NIH Public Access
Author Manuscript
Adv Drug Deliv Rev. Author manuscript; available in PMC 2010 December 17.

Published in final edited form as:
Adv Drug Deliv Rev. 2009 December 17; 61(15): 1391–1401. doi:10.1016/j.addr.2009.09.002.

Micro- and Nanotechnologies for Intelligent and Responsive Biomaterial-Based Medical Systems

Mary Caldorera-Moore[1] and **Nicholas A. Peppas**[1,2]

[1] Department of Biomedical Engineering, University of Texas at Austin, 1 University Station, C0800, Austin, TX 78712-0238, USA

[2] Department of Chemical Engineering, University of Texas at Austin, 1 University Station, C0800, Austin, TX 78712-0238, USA

Abstract

Advances in medical treatments of a wide variety of pathophysiological conditions require the development of better therapeutic agents, as well as a combination of the required therapeutic agents with device-integrated biomaterials that can serve as sensors and carriers. Combination of micro- and nanofabricated systems with intelligent biomaterials that have the ability to sense and respond is a promising avenue for the development of better diagnostic and therapeutic medical systems. Micro- and nano-electromechanical systems (MEMs and NEMs) are now becoming a family of potentially powerful new technologies for drug delivery, diagnostic tools, and tissue engineering. Improvements in micro- and nano-fabrication technology have enhanced the ability to create better performing therapeutic systems for numerous pathophysiological applications. More importantly, MEMS and NEMS-based tissue regeneration scaffolds, biosensors, and drug delivery devices provide new opportunities to mimic the natural intelligence and response of biological systems.

Keywords

Responsive hydrogels; intelligent therapeutics; micro- and nano-electromechanical systems; biosensors; controlled drug delivery; tissue engineering

1. Introduction

In recent years, numerous proteinic and other drugs designed to target various cellular processes have emerged, creating a demand for the development of intelligent drug delivery systems (DDS) that can sense and respond directly to a pathophysiogical conditions. Micro and nano scale intelligent systems can maximize the efficacy of therapeutic treatments in numerous ways because they have the ability to rapidly detect and respond to disease states directly at the site, sparing physiologically healthy cells and tissues and thereby improving a patient's quality of life. This new class of "intelligent therapeutics" refers to intelligent and responsive delivery systems that are designed to perform various functions like detection, isolation and/or release of therapeutic agent for the treatment of diseased conditions [1]. To meet these requirements,

CORRESPONDING AUTHOR: Nicholas A. Peppas Sc.D., Fletcher S. Pratt Chair, Department of Chemical Engineering, CPE 3.466, C0400, 1 University Station, Austin, TX 78712-1062, peppas@che.utexas.edu; Ph: 512-471-6644; Fax: 512-471-8227.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

researchers must be able to interface synthetic and hybrid materials with dynamic biological systems on the micro and nano length scale.

Stimuli responsive biomaterials are very promising carriers for the development of advanced "intelligent therapeutics." A series of environmentally sensitive hydrogel-based materials has been developed for a wide variety of medical and pharmaceutical applications [2]. The development of pH, temperature, and glucose sensitive, [3–14,15] and other biomolecule sensitive hydrogels [16–23] that can be used for control release of biological agents has been reported. Hydrogels that are sensitive to light, magnetic field, and ultrasound have also been developed [4,12,17,24]. Another interesting family of responsive hydrogels being developed is a series of hydrogels with molecular imprinting capability termed "configurational biomimesis". These systems produce polymeric surfaces or polymeric recognitive networks that have three dimensional, stereospecific binding nanocavities based on a given template molecule [5,11,25].

Molecular imprinted polymers (MIPs) refer to a class of synthetic macromolecular networks fabricated to have high binding affinity for a specific molecule. Although research groups have now demonstrated the ability to fabricate analyte sensitive polymers, there is a strong need to combine this sensing element with a transducing element in order to develop miniature diagnostic devices capable of rapidly detecting disease states and releasing therapeutic agents. These microdevices could be implantable, therefore increasing the ability to sense initial disease states, thus improving therapeutic efficacy and reducing patient costs.

Micro- and nanotechnologies can offer new opportunities towards the development of better, intelligent medical systems and devices that have the possibility to profoundly impact medical therapeutic techniques. Advancements in micro and nano fabrication methods has provided new means of fabricating micro and nano devices for drug and gene delivery, tissue engineering, biosensors, and diagnostic systems, like protein and DNA microarrays. In the past decades, micro fabrication methods have been employed for the development of MEMs, microfluidic devices, and microarray analysis systems.

The advent of large-scale, high throughput analysis of gene expression was made possible with the development of microarray gene analysis systems, revolutionizing how researchers analyze gene expression in healthy and diseased cells and tissues [26]. Total microanalysis systems consisting of microvalves, micropumps, and microsensors have been development to create miniature analysis systems integrated all into a small device [27]. Most biological cells are on the order of 100–1000 #m, and components of cells are on the order of nanometers. Cell-cell interactions and cell-biomaterial interactions are microscale events. Device interactions refer to the micro and nano scale. Creating devices that will interact with cells on the micro level will potentially alleviate extreme damage to entire tissues or even organs and reduce inflammatory response while better targeting and treating the problem.

2. Intelligent Biomaterials

Polymers are the preferred materials for biological and life science applications because of their high adaptability and compatibility with biological molecules and cells. Numerous microfabrication methods can be used for molding polymers based on the polymer properties. Controlled drug delivery systems mostly fabricated out of polymers are used in millions of patients yearly [28]. Numerous controlled release systems for proteins have been approved for medical use. Particles "decorated" with poly(ethylene glycol) (PEG) and exhibiting stealth properties have also been approved, showing that biomaterials can be used to improve safety, pharmacokinetics, and duration of release of important therapeutic agents. "Intelligent", polymer-based biomaterials have been developed that have the ability to sense and respond to

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

biomolecule, temperature, or pH stimuli. Use of responsive polymer hydrogels and CIBPs materials are the two most promising approaches for developing intelligent therapeutic systems.

2.1. Responsive Hydrogels

Polymer-based biomaterials are widely used for medical applications. Unfortunately, most biomaterials lack functionality to interact and respond to biological systems. Hydrophilic polymers in their cross-linked form, i.e., hydrogels, allow for specific functionality to be directly incorporated into their networks. Hydrogels are attractive materials for biological and medical use because their properties can be controlled for specific applications, their high affinity for water, and their biocompatibility.

A wide range of hydrogel-based biomaterials has been developed over the past several decades that have the ability to molecularly recognize its environment, including biomolecules, pH, temperature, or a combination of conditions. By modifying the molecular structure of the polymers, hydrogel networks have the ability to interact with their environment in a "intelligent" manner [1]. Figure 1 summarizes different responsive hydrogel networks that have been developed in our laboratories and elsewhere.

Responsive behavior of hydrogels and other biomaterials can be summarized in two major categories. First, materials acting as carriers "passively" respond to external conditions due to physicochemical interactions and associated phenomena. Such phenomena can be pH-dependence, temperature-dependence, ionic strength-dependence, magnetic or electrical dependence and response to thermodynamic compatibility. The second category includes all materials that exhibit a certain intelligence that provides their ability to respond to a surrounding compound. These systems include those that can respond to a biomarker or a bioanalyte in a surrounding medium or materials that are decorated with functional groups that can provide artificial ligand-receptor interactions.

Let's examine now these materials behave starting first with the pH-sensitive materials.

2.1.1 pH Sensitive Hydrogels—In pH sensitive hydrogel systems, the responsive mechanism lies within the side chain groups, branches, and crosslinks of a polymer's chemical structure. In polymer networks that contain weak acid or base groups, absorption and adsorption of water can occur simultaneously. The movement of water into the polymer network results in ionization of the acid and base pendant groups. This phenomenon is controlled by the solution's pH, ionic composition and ionic strength. Therefore, hydrogels composed of ionic polymer networks behave as semi-permeable membranes for counter ions.

The osmotic equilibrium between the external solutions and the hydrogel is dependent on the ion-ion interactions. The equilibrium degree of swelling for hydrogels containing weak acid pending groups increases as the pH of the external solution increases, as demonstrated in Figure 1A. In the same respect, the degree of swelling increases as the pH decreases in the surrounding environment for hydrogels containing weak basic pendant groups. The swelling behavior of the hydrogel is controlled by polymer properties, the ionic concentration and the characteristics of the counter ions. Extensive studies have been conducted on ionic polymers including polyacrylamide (PAAm), poly(acrylic acid) (PAA), poly(diethyl aminoethyl methacrylate) (PDEAEM), poly(dimethyl aminoethyl methacrylate) (PDMAEM), and poly(methacrylic acid) (PMAA) [8–10, 13, 29–43].

Recently, our group [9,10,14] has demonstrated that insulin release can be achieved from pH and complexation-sensitive poly(methacrylic acid-grafted-ethylene glycol) (P(MAA-g-EG) and poly(methacrylic acid-grafted-ethylene glycol) functionalized with wheat germ agglutinin

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

(P(MAA-g-EG) WGA) microparticles. Stimuli sensitive hydrogels have also been ddesigned and produced as 'smart' drug delivery systems and biomimetic tissue engineering scaffolds to sense environmental changes and induce a structural change or degradation [4,16,17,19–22, 44–46].

pH-Sensitive hydrogels can also be used for site specific delivery. For example, Carr et. al. [3,13] demonstrated that microparticles composed of hydrogels of copolymers of methacrylic acid (MAA) and N-vinyl-2-pyrrolidone (NVP) were pH-responsive when transported from gastric to intestinal conditions, and could thus be used for oral protein delivery applications, especially for growth hormones and calcitonin. This microparticle design would provide protections for sensitive biological agents loaded within the hydrogels from the acidity conditions of the stomach. Once the particles reach the intestines, the hydrogel network will swell and release the loaded biological agents.

2.1.2. Temperature Sensitive Hydrogels—Temperature sensitive hydrogels are another type of responsive hydrogels that have been extensively studied mainly for their ability to undergo a reversible volume-phase transition in response to a change in its environmental temperature. Crosslinked polymers like poly(N-isopropyl acrylamide) (PNIPAAm) experience phase separation as the system temperature is increased above a critical temperature known as the lower critical solubility temperature (LCST). Hydrogel networks composed of these polymers swell when the temperature is lower than the polymer's LCST and shrink or collapse as the external temperature is increased above the LCST [6,24,34,47–55]. Temperature-responsive hydrogels have been widely studied for numerous biological applications including drug delivery and tissue engineering. Dual responsive hydrogels have also been developed by combining pH sensitive polymers and temperature sensitive polymers [6,47,52–54].

