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ENVIRONMENTALLY RESPONSIVE POLYMERIC "INTELLIGENT" MATERIALS: THE IDEAL COMPONENTS OF NON-MECHANICAL VALVES THAT CONTROL FLOW IN MICROFLUIDIC SYSTEMS

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Abstract - Miniaturization and commercialization of integrated microfluidic systems has had great success with the development of a wide variety of techniques in microfabrication, since they allowed their construction at a low cost and by following simple step-series procedures. However, one of the major challenges in the design of microfluidic systems is to achieve control of flow and delivery of different chemical reagents. This feature is especially important when using microfluidic systems in the development of cell culture systems, the construction of labs on a chip and the fabrication and design of chemical microreactors. Spatiotemporal control of the microenvironment in microfluidic devices has been only partially achieved by incorporating actuator parts (mechanical and non-mechanical) within these devices; nevertheless, recently there has been enormous progress due to advances in the materials sciences, and the development of novel polymeric "intelligent" materials. These materials have proved to be excellent candidates in the construction of non-mechanical actuators in the form of environmentally responsive valves. These valves can more efficiently control flows because these "intelligent" materials are capable of undergoing conformational changes and phase transitions in response to different local or external environmental stimuli; allowing them to turn the valves from "on" to "off". In addition, these valves have very simple designs, and are easy and cheap to incorporate into microfluidic systems. Therefore, although there are many reviews that focus on the development and design of non-mechanical actuators, the following review proceeds to describe the exciting characteristics, potential uses and synthesis methods of the building blocks of the most recent and innovative non-mechanical valves, environmentally responsive polymeric "intelligent" materials. In addition, the last section of this review will focus on the synthesis of composite materials that are capable of responding to more than one type of stimulus, since these materials are believed to be the future components that will boost the development of microfluidic systems with spatiotemporal controlled microenvironments.

Keywords: Microfluidic systems; Responsive materials; Optically responsive materials; Hybrid materials; Mechanical actuators; Nano-actuators.

INTRODUCTION

Recently, the strong interest to construct and design microfluidic systems has been driven by the trends of miniaturization and high throughput analysis in integrated systems. In addition, development of a wide variety of techniques in microfabrication has allowed constructing microfluidic systems with sophisticated circuitries at a low cost and by following simple step-series procedures. Simplifying their fabrication permitted exploiting the many fascinating properties present in microfluidic systems, such as the ones shown in Figure 1, which include: 1) their capability to

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*To whom correspondence should be addressed manipulate fluids at microscales; 2) the effective mass and heat transfer that develops due to their high surface to volume ratios; and 3) the dominance of viscous forces within these systems, which facilitate the creation of laminar flows (Gravesen et al., 1993) and allow the generation of diffusive chemical gradients when two substances are transported in parallel within the same channel. (Takayama et al., 2001; Hung et al., 2004; Wu et al., 2006).

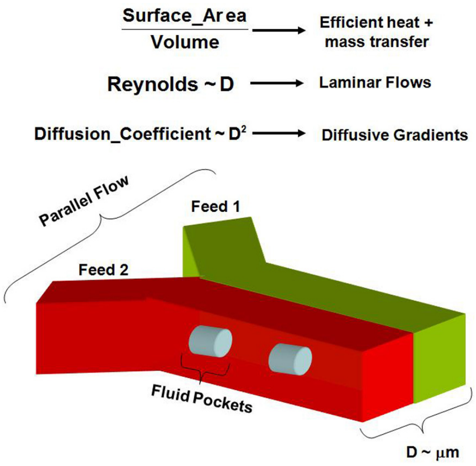

Figure 1: The advantages of microfluidic systems are illustrated. They provide environments with high surface to volume ratios and make heat and mass transfer more efficient. Reynolds numbers depend directly on the dimensions, which makes them very small in microfluidic devices and lead to laminar flows, which allow fluid-fluid interfaces (pockets or parallel flows) that depend purely on diffusion.

Combination of simple fabrication with the properties mentioned above has permitted microfluidic systems to have an impact in many fields, such as: microscale chemistry, drug discovery, drug delivery systems, and studies of cellular behavior. However, there are many challenges in the construction of microfluidic systems, among the most difficult task is being capable of controlling, changing and predicting the conditions within the microscaled system. This has been strongly pursued especially when designing microfluidic systems for applications in the construction of cell cultures, with tightly controlled conditions to study cellular activities; in the building of labs on a chip, to perform high throughput screening experiments; or in the development of chemical microreactors with highly controlled chemical and physical conditions; among many others. Therefore, there is a whole research area that has focused on designing actuator parts (mechanical and non-mechanical) that act as "on" and "off" switches and that can be incorporated into microfluidic devices so that spatiotemporal control of the microenvironment can be achieved.

