure 4e); this silicone backing allows us to create well-defined fluidic connections to the sponge. Figure 4f illustrates the uniformity of mass exchange achieved with a non-patterned version of this dressing when it is run on a model wound bed containing a fluorescent dye. The well-defined mass transfer provided by this microstructured dressing enables applications in diagnostics and drug delivery during treatment, and mechanistic studies of the distinct roles played by mass transfer and mechanical stresses in defining the efficacy of active wound dressings. A clear disadvantage of creating a wound dressing with a predefined structure is that it is less adaptable to specific wound geometries. We envisage overcoming this challenge by forming the dressings as a repeated motif of fluidic modules (~1 cm × 1 cm); a given wound will be fit by trimming the dressing to the necessary pattern of these modules.

Conclusions and Future Directions

As is clear from this review, the development of microfluidic biomaterials is in its infancy. The goal of creating active materials that can be used to orchestrate complex biological processes will require a concerted effort to develop methods of fabrication (e.g., to define arbitrary 3D networks), appropriate materials (e.g., ones that are remodelable by specific cell types), and principles of design (e.g., to control the chemical environment of individual cells). Furthermore, these advances must be made in conjunction with biological and clinical studies that will further elucidate the biological responses that one could hope to control. Finally, we note that the effort to integrate microfluidic control

of chemistry to create active materials is relevant to important applications outside the biomedical arena, such as catalysis and solid-phase organic synthesis.

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