The use of such systems has led to a number of great new applications of nanotechnology. For example, novel intelligent therapeutic nanocomposite systems have been studied where metal nanoparticles such as gold [12] or SiO_2-gold nanoshells [24] have been incorporated into corresponding temperature-responsive interpenetrating polymer networks (IPN). The metal nanoparticles or nanoshells absorb light which is then converted to heat and transmitted locally to the surrounding IPN. As the temperature increases, the polymer swells and releases any encapsulated beneficial agents within the polymer network [12], as shown in Figure 1B.

2.1.3. Bioanalyte-Sensitive Hydrogels—Incorporation of well-evolved biological mechanisms such as highly specific, high affinity binding proteins or highly specific enzymatic cleavable proteins and peptide into synthetic hydrogels can be used to develop responsive biomaterials. Depending on the biological molecular, bioanalyte-incorporated into the hydrogels, these conjugate biomaterials can easily be tailored to respond to different biological conditions. A wide variety of biohybrid hydrogels has been developed for drug delivery [4, 23,56] and tissue engineering [18,20,57–65] applications by incorporating proteins, peptides, and enzymes to polymer networks. An example from our group's work of a biohybrid biomaterial that has been created to respond to biomolecules is the incorporation of activated glucose oxidase into pH-sensitive cationic hydrogels [7,40]. When these hydrogels are exposed to glucose in the body, the glucose oxidase catalyzes the production of gluconic acid, thus lowering the local environment pH and thereby causing the pH-sensitive hydrogels to swell.

The degradation properties of hydrogels can also be tailored by direct incorporation of biological linkers into the polymer network; as demonstrated in Figure 1C. Numerous degradable PEG-based hydrogels with degradable blocks or protease within the network have been reported by the groups of Anseth, Hubbell, West, and other research teams [18–20, 22, 44, 45, 55, 58, 62–64, 66–73]. Enzymatically degradable polymer carriers are beneficial as drug delivery or tissue engineering scaffolds because enzymatic cleavage is highly specific

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

and could be tailored for certain diseased tissues where specific enzymes are up regulated [23].

A series of enzymatically degradable hydrogels, specifically designed to mimic the extracellular matrix (ECM) in tissue engineering applications have been extensively reported [19–22,58]. These designs contain a peptide linkage either in the backbone of the polymer or as a crosslinking agent that is degraded by the presence of tissue specific enzymes (e.g. collagenase, elastase or MMPs). A key relevant finding in these studies reported by Hubbell and collaborators [62] was the highly specific enzyme-controlled release of recombinant human bone morphogenetic protein (rhBMP). West and co-workers [19] showed the differential degradation kinetics of these gels in the presence of various concentrations of the peptide-specific enzymes (collagenase or elastase). Their results indicated that the hydrogels do not degrade in the absence of enzymes while rapid degradation can be achieved by optimizing the enzyme concentrations.

Peptides derived from natural proteins have been incorporated into hydrogels to promote cellular adhesion [19,22,57,58,60,61,66–69,71,74–78]. The most widely used amino acid sequence is RGD which is derived from fibronectin, laminin, and collagen. Synthetic polymers poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA) as well as nature polymers such as alginates have been modified with amino acid sequences.

2.2. Configurationally imprinted biomimetic polymers (CIBPs)

In many biological and pathophysiological applications, control over the molecular recognition properties is required for development of intelligent therapeutic systems. Molecular-recognition systems require a 3D infrastructure whose chemical functionality and structure can be precisely controlled. Hydrogels can be prepared by molecular imprinting to prepare networks with chemical and structural functionalities for recognition of specific molecules.

Such systems exhibit configurational biomimesis. This phenomenon can be easily observed by placing a template molecule in the presence of unreached monomer and a crosslinker as demonstrated in Figure 2. These components need to be mutually soluble in an inert (and often non-toxic) solvent. It is then possible to introduce an initiator which allows a free-radical polymerization to take place. This polymerization produces a mesh-like network which forms hydrogen-bonding complexes with the opposing functionalities from the functional monomers and the template. The hydrogen bonding can then be disrupted and the template can be removed from the network. The polymer is then left with three dimensional cavities (nanocavities or nanovacuoles in the range of 1–3 nm) containing free functionalities. Ultimately these cavities can reform hydrogen bond complexes when contact is reinitiated by the template molecule.

The expanding field of molecular imprinting technology has enormous potential in providing the tools for the creation of intelligent, analyte-sensitive polymers that are capable of controlled drug delivery of therapeutic molecules in response to a recognitive biological event [79,80]. MIP systems have received widespread attention as a new class of drug delivery systems and as diagnostic tools in molecular sensors in the treatment of disease. MIPs have a large potential for use as DDS by providing either the rate-limiting mechanism in controlled release systems or by acting as the trigger for the release of therapeutic beneficial agents in response to external stimuli, or even by being sensing elements to give feedback as part of a biological sensor [80].

New synthetic recognitive biomaterials have been designed to mimic biological recognition, which is ultimately an improvement over the use of expensive, unstable and physiologically sensitive biological macromolecules and ligands.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Over the past decade, a variety of bioanalyte sensitive MIPs have been reported [80]. MIPs have been developed for cholesterol [81], glucose [11,82,83], and lysozyme [84]. Oral and Peppas [65] have reported the development of pH sensitive and recognitive networks selective for glucose, demonstrating the ability to fabricate multi-function networks that can sense and release in response to their environment.

Certain medical conditions hold particular promise for the use of configurationally imprinted biomimetic polymers (CIBPs) as therapeutic agents. One such condition is when a patient over-expresses certain peptides or proteins. Peptides, hormones, and some proteins rhythmically fluctuate up and down as a function of time. Common endocrine rhythms are the *diurnal* ("day-night") or *circadian* ("around the day") rhythms. These rhythms play a role in the pathophysiology of many disease states and may affect therapeutic efficiency and the side effect profile of prescribed treatments. A patient with high levels of peptides or proteins acting as biomarkers can have severe side effects when, during the peak of one of these cycles, the peptide concentration enters levels that are considered toxic for the body. These conditions vary through the course of time and many of these disease states often exhibit unpredictable episodes or unnoticeable symptoms that lead to severe physiological effects. An example of such a hormone peptide is angiotensin II. The blood concentration of this peptide fluctuates throughout the day. It is critical in vasomotor function, and has been implicated in the development of atrial fibrosis and ultimately cardiac arrest when it is present in the bloodstream in increased levels.

Ultimately, it would be beneficial to use polymers that are specifically designed to diagnose, detect and capture biologicals such as angiotensin II before they reached their peak concentrations. Unlike typical pharmaceuticals which react to symptoms, the CIBPs will be able to prevent the symptoms from occurring. For a complete therapeutic effect, the CIBPs will then need to render the over-expressed peptide inactive and be cleared from the body.

The intrinsic properties of polymer-based hydrogels and CIBPs make them easy to fabricate with a wide variety of properties for specific applications. The inherent mesh network of hydrogels can be designed to exhibit recognitive micro- and nanovacuoles ranging from microscale all the way down to angstrom length scale. The mesh architecture of these hydrogels renders them important agents for controlled release systems for drug delivery and tissue regeneration applications. The hydrogel networks can protect sensitive agents from harsh environmental conditions and, in response to a change in environment conditions, can swell to allow the sensitive agents to diffuse out of the network. More control over the release kinetics of hydrogels can be achieved by incorporating a biologically sensitive molecule directly into the polymer network of the hydrogel. When these hydrogels are exposed to the biological agent that the biomolecule is sensitive to, the hydrogel network will degrade, releasing the agents encapsulated within the network. For these hydrogels networks to be effective at delivering their payload directly into a pathophysiological area with a real-time response and release, the hydrogels need to be transformed into micro or nano length scale systems.

3. Micro- and Nanofabrication Techniques of Intelligent Therapeutics

For intelligent therapeutic systems to be capable of responding to biological systems at the molecular level within the body, these systems need to mimic natural biosystems in their structure and size and therefore will need to be fabricated using advanced nanofabrication techniques. Recent advancements have made micro and nanofabrication important tools for modern science and technology. Microstructures provide researchers the ability to interact with cells on the cellular level, providing the opportunity to study basic scientific phenomena that occur at the micron dimension. There are numerous microfabrication techniques for

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

preparation of microstructures for various biomaterials. For example, polymer materials can be replicated using micro-molding and embossing techniques that have lower cost.

The surface properties of polymer substrates such as wettability, adhesion, surface adsorption, and surface reactivity allow the surface of the material to be modified using a variety of surface chemistries. Therefore, the surfaces of polymer microsystems can be tailored for specific applications using self-assembled monolayer (SAMs) techniques or attaching macromolecules like proteins and peptides [85]. The flexibility of polymers allows them to be molded down to the nano scale with high resolution, while also being able to tailor the surface tomography for specific applications, making them attractive materials for fabrication of micro- and nanofabricated medical devices. Micro molding processes are well-developed and can easily be adjusted for fabricating well-defined two-dimensional and three-dimensional structures of varying shapes and sizes.

Numerous microfabrication methods can be used for molding polymers based on their polymer properties. For example, photosensitive polymers can easily be used with photolithographic methods. Polymers can also be functionalized by adding photosensitive side groups such as acrylates to make then light-sensitive. Small amounts of photoinitiators can be added to photosensitive polymers to initiate cross-linking of the polymer solution in the presence of light. Numerous micro and nano lithography processes including soft lithography [86], thermal embossing [87–91], step-and-flash lithography [87,92,93], and UV embossing [94–96] have been employed to fabricate polymer based microdevices.

“Soft polymers” have important properties that allow them to be micro- or nanomolded relatively easily into micro or nano devices. Microfabrication processes for manipulating elastomer materials like poly(dimethyl siloxane) (PDMS) are well developed [85]. PDMS materials have been used in numerous microdevices for biological applications for tissue scaffolds, micro-fluidic devices, microarrays, and biosensors [85]. Photosensitive polymer and thermal sensitive polymers allow for the materials to be micro- or nano molded using well-established micro- and nano- imprinting methods. Numerous photosensitive and temperature sensitive polymers are available that are inert materials for biological applications. There is a great deal of research being conducted in creating better micro- and nano- fabrication devices out of improved biomaterials for drug delivery, tissue engineering, and microarray, microchip, diagnostic devices. Important advancements in these areas of research will be highlighted below.