Several other reviews in the literature have analyzed this field by focusing on the development of microfluidic systems, their different designs, microfabrication methods and the individual characteristics of the actuator components that can be incorporated to control flow (Gravesen et al., 1993; Beebe et al., 2002; Oh and Ahn, 2006). However, there is a lack in the literature of a review that analyses the field by focusing on the work that has recently been done in the development of intelligent materials that serve as the fundamental components of non-mechanical actuators. This work will approach this subject by focusing on three major aspects: 1) briefly introduce the different kinds of actuator systems and highlight the novelty and advantages of non-mechanical actuators in specific; 2) discuss the different reasons for which intelligent materials have been heavily used and are great candidates to construct non-mechanical actuators; and 3) describe the present and future designs of hybrid materials, as well as their synthesis methods, since these are the most promising building blocks for the future generation of mechanical actuators.

DESIGNING ACTUATORS SYSTEMS THAT CONTROL FLOW

The first step of the process to design an actuator part, which will be incorporated within a microfluidic device, is to gather a list of desirable properties in accordance to the level of control in flow and the conditions of the microenvironment expected for a specific application. For the majority of applications explored in the literature, there is a standard list of properties that would enhance the performance of actuator parts, and these include the following: 1) capability to switch between an "on" and an "off" state in response to an external stimulus. 2) The response of transitioning between the "on" and the "off" state must be relatively fast. And 3) the external stimulus required to switch between states must be chosen accordingly so that it does not have a negative effect on the experimental outcome. It is then important to mention that, to date, it has not been possible to incorporate all the properties of this list into a single actuator part, but there have been close attempts. In addition, it is expected that, with the advancements in the development of responsive polymeric materials, this will soon be achieved.

Types of Actuators that Control Flow

The actuator parts developed to date can be categorized into mechanical and non-mechanical (Oh and Ahn, 2006). Mechanical actuators are usually movable mechanical membranes that are constructed by using traditional lithography and sophisticated nanofabrication techniques (Hediger et al., 2000; Li Jeon et al., 2002; Groisman et al., 2005; Keenan et al., 2006). These movable membranes are further coupled to magnetic, piezoelectric or pressure actuated methods which allow external switching. Some examples of mechanical actuators include permeable membranes (Hautojarvi et al., 1996; Kontturi et al., 1996; Ulbricht, 1996; Peng and Cheng, 1998; Peng and Cheng, 1999; Peng and Cheng, 2001; Chu et al., 2003; Gatimu et al., 2006), and nanofabricated reservoirs that act as constant sources of reagents (Groisman et al., 2005; Frevert et al., 2006; Keenan et al., 2006).

On the other hand, non-mechanical actuators are operated using "intelligent" polymeric materials, which have been baptized with the nickname of "smart" or "intelligent" due to their capability of undergoing conformational changes and phase transitions upon local or external environmental stimuli (Gil and Hudson, 2004; Langer and Tirrell, 2004). Some of the environmentally responsive materials that have been previously synthesized include: pH sensitive (Peng and Cheng, 1999), temperature sensitive (Schild, 1992; Nath and Chilkoti, 2001; Frey et al., 2003), pressure actuated, (Juodkazis et al., 2000), materials that respond to light (Kungwatchakun and Irie, 1988; Irie and Kungwatchakun, 1992; Nayak and Lyon, 2004; Slocik et al., 2007) and materials capable of sensing a chemical entity, such as glucose, to further change their conformation (Cartier et al., 1995). Furthermore, these environmentally responsive materials have proven to be not only promising building blocks in the construction of actuators for drug delivery systems and nanofabricated devices (Beebe et al., 2000; Brinker, 2004; Peppas et al., 2006), but also to be the main components of non-mechanical actuators, designed mostly in the form of valves due to the simplicity of their design. (Beebe et al., 2000; Eddington and Beebe, 2004; Wang et al., 2005). Therefore, for instructional purposes and as an important part of this review, the available responsive materials, which have become fundamental parts of different valve designs, will be listed in the following section.