4. Applications

Integration of intelligent biomaterials into MEMs and NEMs based systems is one of the most promising avenues in the development of better diagnostic and treatment systems for pathophysiological conditions. The following section emphasizes current novel intelligent biomaterial based MEM and NEMs systems that have been developed for diagnostic sensing systems, drug delivery systems, and tissue engineering.

4.1 Diagnostic -Sensing Systems

The development of analytical systems like lab-on-a-chip, microfluidic devices, and microarrays systems have all been made possible by employing classical microfabrication techniques. The essential components of these systems are the sensors that can detect a specific entity in the environment. In the case of biosensors, the sensing elements need to be designed to interact and measure the specific biological molecules they are intended to detect.

Environmentally responsive hydrogels incorporated into microscale applications have been used as the sensing component for advance diagnostic sensing systems [5]. Very innovative

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

uses of responsive hydrogels for microfluidic systems have been reported by Beebe and collaborators [97–99]. Micropatterned pH sensitive hydrogels components were incorporated into microchannels to create microvalves that could sense environmental conditions with response times within 10 seconds [97].

More recently, Liang et al. [99] have developed novel adaptive liquid microlenses that are activated by pH responsive hydrogels to adjust the shape of the microlenses and provide focus similar to how the human eye focuses on different distances by placing a pH sensitive hydrogel ring within a microfluidic channel system between a glass plate and an aperture slip that has an opening centered over the hydrogel ring. The microchannels are filled with oil and water, so that the meniscus between the oil and water phase can be used as an optical lens. The curvature of this meniscus can be changed by adjusting its focal length when the stimuli-responsive hydrogel ring senses the presence of ions in the surrounding environment. At the micro length scale, surface tension and ionic diffusion are favorable the response times of the hydrogel occurs within ten to a few tens of seconds. The all-in-one microchannel microlens system design can easily be incorporated into arrays for medical diagnostics, sensing, and lab-on-a-chip technologies [99].

A large scale size-independent precise sensing detector was reported by Dickert et al. [100] by forming MIP hydrogels directly onto the surface of QCMs. These systems could differentiate between specific viruses and enzymes. By incorporating these MIP hydrogels onto microscale devices like microcantilevers, highly specific diagnostic systems and DDS systems could be developed [1,11,80,82,83]. Peppas and collaborators [101–105] have reported the development of a modified photolithography method to pattern pH-sensitive hydrogels onto silicon microcantilevers for the development of pH microsensors. Chip arrays were fabricated using this method that included different response-sensitive or MIP hydrogels on different cantilevers all within one chip. These multi-responsive, ultra-sensitive microsensor arrays have the potential to create implantable microdevices that could monitor a wide variety of biomolecule levels for therapeutic systems.

4.2. Drug Delivery Systems

Advancements in micro- and nano-fabrication technology have enhanced the ability to create better performing therapeutic delivery systems for a wide variety of biological applications. A number of successful implantable and oral drug delivery systems composed of silicon, glass, silicone elastomers (e.g., PDMS) and other polymers have been fabricated using standard microfabrication techniques [106–111]. Controlled release drug delivery is still an important challenge in the way pathophysiological conditions are treated. Microfabrication of bioMEMs devices for controlled release is a potential avenue to develop new treatment methods.

The two most used conventional drug administration methods are oral and parenteral delivery systems. The rate of drug delivery or the target area of the drug is not easily controlled using oral delivery and injection. In most delivery instances, the initial drug concentration after administration is above the toxicity level and then gradually diminishes over time to an insufficient therapeutic level. This is a very ineffective and potentially dangerous way of delivering drugs. The duration of the therapeutic efficacy is dependent on the frequency of administration and the half-life of the drug. High dosages of non-targeted drugs are often administered to achieve an effective blood concentration for treatment which could be damaging to the entire body [112]. Advancements in pharmacokinetics have led to the development of better, more sophisticated siRNA, protein, and DNA-based drugs. Most of these new drugs have a very narrow therapeutic window, and only small amounts of the drug is needed. Toxicity is experienced for concentration peaks and the therapeutic concentration range varies with time with most of these newly developed drugs, so that conventional drug

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

delivery methods are inefficient. The success of these agents depends on our ability to develop efficient and accurate delivery vehicles.

Conventional drug administration methods are also limited in providing long-term treatment, a narrow therapeutic window, complex dosing schedule, combination therapy, and personalization-based dosing [113]. To overcome these limitations, development of combination drug and medical device systems that have the ability to protect active ingredients, precisely control drug release kinetics (time of dose and the amount administered), and deliver multiple doses are required. New medical device and drug combination system also need to have the ability to be controlled and to adjust the release of therapeutic agents. This could be accomplished by integrating sensors and feedback sensors into the device. This helps eliminate the need for frequent injection or even surgery for implantable drug release systems [113].

Microfabricated devices allow for precise control over the surface microarchitecture, topography, and feature size. Biological agents can also be incorporated into microfabricated systems. Microfabrication technology is advantageous for development of drug delivery systems because it permits direct control in the size, shape, reservoir number, reservoir volume, unidirectional openings and surface characteristics, of the drug delivery system [112]. MEMs-based drug delivery systems have unique qualities that make them advantageous for drug delivery applications depending on there design. For reservoir type drug delivery, MEMs devices could supply a patient with exact amounts of therapeutic agent at specific times a day. This type of device would be useful for patients with chronic diseases that require constant administration of drugs like diabetes or Parkinson's. Current developments in micro- reservoir drug delivery system, along with specific application of microfabrication to develop microneedles for transdermal delivery will be presented below.

Top-down micro- and nanofabrication methods can also offer numerous advantages for the fabrication of micro- and nanoparticles over bottom up synthesis techniques. Top down manufacturing methods allow for multiple properties to be incorporated into the micro- and nanocarriers – like stimuli responsive components. Bottom-up synthesis methods including liposomes, micelles, and polymer particles formed using emulsion techniques produce carriers with polydisperse particle size, making their *in vitro* and *in vivo* release kinetics difficult to correlate. Top-down fabrication methods produce highly mono-disperse particles whose shape and size can also be controlled.

4.2.1. Reservoir Type Microchip Drug Delivery Systems—Microfabrication technology has produced a new sophisticated class of controlled release systems for therapeutic delivery based on programmable micro-devices. The small size, ability to integrate microelectronics, and their ability to store and release drugs on demand, makes them very attractive systems for controlled drug release [108]. Advancements in microfabrication technology and biosensors, implantable responsive drug release systems are becoming more realistic for medical applications.

Implantable drug delivery devices for administration of a precise amount of therapeutic agents at a specific time would be an important tool for treatment of numerous diseases that require repeat administration of drugs. There are some large limitations to implantable drug delivery devices. Since the device requires surgery for implantation it needs to have the ability to release drugs over a long period of time and therefore a large amount of drugs. Sufficient storage capacity for a chronic dosing routine and the most potent drugs require microgram quantities a day. If a device needs to have a lifetime of a year, a high concentration of drug will need to be stored in the device safety.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

The ideal implant system would protect the drug from the body until it is needed, allow continuous or time-specific delivery of therapeutic agents, and be controllable externally without surgery. These requirements can be achieved with microscale array of individually sealed reservoirs that could be open on command to release the therapeutic agent contained in the reservoir to the environment. Individual drug containing reservoir microchips designed for drug delivery applications have one important advantage over other designs: they have the ability to totally control drug delivery amount and timing via either continuous or palatial delivery. This design is also very flexible for numerous different applications, because its release characteristics can be governed independently by the release mechanism, drug formulation, or reservoir geometry.

Santini et al. [114] were the first group to fabricate a micro-reservoir microchip for drug delivery applications. The device was fabricated by the sequential processing of a silicon wafer using microelectronic processing techniques including UV photolithography, chemical vapor deposition, electron beam evaporation and reactive ion etching [114]. The fabricated prototype was 17mm by 17mm by 310 #m square silicon device containing an array of 34 square pyramidal reservoirs etched completely through a wafer [114]. Samples of 25 nL reservoirs were sealed at one end by a thin membrane of gold to serve as an anode in an electrochemical reaction. Electrodes were placed on the device to serve as a cathode. The reservoirs were filled through the open end by microsyringe pumps or inkjet printing in conjugation with a computer controlled alignment apparatus. The open end was then covered with a thin adhesive plastic and sealed with waterproof epoxy [114].

When the microfabricated reservoir system is submerged in an electrolyte solution, ions form a soluble complex with the anode material in its ionic form [108]. An applied electric potential oxidizes the anode membrane, forming a soluble complex with the electrolyte ions. The complex dissolves in the electrolyte, the membrane disappears, and the solution within the reservoir is released [108]. The release time from each individual reservoir is determined by the time at which the reservoir’s anode membrane is removed [108]

This first microchip reservoir system laid the foundation of current microchip reservoir systems. Current research on microchip drug delivery systems is focused on integrating active components including battery clocks, reference electrodes and biosensors to achieve a single package for simpler implantation [113]. Development of a passive polymer microchip that contains no electronics, power sources, or microprocessors is another important possibility for creating better drug delivery devices. Polymer microchips that are biodegradable are also a beneficial product because surgery would not be required to retrieve the device.

Self-contained drug delivery chips have been also developed. The microchip, hardware, power supply, electrical components, and wireless communication system are embedded and sealed inside the device. The microchip is composed of a silicon/glass bonded substrate containing 100 individual 300 nL reservoirs. Individual membranes cover each reservoir, and are made of platinum and titanium layers. The membranes covering a reservoir are removed by local resistive heating from an applied current [113]. The microCHIPS drug delivery systems have been shown to deliver a controlled pulsatile release of polypeptide leuprolide from specific reservoirs in a canine model for 6 months. This device is the first completely self-contained microchip implant that provides constant programmed delivery of therapeutic drugs.

A biodegradable polymer version multi-reservoir drug delivery systems consists of reservoirs covered with a restorable membranes [115]. The chemical composition or the physical properties of the membranes will vary their degradation time and, therefore, vary the release time of the therapeutic agent within the reservoir. These polymer devices and reservoirs are

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

made out of compressed-molding polylactic acid (PLA). The ratio of PLA and PGA and the molecular weight of the polymers are varied between membranes to control release[115].

4.2.2. Micro and nano –fabricated drug delivery carriers—Photolithography and micro and nano imprint lithography fabrication methods are promising alternatives for fabricating drug delivery carriers. Micro molding processes are well-developed and can easily be adjusted for fabricating well-defined two-dimensional and three-dimensional structures of varying shapes and sizes. Recently, the nano-imprinting process known as Step and Flash Imprint Lithography (S-FIL) was modified to fabricate environmentally sensitive nanocarriers of specific shape, size and aspect ratios [23]. The versatile S-FIL method allows for nanoscale features of specific shape and size to be fabricated out of UV crosslink able biomaterials. The mild process also allows sensitive bio-molecules like proteins and DNA to be incorporated into the nanoparticles [23]. DeSimone et al. have also demonstrated the ability to form nano-sized particles of various biological polymers using a particle nano-replication (PRINT) fabrication method [116]. Monodisperse features can be achieved using the PRINT method, making it a potential process for fabrication of micro and nano particles for drug delivery applications.

4.3. Tissue Engineering

The goal of tissue engineering is to grow living tissue and organs by using synthetic or natural materials scaffolds that have been fabricated or designed to elicit desirable cellular response. An important requirement of tissue engineering methods is that they provide cells with an environment that maintains their normal functionality. Biodegradable, resorbable, biocompatible materials are required for tissue engineering scaffolds, yet materials must also allow gas and fluid permeation through the scaffold to the cells. Scaffold chemistry and architecture will influence the function and outcome of engrafted cells [117]. Advancements in the architecture of tissue engineering scaffolds are also needed to improve tissue scaffolds.

Creating three-dimensional structures that best mimic the *in vivo* cellular microenvironment is vital for regeneration of tissues since biological tissue has a well-defined organization to it. Typical tissue scaffolds are formed by extrusion, melting, molding, or solvent casting processes. These methods do not allow for control of the size or shape of the microstructure. The structure's pores depend on the processing parameters such as the solvent in the phase separation, the leeching agents, gas foaming, woven fibers, and ice crystal formation and subsequent freeze-drying. Scaffolds fabricated through these processes lack uniformity and organization that is found in *in vivo* tissue. Standard microfabrication – molding processes would allow complete control over the architecture of the scaffold. Polymer molded scaffolds created using soft lithography methods can achieve feature resolution less that 10 μm which is vital since mammalian cells length scale is in that range [118,119].

There is also a great deal of work being conducted in utilizing microfabrication techniques to develop high-organized biodegradable polyester scaffolds for the regeneration of tissue [117, 120]. Poly(lactic acid), poly(glycolic acid), and PLA and PGA copolymers (PLGA) were the first biodegradable polymer used for developing tissue engineering applications. Soft lithography using PDMS elastomers as the microfabrication master mold is employed to fabricate PLGA scaffolds [117,121–124]. This method not only molds the PLGA into uniform structures and shapes that are defined by the master mold, but it also introduces porosity into the structure which is a property of *in vivo* tissue. The PLGA scaffold was formed with a line width of 50 #m and the size of the open square region being 300 #m on a side [117]. PLGA scaffolds do have some disadvantages associated with them. PLGA has rigid mechanical properties, undesirable bulk degradation kinetics, and limited biocompatibility in some applications [120].

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Bettinger et al. have recently started to develop three-dimensional tissue scaffold composed of poly(glycerol sebacate) (PGS) [119], a biocompatible and biodegradable elastomer, to overcome some of the limitations of PLGA scaffolds [120]. Biocompatibility studies demonstrated improved cellular response and morphology of PGS compared to PLGA. PGS is also a gas permeable (oxygen and carbon dioxide) material, which is a vital property for materials that will be in contact with mammalian cells for controlling a suitable cellular environment. The mechanical microenvironment is also critical to mimicking *in vivo* tissue. To address this issue, Bettinger et al. has developed a network of micro-molded PGS single layer microfluidic scaffolds stacked and bonded to create a three-dimensional scaffold network with high spatial densities of microchannels.

Synthetic hydrogels were some of the first materials utilized for the development of tissue engineering scaffolds [120]. Hydrogels are attractive for tissue engineering applications because of their high biocompatibility, hydrophilicity, and tissue-like architecture. Hydrogel materials give researchers the ability to incorporate physical properties into devices to obtain the necessary physiological responses such as encapsulating growth factors into the hydrogel to promote growth and proliferation of cells. Poly(lactic acid)-g-poly(vinyl alcohol) (PLA-g-PVA) hydrogels have been developed for heart valve replacement and promotion of cell grow onto the valve [66].

More recently, hybrid biomaterials have been used for tissue engineering applications. These polymers are conjugated or functionalized with peptides or proteins that offer special properties to the material to elicit specific biological responses. For example, mixtures of peptides and synthetic polymers are combined in order to better imitate natural extracellular matrix. These materials can be used to promote wound healing while reducing the formation of fibrous encapsulation. Peptide sequences from fibronectin and collagen like RGD has also been incorporated into tissue engineering scaffolds to promote cell proliferation [74].

Hydrogel materials have been used for better tissue engineering scaffolds because of their ability to provide structural support and high tissue density while still maintaining an environment similar to that found *in vivo*. Numerous water-swollen polymers can be formed in relatively mild conditions so that cells can be directly incorporated into the hydrogel during the curing process [125].

PEG-based hydrogels are very attractive for creating cell encapsulated hydrogels because of their biocompatibility, hydrophilicity, and the ability to adjust the hydrogel architecture by changing the chain length to tailor transport properties [4]. These hydrogels have been shown to encapsulate vascular smooth muscle cells [19], chondrocytes [59,126], fibroblast [22,60], osteoblast [61] and embryonic carcinoma (EC) cells [127]. PEG hydrogels are also flexible materials that allow the integration of adhesion promoting extracellular matrix proteins, growth factors to adjust cell function, and degradable linkages to make the hydrogel biodegradable over certain time periods [19,60,61,66,68,69,75,76,128].

Photopolymerization of hydrogels for the development of tissue engineering is a growing field due to their chemical flexibility to customize for specific biological applications. Photosensitive polymer – cell hybrid hydrogels can be formed using the same basic UV micro-molding techniques. In this method, live cells suspended in a polymer solution are photoimmobilized in a controlled hydrogel structure. The uncross-linked polymer and cells are then rinsed away; the process can be repeated numerous times to build up 3D cellular hydrogel scaffolds. Hydrogel features as small as 50 μm containing cells have been fabricated [129]. Recently, S-FIL was utilized to create nanopatterned surfaces for studying cell behavior on nano feature surfaces [130].

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

A number of natural materials have been also incorporated into hydrogel structures for tissue engineering applications including collagen, hyaluronic acid [131] [132,133], alginate, and chitosan [134–136]. Biological hydrogels like fibrin and collagen have also be explored for encapsulating cells. Hubbell and colleagues have functionalized fibrin gels to promote cell adhesion and proteolytic remodeling [57,58,67,127]. Tan et al. [137] have constructed collagen gels containing cells by using microfluidic molding methods. These biological materials may be useful for regeneration of single layer tissues but 3D architectures are difficult to achieve because of the constraints of microfluidic network on a flat surface. Recently, Hubbell and collaborators have demonstrated that 3D MMP-sensitive PEG based hydrogels can directly differentiate embryonal carcinoma (EC) cells to express early cardiac transcription factors. The soft PEG based hydrogel matrices mimics the elasticity of embryonic cardiac tissues, facilitating differentiation of pluripotent cardioprogenitors [127]. These 3D biomimetic hydrogels are promising alternatives to natural matrices for the production of cardiac tissue structures for therapeutic applications.

Development of better biomaterials that elicit a more desirable response from cells is progressing toward the goal of complete tissue and organ regeneration. There is a large amount of research being conducted to create better scaffold chemistry by developing new polymer materials like PGS [119] and creating polymer/cell hydrogel hybrids. UV and thermal micro-molding techniques can be used to create well-organized scaffold that better model *in vitro* cells. The combination of new biomaterials and microfabrication methods show promise as means of creating functional tissues and organs.

4.4 Recognitive Systems

Novel imprinted chronotherapeutic systems are particularly promising when trying to regulate overexpressed peptides or proteins. Angiotensin II is an example of peptide that is often overexpressed and has benefited from such a therapeutic system. The renin-angiotensin-aldosterone system (RAS) is a well defined complex regulatory system with many identifiable actions. However it is best known for being a regulatory system for the conservation of salt and blood volume, and the preservation of blood pressure. The major end product of the RAS cascade is angiotensin II. Angiotensin II is the active form of angiotensin I. Angiotensin I is first cleaved by an angiotensin converting enzyme (ACE) which creates angiotensin II. Angiotensin II then acts on either type 1 or type 2 angiotensin receptors.

Angiotensin II is an octapeptide with the following structure: asp-arg-val-tyr-ile-his-pro-phe. It is naturally cleaved by three aminopeptidases in the body which are call aminopeptidase A, B, and C. Aminopeptidase C cleaves the angiotensin II between the seventh and eighth amino acid to create angiotensin. It is this form of angiotensin that counteracts the effects of the angiotensin II. The most common way to treat a patient who displays an overexpression of angiotensin II is to administer ACE inhibitors or angiotensin receptor blockers (ARBs). However both these treatments often have several side effects including birth defects, elevated potassium levels, cough, and dizziness. Extreme side effects include kidney failure and decrease of white blood cells [53].

By explicitly choosing components and tailoring reaction conditions it was possible to effectively design a polymer network that was specifically imprinted for an Angiotensin II and subsequent release of pressure reducing agents. These polymer networks were able to rapidly recognize the biological molecules in physiological conditions [138].

5. Conclusions and Future Perspectives

Advance medical treatments for a wide variety of pathophysiological conditions require more than the development of better pharmaceutical medicines, but also the development of

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

intelligent therapeutics that can sense, respond, and release therapeutic agents or diagnostic agents. Environmental and biomolecular responsive polymers and specifically hydrogels have been widely studied over the past couple of decades but their clinical success still relies on how they interact in a biological host. The integration of responsive and molecular recognition hydrogel-based materials into micro- and nano scale systems is one of the most promising avenues towards the development of the next generation drug delivery, tissue regeneration, and biosensor systems.

Micro- and nanotechnology offers new opportunities to mimic biological systems. Micro and nano material devices for tissue engineering, drug and gene delivery, cellular monitoring biosensors, as well as micro- and nanomanupulation for altering of surfaces all have the possibility to profoundly impact current therapeutic methods. We expect that such developments will provide a significant increase of the scope and application of such systems in drug delivery and the general therapeutic fields.