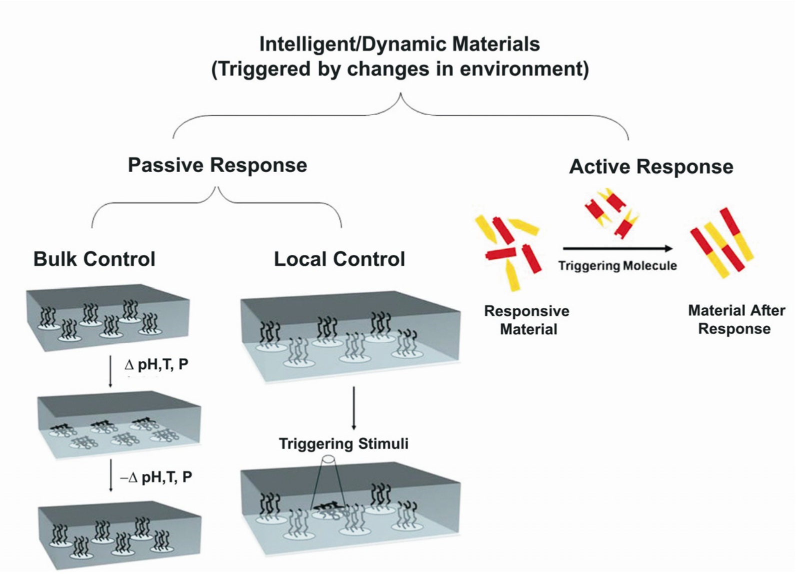

Figure 2: Environmentally responsive materials can be categorized into three different types: The passive responsive materials, which respond to the presence or absence of a specific molecule; active responsive materials, which can be reversibly triggered externally in response to a stimulus. Among these active materials there are two categories. The categories include materials that respond to bulk changes in their surroundings, such as pH and temperature, and materials that respond to local changes such as light.

CLASSIFICATION OF "INTELLIGENT" MATERIALS

"Intelligent" polymeric materials are usually categorized based on the way they can be triggered; a schematic of these is shown in Figure 2. They are typically separated into two categories: the locally-triggered materials and the bulk-triggered materials. Among these, five types of materials have had impactful success in the development of non-mechanical actuators, these include: 1) The bulk-triggered temperature sensitive polymers, such as the widely used poly-N-isopropyl acrylamide (PNIPAM) (Schild, 1992). 2) The bulk-triggered pH sensitive polymers (Peppas and Khare, 1993; Eddington and Beebe, 2004; Dai et al., 2008), such as the commonly used acrylic acid (Hilt et al., 2002). 3) Other polymers with bulk-triggered sensitivities to a wide range of physical stimuli such as pressure and applied voltage (Shoenfeld and Grodzinsky, 1980; Zheng et al., 2008). 4) The locally triggered materials that respond to light (Kungwatchakun and Irie, 1988; Irie and Kungwatchakun, 1992; Nayak and Lyon, 2004; Radt et al., 2004; Jiang et al., 2006; Slocik et al., 2007; Szilagyi et al., 2007). 5) And lastly, the hybrid materials, which are materials that have been coupled to or modified with specific functional chemical groups and, therefore, exhibit combinatory responses. The following sections will list some of the uses of these materials in the construction of mechanical actuators.

CONSTRUCTING NON-MECHANICAL VALVES USING BULK-TRIGGERED RESPONSIVE MATERIALS

Bulk-triggered responsive materials have found a series of applications in the delivery and precise release of chemical reagents, such as drugs and growth factors, both in vivo and in vitro. Some examples include hydrogels, capable of responding to different chemical and physical external stimuli (such as pH and temperature), that release a drug (protein or peptide) at specific sites in the body (Peppas et al., 2006). Other systems with higher complexity have been designed to be able to respond to specific enzymes (Shimoboji et al., 2002; Shimoboji et al., 2003) and chemical entities, allowing them to perform sophisticated cellular targeting and delivery mechanisms. An example of this is the hydrogels employed as insulin delivery systems, which are capable of responding to the presence of glucose (Qiu and Park, 2001). These and other cleverly designed delivery devices have improved therapies for a wide variety of diseases (Qiu and Park, 2001; Bashir et al., 2002; Peppas and Kim, 2006).

Additional applications, which are of most interest for the purpose of this review, are their use to deliver reagents into in vitro microfluidic systems. In fact, the most successful attempts to fabricate valves have been accomplished using bulk-triggered responsive materials. These systems present several advantages, such as being capable of externally controlling flows (redirecting) and introducing chemical reagents with fast response times by simply changing the bulk conditions of the system. Non-mechanical valves have been constructed using hydrogels that respond to pH (Park et al., 2005), membranes that move in response to pneumatic pressure (Grover et al., 2003), hydrogels that expand and contract in respond to temperature (Stoeber et al., 2005), pluronic sol-gel phase change materials that respond to temperature by changing their conformation from a liquid to a liquid crystalline gel (Liu et al., 2002), or materials that respond to specific chemical entities, such as glucose (Cartier et al., 1995). However, there is a big limitation in their design, which is that the mechanical action can only be triggered when the bulk conditions of the whole microfluidic environment are changed. As a consequence, this is a limitation for biological applications, due to the strict environments that are required for cell survival, and also for the construction of chemical reactors where the chemistry is negatively affected by changes in the bulk conditions.

Hence, the necessity to synthesize and design materials that can respond to localized stimuli, without changing the bulk conditions of the system. Recently there has been interest in developing materials that present localized response to light, (Liu et al., 2005; Sershen et al., 2005), or through the implementation of nanofabricated sources containing chemical reagents that are dispensed to the system through pressure (Keenan et al., 2006), or simple diffusion (Abhyankar et al., 2006). However, even though up until now the use of pressurized reagent sources has been the most successful, they require complicated circuitry and do not offer the capability of stimulating highly specific sites; therefore, light responsive materials are the preferred option since their response can be easily triggered at highly localized sites (using lasers) without requiring physical contact.

CONSTRUCTING NON-MECHANICAL VALVES USING LOCALLY-TRIGGERED RESPONSIVE MATERIALS

Optically responsive materials are the most appropriate locally responsive materials that present the appropriate characteristics to be used in mechanical actuators to control flow and delivery of chemical reagents (Brinker, 2004). Light responsive materials are typically triggered by two methods: 1) due to conformational changes of certain dye molecules found either in the polymer backbones or as pendent groups in the polymer chemical structure (Higuchi et al., 2004; Edahiro et al., 2005; Jiang et al., 2006; Nayak et al., 2006; Garcia et al., 2007; Zhu et al., 2007); 2) due to local heat generation of dyes linked to a thermally responsive polymer or hydrogel (Nayak and Lyon, 2004; Slocik et al., 2007). However, dyes are usually chemically reactive, susceptible to bleaching, and their responses are generally very slow (Kungwatchakun and Irie, 1988; Hugel et al., 2002; Shimoboji et al., 2002; Brinker, 2004). Therefore, research has been focused on developing hybrid materials, such as nanocomposites that couple two or more different materials and synergize their individual physical properties. The synthesis and characteristics of hybrid materials that can be locally triggered through the synergy of the physical properties of nanostructures and the responsive stimuli of responsive polymeric materials will be the focus of the remainder of this piece. These currently represent the most novel and innovative materials being developed for the construction of mechanical actuators.

CONSTRUCTING NON-MECHANICAL VALVES USING HYBRID RESPONSIVE MATERIALS

There are several valves that have been developed using materials that can respond to multiple stimuli. Among these, the most successful ones have been proposed by Peng and Cheng (2001), where a porous membrane was functionalized with a copolymer of p-N-isopropyl acrylamide (temperature sensitive) and p-methyl-acrylic acid (pH sensitive) which allowed controlling flow using both stimuli. In addition, there is a new area of research that has focused on coupling metallic nanostructures with polymeric materials (named nanocomposites) and trying to synergize the exciting properties of both materials.

Developing hybrid or nanocomposite materials that couple metallic nanoparticles to responsive polymers is a field of research that has gotten a lot of attention due to the extensive research done in the synthesis and design of each of the individual components (responsive polymers and metallic nanoparticles). Satarkar et al. (2009) were able to couple metallic nanostructures with environmentally responsive hydrogels and build a non-mechanical actuator that controlled flow in response to both temperature and an electromagnetic field. A similar valve was constructed by Sershen et al. (2005) by synergizing the optical properties of gold-silicon nanoshells with the thermal response capabilities of a thermally responsive polymer hydrogel.. In particular, coupling thermally responsive polymers to metallic nanoparticles has allowed the development of materials that can be triggered both optically and thermally since the incorporated metallic nanoparticles act as amplifiers and converters of light of a specific wavelength into heat (Chou et al., 2005). There are two major advantages of these materials over the traditional optically responsive polymers (using dyes). First, both the nanoparticles and the polymer have a higher chemical stability. Second, nanocomposites have faster optical responses since they are triggered by a coupled mechanism between the fast thermal response of the polymer and the capability of metallic nanoparticles to convert absorbed light into heat, taking advantage of the rapid heat conduction at small scales.

The following sections will describe briefly each of the components of the hybrid materials (PNIPAM and metallic nanoparticles) and this work will conclude with a section focused on some of the synthesis developed and being investigated to produce opto-thermally responsive nanocomposites.