The growing applications of lithographic technologies like nanoimprint lithography have the possible to make nanoscale engineering a powerful tool for the development of biological applications. Micro- and nanofabrication technology can be used for molding of a variety of polymers, including responsive hydrogels, at a high-throughput, low-cost production, which is necessary for successful integrations into clinical applications. Recent research critically analyzed here exhibits how the synthesis of responsive hydrogel biomaterials, improvement of nano imprint lithography methodology, and the combination of the two can lead to development of multi-functional drug delivery, tissue engineering, and biosensors systems.

Controlled drug delivery systems have already made an enormous impact on the medical field with over a million patients a year using a form of controlled release system or another. Despite the success of controlled release systems there are still significant challenges remaining to make next generation drug delivery systems that can target and respond to specific diseased conditions. These challenges have only sparked increasing interest in the biomedical field. Environmental and biomolecular responsive hydrogels have been widely evaluated over the past couple of decades and have demonstrated promising results towards the development of intelligent biomaterials for DDS and biosensors. The facile design and fabrication of hydrogel materials render them incredibly versatile, allowing them to be modified with biomolecules relatively easily. This adaptability of hydrogel based materials makes them a powerful tool for the development of therapeutic systems that can be easily modified by changing the bio-molecule or molecular configuration within the hydrogel to be sensitive for the specific disease of interest.

The development of intelligent therapeutic and diagnostic systems has transformed the research field of controlled drug delivery, tissue engineering, and biosensors. Within the next couple of years, a significant amount of these intelligient therapeutic systems will start pre-clinical trials for FDA approval. Intelligent therapeutic systems that are fabricated using nano lithography fabricated processes have the possibility to perform better in clinical trials because multiple components can be incorporated into nanoscale features in one fabrication step making it a high-throughput, low-cost production, which is necessary for successful integrations into clinical applications.

Ultimately, we believe that this growing need in the medical field for devices that can provide patients with custom doses of a therapeutic agent in response to external triggers or biomarkers will be a new field of endeavor of drug delivery. More importantly, these devices will be “intelligent” and will release the drug when the patient is in need of its therapeutic effects.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Acknowledgments

Work discussed here was supported in part by grants from the National Science Foundation and the National Institutes of Health (grant EB-000246). MCM is a National Science Foundation Fellow.

References

1. Hilt JZ, Khademhosseini A, Langer R, Peppas NA. Hydrogels in Biology and Medicine: From Molecular Principles to Bionanotechnology. Adv Mater 2006;18:1345–1360.
2. Langer R, Peppas NA. Advances in Biomaterials, Drug Delivery, and Bionanotechnology. AIChE Journal 2003;49:2990–3006.
3. Carr DA, Peppas NA. Molecular Structure of Physiologically-Responsive Hydrogels Controls Diffusive Behavior. Macromol Biosci 2009;9:497–505. [PubMed: 19016502]
4. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in Pharmaceutical Formulations. Eur J Pharm Biopharm 2000;50:27–46. [PubMed: 10840191]
5. Byrne ME, Park K, Peppas NA. Molecular Imprinting within Hydrogels. Adv Drug Deliv Rev 2002;54:149–161. [PubMed: 11755710]
6. Brazel CS, Peppas NA. Synthesis and Characterization of Thermo- and Chemomechanically Responsive Poly(N-Isopropylacrylamide-Co-Methacrylic Acid) Hydrogels. Macromolcules 1995;28:8016–8020.
7. Podual K, Doyle FJ, Peppas NA. Glucose-Sensitivity of Glucose Oxidase-Containing Cationic Copolymer Hydrogels Having Poly(Ethylene Glycol) Grafts. J Controlled Release 2000;67:9–17.
8. Lowman AM, Morishita M, Kajita M, Nagai T, Peppas NA. Oral Delivery of Insulin Using Ph-Responsive Complexation Gels. Journal of Pharm Sci 1999:933–937. [PubMed: 10479357]
9. Wood KM, Stone G, Peppas NA. Lectin Functionalized Complexation Hydrogels for Oral Protein Delivery. J Controlled Release 2006;116:e66–e68.
10. Wood KM, Stone GM, Peppas NA. Wheat Germ Agglutinin Functionalized Complexation Hydrogels for Oral Insulin Delivery. Biomacromolcules. 2008
11. Byrne ME, Hilt JZ, Peppas NA. Recognitive Biomimetic Networks with Moiety Imprinting for Intelligent Drug Delivery. J Biomed Mater Res A 2008;84A:137–147. [PubMed: 17600334]
12. Owens DE III, Eby JK, Jian Y, Peppas NA. Temperature-Responsive Polymer-Gold Nanocomposites as Intelligent Therapeutic Systems. J Biomed Mater Res A 2007;83A:692–695. [PubMed: 17530631]
13. Daniel AC, Nicholas AP. Assessment of Poly(Methacrylic Acid-Co-N-Vinyl Pyrrolidone) as a Carrier for the Oral Delivery of Therapeutic Proteins Using Caco-2 and Ht29-Mtx Cell Lines. J Biomed Mater Res A. 200910.1002/jbm.a.32395: pPublished Online: Feb 11 2009
14. Wood, KM.; Stone, GM.; Peppas, NA. Acta Biomater. The Effect of Complexation Hydrogels on Insulin Transport in Intestinal Epithelial Cell Models. In Press, Uncorrected Proof
15. Wood K, Stone G, Peppas NA. Insulin Transport in Caco-2 and Caco2/Ht29-Mtx Co-Cultured Cells in the Presence of Wheat Germ Agglutinin Functionalized Complexation Hydrogels. Acta Biomater. Published on line May 28, 2009
16. Miyata T, Uragami T, Nakamae K. Biomolecule-Sensitive Hydrogels. Adv Drug Deliv Rev 2002;54:79–98. [PubMed: 11755707]
17. Qiu Y, Park K. Environment-Sensitive Hydrogels for Drug Delivery. Adv Drug Deliv Rev 2001;53:321–339. [PubMed: 11744175]
18. Lutolf MP, Lauer-Fields JL, Schmoekel HG, Metters AT, Weber FE, Fields GB, Hubbell JA. Synthetic Matrix Metalloproteinase-Sensitive Hydrogels for the Conduction of Tissue Regeneration: Engineering Cell-Invasion Characteristics. PNAS 2003;100:5413–5418. [PubMed: 12686696]
19. Mann BK, Gobin AS, Tsai AT, Schmedlen RH, West JL. Smooth Muscle Cell Growth in Photopolymerized Hydrogels with Cell Adhesive and Proteolytically Degradable Domains: Synthetic Ecm Analogs for Tissue Engineering. Biomaterials 2001;22:3045–3051. [PubMed: 11575479]
20. Seliktar D, Zisch AH, Lutolf MP, Wrana JL, Hubbell JA. Mmp-2 Sensitive, Vegf-Bearing Bioactive Hydrogels for Promotion of Vascular Healing. J Biomed Mater Res A 2004;68A:704–716. [PubMed: 14986325]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

21. Lutolf MP, Weber FE, Schmoekel HG, Schense JC, Kohler T, Muller R, Hubbell JA. Repair of Bone Defects Using Synthetic Mimetics of Collagenous Extracellular Matrices. Nat Biotech 2003;21:513–518.
22. Gobin AS, West JL. Cell Migration through Defined, Synthetic Ecm Analogs. The FASEB Journal: Official Publication Of The Federation Of American Societies For Experimental Biology 2002;16:751–753. [PubMed: 11923220]
23. Glangchai LC, Caldorera-Moore M, Shi L, Roy K. Nanoimprint Lithography Based Fabrication of Shape-Specific, Enzymatically-Triggered Smart Nanoparticles. J Controlled Release 2008;125:263–272.
24. Bikram M, Gobin AM, Whitmire RE, West JL. Temperature-Sensitive Hydrogels with Sio2-Au Nanoshells for Controlled Drug Delivery. J Controlled Release 2007;123:219–227.
25. Bergmann NM, Peppas NA. Configurational Biomimetic Imprinting for Protein Recognition: Structural Characteristics of Recognitive Hydrogels. Ind Eng Chem Res 2008;47:9099–9107.
26. Gershon D. Microarray Technology: An Array of Opportunities. Nature 2002;416:885–891. [PubMed: 11976691]
27. Thorsen T, Maerkl SJ, Quake SR. Microfluidic Large-Scale Integration. Science 2002;298:580–584. [PubMed: 12351675]
28. Langer R, Tirrell DA. Designing Materials for Biology and Medicine. Nature 2004;428:487–492. [PubMed: 15057821]
29. Brannon-Peppas L. Biomaterial Polymers in Controlled Drug Delivery. Medical Plastics and Biomaterials Magazine. 1997
30. Torres-Lugo M, Peppas NA. Molecular Design and in Vitro Studies of Novel Ph-Sensitive Hydrogels for the Oral Delivery of Calcitonin. Macromolecules 1999;32:6646–6651.
31. Brannon-Peppas L, Peppas NA. Equilibrium Swelling Behavior of Ph-Sensitive Hydrogels. Chem Eng Sci 1991;46:715–22.
32. Chen SC, Wu YC, Mi FL, Lin YH, Yu LC, Sung HW. A Novel Ph-Sensitive Hydrogel Composed of N,O-Carboxymethyl Chitosan and Alginate Cross-Linked by Genipin for Protein Drug Delivery. J Controlled Release 2004;96:285–300.
33. Akala EO, Kopecková P, Kopecek J. Novel Ph-Sensitive Hydrogels with Adjustable Swelling Kinetics. Biomaterials 1998;19:1037–1047. [PubMed: 9692802]
34. Wu J, Su ZG, Ma GH. A Thermo- and Ph-Sensitive Hydrogel Composed of Quaternized Chitosan/Glycerophosphate. Int J Pharm 2006;315:1–11. [PubMed: 16616819]
35. Mao J, McShane MJ. Transduction of Volume Change in Ph-Sensitive Hydrogels with Resonance Energy Transfer. Adv Mater 2006;18:2289–2293.
36. Betancourt T, Brown B, Brannon-Peppas L. Doxorubicin-Loaded Plga Nanoparticles by Nanoprecipitation: Preparation, Characterization and Inâ vitro Evaluation. Nanomedicine 2007;2:219–232. [PubMed: 17716122]
37. Peppas NA, Kavimandan NJ. Nanoscale Analysis of Protein and Peptide Absorption: Insulin Absorption Using Complexation and Ph-Sensitive Hydrogels as Delivery Vehicles. Eur J Pharm Sci 2006;29:183–197. [PubMed: 16777391]
38. Berger J, Reist M, Mayer JM, Felt O, Peppas NA, Gurny R. Structure and Interactions in Covalently and Ionically Crosslinked Chitosan Hydrogels for Biomedical Applications. Eur J Pharm Biopharm 2004;57:19–34. [PubMed: 14729078]
39. Serra L, Doménech J, Peppas NA. Drug Transport Mechanisms and Release Kinetics from Molecularly Designed Poly(Acrylic Acid-G-Ethylene Glycol) Hydrogels. Biomaterials 2006;27:5440–5451. [PubMed: 16828864]
40. Farmer TG, Edgar TF, Peppas NA. In Vivo Simulations of the Intravenous Dynamics of Submicrometer Particles of Ph-Responsive Cationic Hydrogels in Diabetic Patients. Ind Eng Chem Res 2008;47:10053–10063.
41. Besheer A, Wood KM, Peppas NA, Mäder K. Loading and Mobility of Spin-Labeled Insulin in Physiologically Responsive Complexation Hydrogels Intended for Oral Administration. J of Controlled Release 2006;111:73–80.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