COUPLING THERMALLY RESPONSIVE POLYMERS AND METALLIC NANOPARTICLES TO CONSTRUCT HYBRID MATERIALS

Thermally Responsive Poly-N-Isopropyl Acrylamide: The Source of Rapid Mechanical Response

Poly-N-Isopropyl Acrylamide (PNIPAM) is one of the most studied thermally responsive materials in the literature. PNIPAM is a polymer that contains both hydrophobic and hydrophilic chemical groups, as illustrated in Figure 3. Due to these chemical characteristics, it has been studied and determined to be a temperature responsive polymer with a lower critical solubility temperature (LCST) of around 32ºC, in water. Such behavior of solubility in water can be explained thermodynamically with the Gibbs free energy equation of the PNIPAM/water system: $\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix}$. Since a negative Gibbs free energy determines spontaneous processes, and PNIPAM has been determined to have a LCST, then we must assume that both ΔH_{mix} and ΔS_{mix} must be negative. In this case as the T increases the entropy term becomes more positive and eventually reaches the enthalpy term to switch the Gibbs energy from a negative value that determines a miscible system, to a positive value that determines an immiscible system.

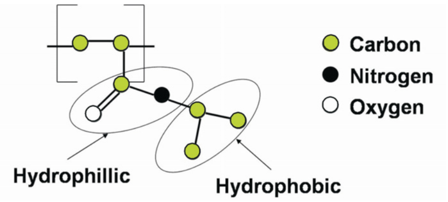

Figure 3: Chemical structure of poly-N-Isopropylacrylamide. The hydrophilic amide groups are capable of forming hydrogen bonds at temperatures below 32ºC. The hydrophobic isopropyl group becomes dominant at 32ºC and causes the polymer to phase separate from an aqueous environment. This gives the polymer its responsive characteristics.

This phenomenon can also be explained from the hydrophilic/hydrophobic chemical nature of PNIPAM. At lower temperatures it is water soluble and hydrophilic. When the temperature increases, PNIPAM becomes more hydrophobic due to the breaking of the hydrogen bonds between water and the NH and CO groups, and so there is a preference for the polymer to associate with itself instead of associating with the solvent. This leads to a phase separation, forming two pure phases. This translates into a decrease in entropy and a positive increase in the Gibbs energy.

The conformation of the polymer chains above the LCST is a hydrated and expanded state and, below the LCST, the chains are dehydrated and aggregated. This behavior exhibited by PNIPAM has been used for several application such as sensors, externally triggered drug delivery systems, and biological separations (Bergbreiter et al., 1998; Akiyama and Tamaoki, 2004).

Noble Metal Nanoparticles

Fascinating Optical Properties

Metallic nanostructures have gotten a lot of attention since they exhibit very different optical, electrical, thermodynamic, and chemical properties than the bulk material. These novel properties found in these materials have found applications in sensors (Nath and Chilkoti, 2004), molecular labels (Bruchez et al., 1998), and even as biocides and antimicrobials (Elechiguerra et al., 2005; Morones et al., 2005). Such properties exhibited at the nanoscale are exemplified in the way gold interacts with light at different scales. Gold in the bulk looks shiny yellow in reflected light, but when very thin gold films are prepared it looks blue in transmitted light. Additionally, the colors change to orange and several tones of purple and red as the film thickness decreases up to a few nanometers. Such phenomenon is due to the collective oscillation of conduction electrons at the interface between the metal film and the surrounding dielectric (Carotenuto et al., 2000; Liz-Marzan, 2004). The conducting electrons at the interface of metallic nanostructures respond to electromagnetic fields with electronic resonant absorption in the visible wavelength range, called localized surface plasmon resonance (LSPR), and gives rise to very intense colors.

The LSPR is highly sensitive to size and shape of the nanostructures, as well as to other parameters such as the refractive index of the surrounding medium and the distance between neighboring particles. When the nanostructures are non-spherical and exhibit higher growth in one dimension, to form wires or rods, the plasmon band splits into two bands, corresponding to oscillation of the conducting electrons along (longitudinal) and perpendicular (transverse) to the long axis (Xia and Halas, 2005). The transverse mode resonance resembles the observed peak for spheres, but the longitudinal mode is considerably red-shifted and depends strongly on the difference in length compared to width. The absorption spectrum can be shifted from the blue to the red by forming elongated wires, tubes, belts, and other more sophisticated structures (stars, rings, cubes, nanoshells and onion-like structures) that incorporate different metals (Aizpurua et al., 2003; Lu et al., 2004; Chen et al., 2005; Halas, 2005; Hirsch et al., 2006). All these shapes have been synthesized to move the absorption peaks across the absorption spectrum and design sensors and molecular labels. The high sensitivity that the absorption peaks present to size and shape requires the development of syntheses that produce highly monodisperse metallic structures within the hybrid materials previously described.

Energy Conversion of Light into Heat

Metallic nanoparticles interact with light at different light wavelengths through scattering and absorption. The scattering component of light is enhanced by increasing particle size above ~100 nm; however, the absorption stays mostly constant and slowly increases with size. The nanoparticles show an extinction spectrum, with a higher intensity at the surface-plasmon-resonance wavelength, and follow a photo-thermal phenomenon where, due to energy relaxation of the surface electrons to the phonon bath, the resonant energy is dissipated as heat to the local surroundings (Figure 4). This raises the temperature of the surroundings of the particles when illuminated by a light source, such as a laser. Smaller particles and structures such as nanorods, nanorings and nanoshells convert most of the absorbed energy into heat since they present larger surface to volume ratios and present less scattering, which therefore enhances the opto-thermal conversion efficiency and produces larger increments of the temperatures of the surrounding environments. (Lu et al., 2004; Liu et al., 2005).

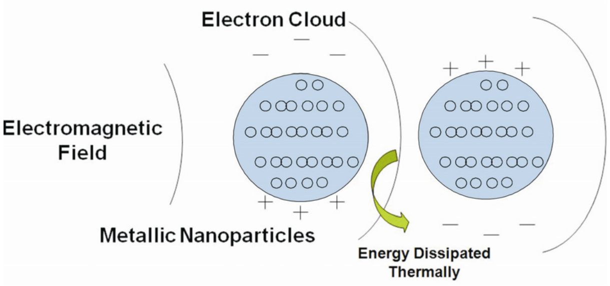

Figure 4: Illustration of the mechanism of heat dissipation by the surface electrons present in metallic nanoparticles when they are exposed to a specific wavelength and excited by an electric field.

Temperature increments of gold and silver nanoparticles have been measured using polarization interference, which allows detection of slight phase changes induced by heating. Efficient energy conversion increases the local temperature in the immediate particle vicinity up to 15 K (Boyer et al., 2002) and work on different structures such as nanocrescents has achieved increments of up to 60 K in the nanostructures' vicinities (Liu et al., 2005).

Synthesis Routes of Environmental Sensitive Polymer-Metal Nanoparticle Hybrids

Synthesis of Hybrid Hydrogels

Polymer-metal hybrid nanocomposites have been synthesized in a variety of ways. The most common synthesis involves using temperature responsive PNIPAM hydrogels to entrap metallic particles within their structure. Furthermore, these hydrogels have been incorporated successfully into microfluidic systems and achieved optical flow control. (Sershen et al., 2001; Sershen et al., 2002; Jones and Lyon, 2003; Sershen et al., 2005) The synthesis of these systems is advantageous since it is simple to physically entrap nanoparticles within the hydrogel; however, the downside is the long time to trigger the response of these systems and the fact that they require high power lasers. This challenge has motivated the development of synthetic routes that couple polymer chains, instead of the bulky hydrogels, to metallic nanoparticles and obtain stable nanocomposites. These can be further used as "on-off" valves to control flow in microfluidic systems since they present faster switching times and will use lower power lasers.

Synthesis of Hybrid Nanoactuators

A popular synthesis method to produce hybrid nanomaterials is through wet chemistry reactions, since they are relatively cheap and capable of producing colloidal suspensions of homogenous particles in large quantities. The ingredients in the liquid phase are the metal salt precursor, which is reduced to its metallic form by a reducing agent such as ethylene glycol (Silvert et al., 1996; Silvert et al., 1997; Carotenuto et al., 2000), sodium citrate (Kim et al., 2003; Raula et al., 2003), or sodium borohydrate (Hyning and Zukoski, 1998; Hyning et al., 2001). Previous review papers have discussed several mechanisms for the formation of the metallic particles by wet chemistry methods. The steps described include the creation of metal seeds, followed by growth to metallic clusters, and finally agglomeration and growth of the metallic clusters to form nanoparticles that reach sizes of a few nanometers in diameter (Illustrated in Figure 5). Control on the nucleation, aggregation and growth steps of the reaction is key in the production of metallic structures with homogeneous sizes and shapes (Silvert et al., 1996; Silvert et al., 1997; Y. Xiong, 2007). However, this is not a thermodynamically stable process since particles in the colloid will tend to minimize their surface energy by agglomerating with other particles. This leads to the formation of large agglomerates with polydisperse sizes and shapes. Size and shape can be controlled by the addition of a surface stabilizer present in the surrounding solvent during the formation of the metallic structures. These surface stabilizers are molecules, usually organic polymers, that present high affinity for the metal surface and the metallic ions (Zhang et al., 1996; He et al., 2004). The final material is then a hybrid polymer-metal nanocomposite where the polymers act as capping agents; they control the growth of the particles in the synthesis process and prevent surface contact of the particles, which prevents agglomeration during synthesis and storage (Zhang et al., 1996; Carotenuto et al., 2000; Shan et al., 2005; Wiley et al., 2005).