42. Kamei N, Morishita M, Chiba H, Kavimandan NJ, Peppas NA, Takayama K. Complexation Hydrogels for Intestinal Delivery of Interferon [Beta] and Calcitonin. J of Controlled Release 2009;134:98–102.
43. Serra L, Doménech J, Peppas NA. Engineering Design and Molecular Dynamics of Mucoadhesive Drug Delivery Systems as Targeting Agents. Eur J Pharm Biopharm 2009;71:519–528. [PubMed: 18976706]
44. Urech L, Bittermann AG, Hubbell JA, Hall H. Mechanical Properties, Proteolytic Degradability and Biological Modifications Affect Angiogenic Process Extension into Native and Modified Fibrin Matrices in Vitro. Biomaterials 2005;26:1369–1379. [PubMed: 15482824]
45. Ehrbar M, Metters A, Zammaretti P, Hubbell JA, Zisch AH. Endothelial Cell Proliferation and Progenitor Maturation by Fibrin-Bound Vegf Variants with Differential Susceptibilities to Local Cellular Activity. J of Controlled Release 2005;101:93–109.
46. Betancourt JPT, Soo K, Peppas NA. Characterization of Ph-Responsive Hydrogels of Poly(Itaconic Acid)-G-Poly(Ethylene Glycol) Prepared by Uv-Initiated Free Radical Polymerization as Biomaterials for Oral Delivery of Biological Compounds. J Biomed Mater Res. 200910.1002/jbm.a.32510Published on line June 17, 2009
47. Park TG, Hoffman AS. Synthesis and Characterization of Ph- and/or Temperature-Sensitive Hydrogels. J Appl Polym Sci 1992;46:659–671.
48. Kim S, Healy KE. Synthesis and Characterization of Injectable Poly(Isopropylacrylamide-Co-Acrylic Acid) Hydrogels with Proteolytically Degradable Cross-Links. Biomacromolecules 2003;4:1214–1223. [PubMed: 12959586]
49. Qiu Y, Park K. Environment-Sensitive Hydrogels for Drug Delivery. Adv Drug Deliv Rev 2001;53:321–39. [PubMed: 11744175]
50. Zhang J, Peppas NA. Synthesis and Characterization of Ph- and Temperature-Sensitive Poly (Methacrylic Acid)/Poly(N-Isopropylacrylamide) Interpenetrating Polymeric Networks. Macromolecules 2000;33:102–107.
51. Ramanan RMK, Chellamuthu P, Tang L, Nguyen KT. Development of a Temperature-Sensitive Composite Hydrogel for Drug Delivery Applications. Biotechnol Prog 2006;22:118–125. [PubMed: 16454501]
52. Liang HF, Hong MH, Ho RM, Chung CK, Lin YH, Chen CH, Sung HW. Novel Method Using a Temperature-Sensitive Polymer (Methylcellulose) to Thermally Gel Aqueous Alginate as a Ph-Sensitive Hydrogel. Biomacromolecules 2004;5:1917–1925. [PubMed: 15360306]
53. He C, Kim SW, Lee DS. In Situ Gelling Stimuli-Sensitive Block Copolymer Hydrogels for Drug Delivery. J Controlled Release 2008;127:189–207.
54. Park TG. Temperature Modulated Protein Release from Ph/Temperature-Sensitive Hydrogels. Biomaterials 1999;20:517–521. [PubMed: 10213354]
55. Anseth KS, Metters AT, Bryant SJ, Martens PJ, Elisseeff JH, Bowman CN. In Situ Forming Degradable Networks and Their Application in Tissue Engineering and Drug Delivery. J Control Release 2002;78:199–209. [PubMed: 11772461]
56. Farokhzad OC, Jon S, Khademhosseini A, Tran TNT, LaVan DA, Langer R. Nanoparticle-Aptamer Bioconjugates: A New Approach for Targeting Prostate Cancer Cells. Cancer Res 2004;64:7668–7672. [PubMed: 15520166]
57. Halstenberg S, Panitch A, Rizzi S, Hall H, Hubbell JA. Biologically Engineered Protein-Graft-Poly (Ethylene Glycol) Hydrogels: A Cell Adhesive and Plasmin-Degradable Biosynthetic Material for Tissue Repair. Biomacromolecules 2002;3:710–723. [PubMed: 12099815]
58. Lutolf MP, Lauer-Fields JL, Schmoekel HG, Metters AT, Weber FE, Fields GB, Hubbell JA. Synthetic Matrix Metalloproteinase-Sensitive Hydrogels for the Conduction of Tissue Regeneration: Engineering Cell-Invasion Characteristics. Proceedings of the National Academy of Sciences of the United States of America 2003;100:5413–5418. [PubMed: 12686696]
59. Bryant SJ, Anseth KS. Hydrogel Properties Influence Ecm Production by Chondrocytes Photoencapsulated in Poly(Ethylene Glycol) Hydrogels. J Biomed Mater Res 2002;59:63–72. [PubMed: 11745538]
60. Hern DL, Hubbell JA. Incorporation of Adhesion Peptides into Nonadhesive Hydrogels Useful for Tissue Resurfacing. J Biomed Mater Res 1998;39:266–276. [PubMed: 9457557]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

61. Behravesh E, Zygourakis K, Mikos AG. Adhesion and Migration of Marrow-Derived Osteoblasts on Injectable in Situ Crosslinkable Poly(Propylene Fumarate-Co-Ethylene Glycol)-Based Hydrogels with a Covalently Linked Rgds Peptide. J Biomed Mater Res A 2003;65:260–270. [PubMed: 12734821]

62. Lutolf MP, Weber FE, Schmoekel HG, Schense JC, Kohler T, Muller R, Hubbell JA. Repair of Bone Defects Using Synthetic Mimetics of Collagenous Extracellular Matrices. Nat Biotechnol 2003;21:513–8. [PubMed: 12704396]

63. Park Y, Lutolf MP, Hubbell JA, Hunziker EB, Wong M. Bovine Primary Chondrocyte Culture in Synthetic Matrix Metalloproteinase-Sensitive Poly(Ethylene Glycol)-Based Hydrogels as a Scaffold for Cartilage Repair. Tissue Eng 2004;10:515–22. [PubMed: 15165468]

64. Seliktar D, Zisch AH, Lutolf MP, Wrana JL, Hubbell JA. Mmp-2 Sensitive, Vegf-Bearing Bioactive Hydrogels for Promotion of Vascular Healing. J Biomed Mater Res A 2004;68:704–16. [PubMed: 14986325]

65. Ebru Oral NAP. Responsive and Recognitive Hydrogels Using Star Polymers. J Biomed Mater Res, A 2004;68A:439–447. [PubMed: 14762923]

66. Nuttelman CR, Henry SM, Anseth KS. Synthesis and Characterization of Photocrosslinkable, Degradable Poly(Vinyl Alcohol)-Based Tissue Engineering Scaffolds. Biomaterials 2002;23:3617–3626. [PubMed: 12109687]

67. Sakiyama SE, Schense JC, Hubbell JA. Incorporation of Heparin-Binding Peptides into Fibrin Gels Enhances Neurite Extension: An Example of Designer Matrices in Tissue Engineering. FASEB Journal 1999;13:2214–2224. [PubMed: 10593869]

68. Kao WJ, Hubbell JA. Murine Macrophage Behavior on Peptide-Grafted Polyethyleneglycol-Containing Networks. Biotechnol and Bioeng 1998;59:2–9.

69. Sawhney AS, Pathak CP, Van Rensburg JJ, Dunn RC, Hubbell JA. Optimization of Photopolymerized Bioerodible Hydrogel Properties for Adhesion Prevention. J Biomed Mater Res 1994;28:831–838. [PubMed: 8083251]

70. Bryant SJ, Bender RJ, Durand KL, Anseth KS. Encapsulating Chondrocytes in Degrading Peg Hydrogels with High Modulus: Engineering Gel Structural Changes to Facilitate Cartilaginous Tissue Production. Biotechnol Bioeng 2004;86:747–55. [PubMed: 15162450]

71. Gonzalez AL, Gobin AS, West JL, McIntire LV, Smith CW. Integrin Interactions with Immobilized Peptides in Polyethylene Glycol Diacrylate Hydrogels. Tissue Eng 2004;10:1775–86. [PubMed: 15684686]

72. Martens PJ, Bryant SJ, Anseth KS. Tailoring the Degradation of Hydrogels Formed from Multivinyl Poly(Ethylene Glycol) and Poly(Vinyl Alcohol) Macromers for Cartilage Tissue Engineering. Biomacromolecules 2003;4:283–92. [PubMed: 12625723]

73. Weber FE, Lutolf MP, Schmokel HG, Gratz KW, Hubbell JA. Synthetic Rhbmp-2 Delivery Systems: From Surface Erosion to Cell Triggered Rhbmp Release. European Cells and Materials 2003;5:33.