Various studies have focused on the coupling of polymer and metal nanoparticles to form hybrids. Some of the methods developed (Figure 6) include surface grafting by functionalizing the responsive polymers with thiol groups to promote adsorption on the surface, and surface initiated polymerization by previously treating the metallic nanoparticle surface with radical polymerization initiators (Kim et al., 2003; Raula et al., 2003). Previous reports have observed a strong interaction of molecules that contain chemical groups with N and O, such as PVP and the amide group in PNIPAM and PAAm, with noble metals: platinum (Chen and Akashi, 1997; Chen and Akashi, 1997; Miyazaki and Nakano, 2000), gold (Sun and Xia, 2002) and silver (Silvert et al., 1996; Silvert et al., 1997; Kim et al., 2006). The interaction with the surface of the metallic particles has been attributed to hydrophobic forces, as well as possible chemical coordination bonds between the polymer and the metal surface. PNIPAM has been previously used as a capping and stabilizing agent in the synthesis of platinum particles reduced with ethanol (Chen and Akashi, 1997; Chen and Akashi, 1997; Miyazaki and Nakano, 2000).

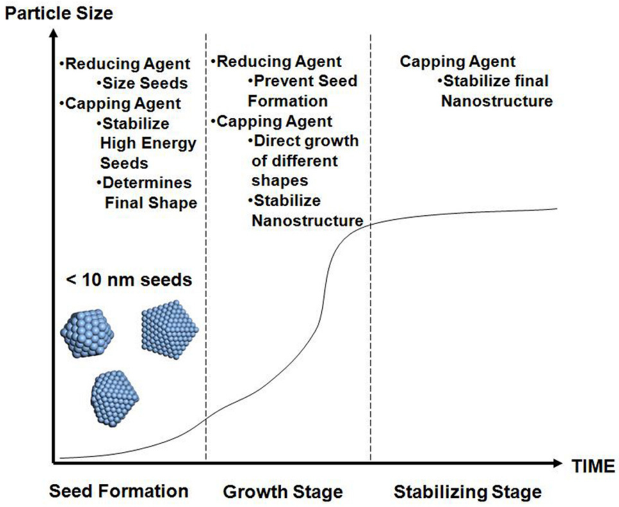

Figure 5: Graphs show the different stages observed for metallic nanoparticle synthesis. The seeding stage consists of formation of particles with diameters less than 10 nm. In this stage, the reducing agent plays a major role in the size of the particles, depending on how fast it reduces the metallic salts. The stabilizing agent therefore plays a role in stabilizing different particle shapes of different surface energies; the appropriate stabilization leads to the formation of various shapes (spheres, wires, tripods, cubes, stars, etc.). The growth stage involves agglomeration and growth of small particles. The capping and reducing agent must inhibit seed formation and promote growth, which leads to homogenous size and shape distributions. The stabilizing stage only involves the capping agent being able to stabilize the resulting metallic nanostructures.