74. Hersel U, Dahmen C, Kessler H. Rgd Modified Polymers: Biomaterials for Stimulated Cell Adhesion and Beyond. Biomaterials 2003;24:4385–4415. [PubMed: 12922151]

75. Koo LY, Irvine DJ, Mayes AM, Lauffenburger DA, Griffith LG. Co-Regulation of Cell Adhesion by Nanoscale Rgd Organization and Mechanical Stimulus. J Cell Sci 2002;115:1423–1433. [PubMed: 11896190]

76. Schmedlen RH, Masters KS, West JL. Photocrosslinkable Polyvinyl Alcohol Hydrogels That Can Be Modified with Cell Adhesion Peptides for Use in Tissue Engineering. Biomaterials 2002;23:4325–4332. [PubMed: 12219822]

77. Gobin AS, West JL. Cell Migration through Defined, Synthetic Ecm Analogs. Faseb J 2002;16:751–3. [PubMed: 11923220]

78. Jun HW, West JL. Modification of Polyurethaneurea with Peg and Yigsr Peptide to Enhance Endothelialization without Platelet Adhesion. J Biomed Mater Res B Appl Biomater 2005;72:131–9. [PubMed: 15389489]

79. Ye L, Mosbach K. Molecularly Imprinted Microspheres as Antibody Binding Mimics. React Funct Polym 2001;48:149–157.

80. Hilt JZ, Byrne ME. Configurational Biomimesis in Drug Delivery: Molecular Imprinting of Biologically Significant Molecules. Adv Drug Deliv Rev 2004;56:1599–1620. [PubMed: 15350291]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

81. Spizzirri UG, Peppas NA. Structural Analysis and Diffusional Behavior of Molecularly Imprinted Polymer Networks for Cholesterol Recognition. Chem Mater 2005;17:6719–6727.
82. Hilt JZ, Byrne ME, Peppas NA. Microfabrication of Intelligent Biomimetic Networks for Recognition of D-Glucose. Chem Mater 2006;18:5869–5875.
83. Byrne ME, Oral E, Hilt JZ, Peppas NA. Networks for Recognition of Biomolecules: Molecular Imprinting and Micropatterning Poly(Ethylene Glycol)- Containing Films. Polym Adv Technol 2002;13:798–816.
84. Bergmann NM, Peppas NA. Molecularly Imprinted Polymers with Specific Recognition for Macromolecules and Proteins. Prog Polym Sci 2008;33:271–288.
85. Manz, A.; Becker, H. Microsystem Technology in Chemistry and Life Sciences. New York: Springer; 1999.
86. Xia Y, Whitesides GM. Soft Lithography. Angew Chem, Int Ed 1998;37:550–575.
87. Resnick DJ, Sreenivasan SV, Wilson CG. Step and Flash Imprint Lithography. Materials Today 2005:34–42.
88. Koh WG, Revzin A, Pishko MV. Poly(Ethylene Glycol) Hydrogel Microstructures Encapsulating Living Cells. Langmuir 2002;18:2459–2462. [PubMed: 12088033]
89. Stephen YC, Peter RK, Preston JR. Imprint of Sub-25 Nm Vias and Trenches in Polymers. Appl Phys Lett 1995;67:3114–3116.
90. Chou SY, Krauss PR, Renstrom PJ. Imprint Lithography with 25-Nanometer Resolution. Science 1996;272:85–87.
91. Bacher W, Bade K, Matthis B, Saumer M, Schwarz R. Fabrication of Liga Mold Inserts. Microsystem Technologies 1998;4:117–119.
92. Matthew C, Annette G, Byung Jin C, Marie A, Todd B, Sreenivasan SV, John GE, Willson CG. Patterning Nonflat Substrates with a Low Pressure, Room Temperature, Imprint Lithography Process. Journal of Vacuum Science & Technology B: Microelectronics and Nanometer Structures 2001;19:2162–2172.
93. Jan, H.; Martin, V.; Kees van den, H.; Jan van den, B. Mold-Assisted Nanolithography: A Process for Reliable Pattern Replication. AVS; 1996.
94. Bender M, Otto M, Hadam B, Vratzov B, Spangenberg B, Kurz H. Fabrication of Nanostructures Using a Uv-Based Imprint Technique. Microelectronic Engineering 2000;53:233–236.
95. Gale MT. Replication Techniques for Diffractive Optical Elements. Microelectronic Engineering 1997;34:321–339.
96. Shvartsman FP. Holographic Optical Elements by Dry Photopolymer Embossing. SPIE 1991;1461:313–320.
97. Beebe DJ, Moore JS, Bauer JM, Yu Q, Liu RH, Devadoss C, Jo BH. Functional Hydrogel Structures for Autonomous Flow Control inside Microfluidic Channels. Nature 2000;404:588–590. [PubMed: 10766238]
98. Johnson BD, Beebe DJ, Crone WC. Effects of Swelling on the Mechanical Properties of a Ph-Sensitive Hydrogel for Use in Microfluidic Devices. Mater Sci Eng, C 2004;24:575–581.
99. Dong L, Agarwal AK, Beebe DJ, Jiang H. Adaptive Liquid Microlenses Activated by Stimuli-Responsive Hydrogels. Nature 2006;442:551–554. [PubMed: 16885981]
100. Dickert FL, Hayden O, Lieberzeit P, Haderspoeck C, Bindeus R, Palfinger C, Wirl B. Nano- and Micro-Structuring of Sensor Materials--from Molecule to Cell Detection. Synthetic Metals 2003;138:65–69.
101. Byrne M, Oral E, Hilt J, Peppas N. Networks for Recognition of Biomolecules: Molecular Imprinting and Micropatterning Poly(Ethylene Glycol)-Containing Films. Polym Adv Technol 2002;13:798–816.
102. PNA. Intelligent Biomaterials as Pharmaceutical Carriers in Microfabricated and Nanoscale Devices. Mater Res Soc Bull 2006;31:888–93.
103. Jennifer HW, Rashid B, Nicholas AP. Micropatterning of Biomedical Polymer Surfaces by Novel Uv Polymerization Techniques. J Biomed Mater Res 2001;56:351–360. [PubMed: 11372052]
104. Bashir HJR, Elibol O, Gupta A, Peppas N. Micromechanical Cantilever as an Ultrasensitive Ph Microsensor. Appl Phys Lett 2002;81:3091–3.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

105. Hilt JZ, Gupta AK, Bashir R, Peppas NA. Ultrasensitive Biomems Sensors Based on Microcantilevers Patterned with Environmentally Responsive Hydrogels. Biomedical Microdevices 2003;5:177–184.
106. Desai TA, Wen Hwa C, Tu JK, Beattie GM, Hayek A, Ferrari M. Microfabricated Immunoisolating Biocapsules. Biotechnol Bioeng 1998;57:118–120. [PubMed: 10099185]
107. Lu Y, Chen SC. Micro and Nano-Fabrication of Biodegradable Polymers for Drug Delivery. Adv Drug Deliv Rev 2004;56:1621–1633. [PubMed: 15350292]
108. Santini JT Jr, Richards AC, Scheidt R, Cima MJ, Langer R. Microchips as Controlled Drug-Delivery Devices. Angewandte Chemie - International Edition 2000;39:2396–2407.
109. Ahmed A, Bonner C, Desai TA. Bioadhesive Microdevices with Multiple Reservoirs: A New Platform for Oral Drug Delivery. J Controlled Release 2002;81:291–306.
110. Reed ML, Wu C, Kneller J, Watkins S, Vorp DA, Nadeem A, Weiss LE, Rebello K, Mescher M, Smith AJC, Rosenblum W, Feldman MD. Micromechanical Devices for Intravascular Drug Delivery. J Pharm Sci 1998;87:1387–1394. [PubMed: 9811495]
111. James LW, Amit K, Hans AB, Enoch K, George MW. Microcontact Printing of Self-Assembled Monolayers: Applications in Microfabrication. Nanotechnology 1996;7:452.
112. Tao SL, Desai TA. Microfabricated Drug Delivery Systems: From Particles to Pores. Adv Drug Deliv Rev 2003;55:315–328. [PubMed: 12628319]
113. Mark S, Karen D, Michael JC, Robert L. Application of Micro- and Nano-Electromechanical Devices to Drug Delivery. Pharm Res 2006;V23:847–863.
114. Santini JT Jr, Cima MJ, Langer R. A Controlled-Release Microchip. Nature 1999;397:335–338. [PubMed: 9988626]
115. Leoni L, Boiarski A, Desai TA. Characterization of Nanoporous Membranes for Immunoisolation: Diffusion Properties and Tissue Effects. Biomedical Microdevices 2002;4:131–139.
116. Rolland JP, Maynor BW, Euliss LE, Exner AE, Denison GM, DeSimone JM. Direct Fabrication and Harvesting of Monodisperse, Shape-Specific Nanobiomaterials. J Am Chem Soc 2005;127:10096–10100. [PubMed: 16011375]
117. Vozzi G, Flaim C, Ahluwalia A, Bhatia S. Fabrication of Plga Scaffolds Using Soft Lithography and Microsyringe Deposition. Biomaterials 2003;24:2533–2540. [PubMed: 12695080]
118. Mapili G, Lu Y, Chen S, Roy K. Laser-Layered Microfabrication of Spatially Patterned Functionalized Tissue-Engineering Scaffolds. J Biomed Mater Res B Appl Biomater 2005;75:414–24. [PubMed: 16025464]
119. Bettinger CJ, Weinberg EJ, Kulig KM, Vacanti JP, Wang Y, Borenstein JT, Langer R. Three-Dimensional Microfluidic Tissue-Engineering Scaffolds Using a Flexible Biodegradable Polymer. Adv Mater 2006;18:165–169.
120. Mikos AG, Lyman MD, Freed LE, Langer R. Wetting of Poly(-Lactic Acid) and Poly(-Lactic-Co-Glycolic Acid) Foams for Tissue Culture. Biomaterials 1994;15:55–58. [PubMed: 8161659]
121. McDonald JC, Duffy DC, Anderson JR, Chiu DT, Wu H, Schueller OJA, Whitesides GM. Fabrication of Microfluidic Systems in Poly(Dimethylsiloxane). Electrophoresis 2000;21:27–40. [PubMed: 10634468]
122. Folch A, Jo BH, Hurtado O, Beebe DJ, Toner M. Microfabricated Elastomeric Stencils for Micropatterning Cell Cultures. J Biomed Mater Res 2000;52:346–353. [PubMed: 10951374]
123. Chiu DT, Noo Li J, Huang S, Kane RS, Wargo CJ, Choi IS, Ingber DE, Whitesides GM. Patterned Deposition of Cells and Proteins onto Surfaces by Using Three- Dimensional Microfluidic Systems. Proceedings of the National Academy of Sciences of the United States of America 2000;97:2408–2413. [PubMed: 10681460]
124. Borenstein JT, Terai H, King KR, Weinberg EJ, Kaazempur-Mofrad MR, Vacanti JP. Microfabrication Technology for Vascularized Tissue Engineering. Biomedical Microdevices 2002;4:167–175.
125. Liu Tsang V, Bhatia SN. Three-Dimensional Tissue Fabrication. Adv Drug Deliv Rev 2004;56:1635–1647. [PubMed: 15350293]
126. Elisseeff J, McIntosh W, Anseth K, Riley S, Ragan P, Langer R. Photoencapsulation of Chondrocytes in Poly(Ethylene Oxide)-Based Semi- Interpenetrating Networks. J Biomed Mater Res 2000;51:164–171. [PubMed: 10825215]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

127. Kraehenbuehl TP, Zammaretti P, Van der Vlies AJ, Schoenmakers RG, Lutolf MP, Jaconi ME, Hubbell JA. Three-Dimensional Extracellular Matrix-Directed Cardioprogenitor Differentiation: Systematic Modulation of a Synthetic Cell-Responsive Peg-Hydrogel. Biomaterials 2008;29:2757–2766. [PubMed: 18396331]

128. Alsberg E, Anderson KW, Albeiruti A, Rowley JA, Mooney DJ. Engineering Growing Tissues. Proceedings of the National Academy of Sciences of the United States of America 2002;99:12025–12030. [PubMed: 12218178]

129. Liu VA, Bhatia SN. Three-Dimensional Photopatterning of Hydrogels Containing Living Cells. Biomedical Microdevices 2002;4:257–266.

130. Gaubert HE, Frey W. Highly Parallel Fabrication of Nanopatterned Surfaces with Nanoscale Orthogonal Biofunctionalization Imprint Lithography. Nanotechnology 2007;18:135101.

131. Leach JB, Schmidt CE. Characterization of Protein Release from Photocrosslinkable Hyaluronic Acid-Polyethylene Glycol Hydrogel Tissue Engineering Scaffolds. Biomaterials 2005;26:125–135. [PubMed: 15207459]

132. Scott AZ, Quan T, Christine ES. Drug-Binding Hydrogels of Hyaluronic Acid Functionalized with Beta-Cyclodextrin. J Biomed Mater Res A 2008;87A:1044–1052.

133. Zawko SA, Suri S, Truong Q, Schmidt CE. Photopatterned Anisotropic Swelling of Dual-Crosslinked Hyaluronic Acid Hydrogels. Acta Biomater 2009;5:14–22. [PubMed: 18929518]

134. Crompton KE, Goud JD, Bellamkonda RV, Gengenbach TR, Finkelstein DI, Horne MK, Forsythe JS. Polylysine-Functionalised Thermoresponsive Chitosan Hydrogel for Neural Tissue Engineering. Biomaterials 2007;28:441–449. [PubMed: 16978692]

135. Drury JL, Mooney DJ. Hydrogels for Tissue Engineering: Scaffold Design Variables and Applications. Biomaterials 2003;24:4337–4351. [PubMed: 12922147]

136. Fukuda J, Khademhosseini A, Yeo Y, Yang X, Yeh J, Eng G, Blumling J, Wang CF, Kohane DS, Langer R. Micromolding of Photocrosslinkable Chitosan Hydrogel for Spheroid Microarray and Co-Cultures. Biomaterials 2006;27:5259–5267. [PubMed: 16814859]

137. Tan W, Desai TA. Microfluidic Patterning of Cells in Extracellular Matrix Biopolymers: Effects of Channel Size, Cell Type, and Matrix Composition on Pattern Integrity. Tissue Eng 2003;9:255–267. [PubMed: 12740088]

138. Lauten EH, Peppas NA. Intelligent Drug Release Using Molecular Imprinting Methods. J Drug Deliv Sci and Technol. in press

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

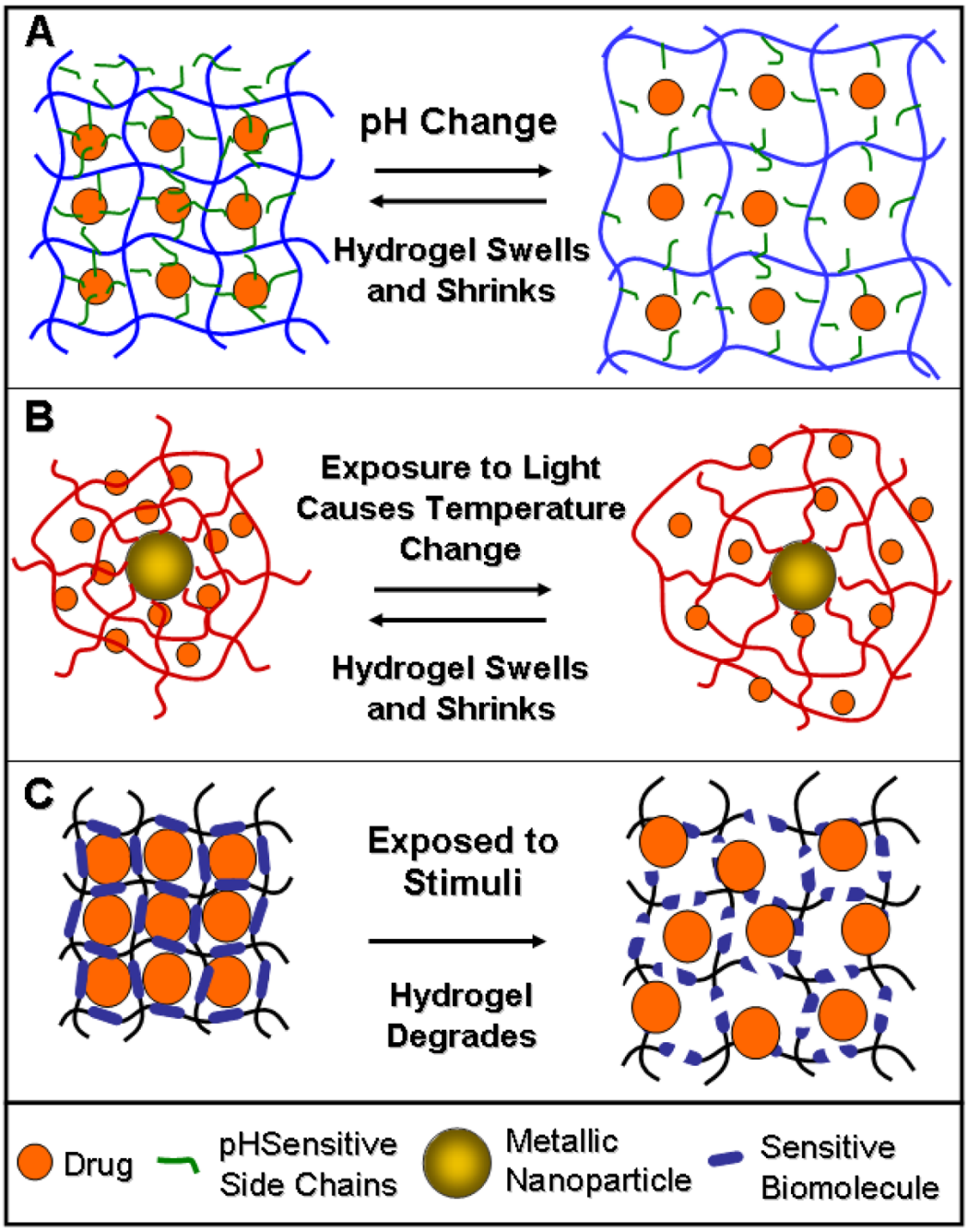

Figure 1. Versatility of Hydrogel Networks

(A) pH sensitive hydrogels: When the hydrogel is in a low pH environment, the polymer network entraps the loaded agents within the network but once the network is exposed to a higher pH environment, the polymer network swells and releases the drug. **(B) temperature sensitive hydrogels:** When the hydrogel is exposed to a temperature change, the hydrogel network will either swell and release encapsulated agents or shrink to encapsulate agents. **(C) biomolecule sensitive hydrogels:** These gels have a stimuli responsive biomolecule incorporated directly into their polymer hydrogel network. When these molecules are exposed to the particular agent they are sensitive to, the biomolecule will breakdown and in turn the hydrogel network will degrade and release the drug that was encapsulated within the gel.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

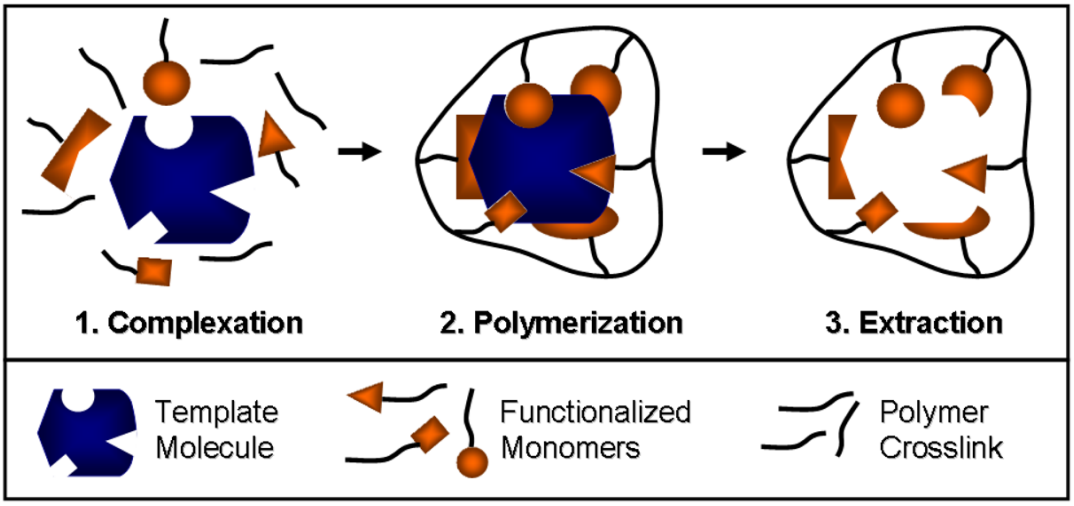

Figure 2. Molecular Imprinting Methodology

(1) Complexation: The desired template molecule is incubated in a solvent containing its corresponding functional monomers, a initiator molecule, and polymer crosslinker, forming a "complex" between the functional monomers and the template molecule. **(2) Polymerization:** The solution is polymerized to form a crosslinked network. **(3) Extraction:** The template molecule is "extracted" from the network to create an imprinted recognitive cavity specific for that molecule.