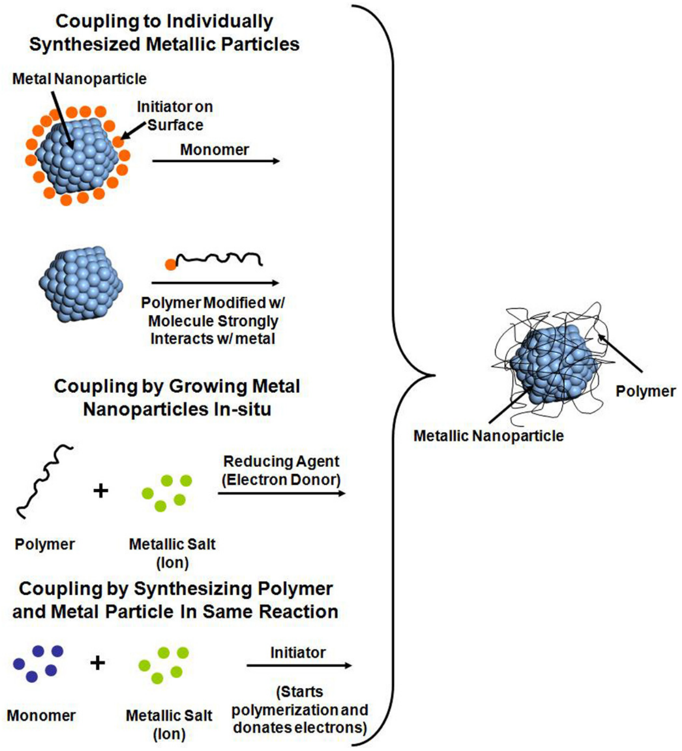

Figure 6: Different mechanisms to couple metallic nanoparticles and polymeric materials are illustrated and labeled in this figure. The first process involves making the metal particles separately and then treating their surface to start polymerization on them or treating a polymer with functional groups that attach to the metal. The second process involves in-situ reduction of metal salts in the presence of the polymer. The last process involves using the initiator as an electron donor and initiator of a polymerization; therefore, both polymerization of the monomer and formation of particles are performed at the same time. All these lead to synthesis of coupled polymer-metal nanocomposites with different characteristics.

Additionally, synthesis of silver (Chen et al., 1998; Chen et al., 1999) and bimetallic platinum-gold (Chen et al., 2002) colloids has been approached by using simultaneous dispersion polymerization of polystyrene and NIPAAm in the presence of the metallic precursors. The products yield metallic particles within the PNIPAM grafts on the surface of polystyrene spheres, allowing enhanced catalytic properties and effective ways of recuperating precious metals. They found that the peaks for the carboxyl and nitrogen hydrogen bonds are shifted, meaning that there is an interaction of the silver with these specific groups, which was taken advantage of to produce highly stable silver (Morones and Frey, 2007) and gold (Morones and Frey, 2009) nanoparticles coupled with PNIPAM to create opto-thermally responsive nanoactuators. This interaction and synthesis process provides a potential to develop novel synthesis routes to synthesize colloidal hybrid nanomaterials in the future.

Two new simpler synthetic routes were developed to build optically and thermally responsive nanocomposite materials by coupling PNIPAM, a temperature responsive polymer, to gold (Morones and Frey, 2009) and silver metallic nanoparticles (Morones and Frey, 2007), which have the capability of converting absorbed light at specific wavelengths into heat. PNIPAM was found to be capable of acting as a capping and nucleating agent in redox synthesis between a silver salt and sodium borohydride to produce silver nanoparticles and as a capping and stabilizing agent in the redox synthesis between a gold salt and ascorbic acid to produce gold nanoparticles. PNIPAM stabilizes the metallic nanoparticles by forming shell-like structures around them and is capable of achieving a size and shape control in the production of gold and silver nanoparticles comparable to the most common stabilizing agents found in the literature, such as sodium citrate for gold and PVP for silver.

Experimentally, the silver nanocomposites were proven to exhibit reversible switching with temperature. Furthermore, the gold nanoparticles showed similar switching behavior when exposed to light and heat, with very fast response times. The synthesis produced the first fast responsive nanoactuators that can be triggered by exposure to heat and light and they present a novel material to build mechanical actuators, as well as a variety of other switches for applications in many other fields.

CONCLUSIONS

Acquiring external control of the chemical and physical conditions within microfluidic systems is required for many different applications, such as the construction of cell culture systems and microchemical reactors. Therefore, intense research has been developed to build responsive mechanical actuators, such as "on-off" valves, that can achieve rapid, remote, noninvasive and localized control of flows and delivery of chemical reagents. The main component of these mechanical actuators is the responsive material, capable of undergoing conformational changes in response to different stimuli, since this allows for the "on-off" switching capability. Therefore, development of these responsive materials and other composite materials, capable of synergizing the properties of each of their components, is an area of research that has great appeal to be able to construct these switches and sensors. Although there are many different responsive materials mentioned within this review, the emphasis has been on materials that can be stimulated with localized triggers, in particular, hybrid materials that couple metallic nanoparticles and temperature-responsive polymers, which present the most suitable characteristics for these applications. The challenges that arise, therefore, are the synthetic pathways to couple both metal particles and the responsive polymer. One of the solutions proposed has been to take advantage of the reported interaction of N and O containing compounds, such as PNIPAM, with different metals, such as silver and gold, and perform in-situ wet chemistry reduction of metallic salts to achieve stable, well-controlled particles coupled with the responsive polymer.

The development of novel syntheses to design fast responsive materials to optical stimuli will provide a platform for the development of more efficient valves, which will translate into better spatiotemporal control conditions in microfluidic systems. Finally, it will revolutionalize its applications in, for example, chemical synthesis in microreactors and the emulation of in-vivo like environments in vitro to perform cell studies and their behavior to different therapeutics.

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