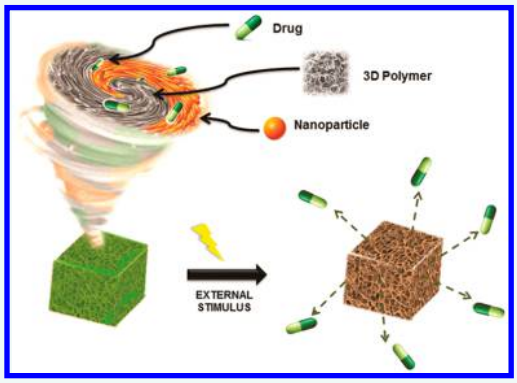
Nanocomposite Hydrogels: 3D Polymer–Nanoparticle Synergies for On-Demand Drug Delivery

Sonia Merino,*,† Cristina Martín,† Kostas Kostarelos,‡ Maurizio Prato,*,§ and Ester Vázquez*,†

†Departamento de Química Orgánica, Facultad de Ciencias y Tecnologías Químicas-IRICA, Universidad de Castilla—La Mancha, 13071 Ciudad Real, Spain, ‡Nanomedicine Lab, Faculty of Medical and Human Sciences & National Graphene Institute, AV Hill Building, The University of Manchester, Manchester M13 9PT, United Kingdom, and §Department of Chemical and Pharmaceutical Sciences, University of Trieste, Piazzale Europa 1, 34127 Trieste, Italy

ABSTRACT Considerable progress in the synthesis and technology of hydrogels makes these materials attractive structures for designing controlled-release drug delivery systems. In particular, this review highlights the latest advances in nanocomposite hydrogels as drug delivery vehicles. The inclusion/incorporation of nanoparticles in three-dimensional polymeric structures is an innovative means for obtaining multicomponent systems with diverse functionality within a hybrid hydrogel network. Nanoparticle-hydrogel combinations add synergistic benefits to the new 3D structures. Nanogels as carriers for cancer therapy and injectable gels with improved self-healing properties have also been described as new nanocomposite systems.



KEYWORDS: hydrogel · nanoparticle · nanocomposite · nanogel · self-healing · on-demand delivery · stimuli-response · external field

The development of multifunctional polymer-based matrices for controlled drug delivery purposes has been the subject of intense research during the last six decades.[1] After initial efforts for understanding drug release mechanisms and for maintaining a constant drug concentration in the blood, research moved into the advancement of polymers or hydrogels, as smart materials where the delivery of the drug is triggered by changes in environmental factors. The generation of clinical products with the ability to deliver drug molecules, at the right place and according to patients' needs, has been a challenge that has gained even more attention with the development of nanotechnology. The achievements of this new applied science have encouraged several research groups to use nanoparticles, as advanced systems with the promise of delivering drugs to target cells, especially in cancer therapy.[2] However, clinical applications of these systems are still scarce.

In general, precise control over the drug quantity and the release rate, in specific parts of the body, has numerous advantages over conventional drug release, such as enhancing bioavailability and minimizing deleterious side effects. These benefits are even more important for patients suffering from chronic diseases that require multiple dosage regimes. In these cases, the route of drug administration is also important, not only because it affects drug metabolism and dose, but also because it can improve patients' quality of life. Nevertheless, the most challenging delivery systems are the ones with reversible on–off switching capability. Many vital functions, frequently found in a living body, are regulated by pulses of active molecules at specific time and place; the release of insulin is an example of this mechanism. In general, a pulsatile delivery can be achieved if the drug carrier is designed to exhibit predictable and reproducible changes in response to an internal or external stimulus within a matter of minutes, or even seconds.

Among the synthetic and natural polymers that can be used for drug delivery, hydrogels represent a class of soft materials of particular interest.[3] Previous review articles have been

* Address correspondence to sonia.merino@uclm.es, prato@units.it, ester.vazquez@uclm.es.

Received for review March 6, 2015 and accepted May 4, 2015.

Published online May 04, 2015
10.1021/acsnano.5b01433

published covering various aspects of novel and smart biocompatible hydrogels,[4,5] including supramolecular gels[6] and low-molecular weight gelators.[7] Recent trends have focused on incorporating nanoparticles, such as polymeric, metallic, and carbon-based nanomaterials, within the hydrogel network to obtain nanocomposite hydrogels[8,9] with reinforced properties for various biomedical applications.

The objective of this review is to focus the attention on the synergies resulting from the combination of these materials. Nanoparticles can promote the response of hydrogels to a new stimulus, which can be modulated in a versatile way, with the modification of the nanoparticle. Moreover, the hybrid systems could enable routes of drug administration with limited systemic absorption but that can be useful in long-term delivery systems. On the other hand, hydrogels could provide nanoparticles with the clinically useful formulation needed for their clinical applications. The review, which includes a survey of recent advances combining nanoparticles and hydrogels, is not meant to be an exhaustive review of hydrogel technology. It aims to highlight some noteworthy examples and discuss some novel perspectives in order to offer researchers consideration of this synergic combination for the design of novel on-demand drug delivery systems.

HYDROGELS AS ON-DEMAND DELIVERY SYSTEMS: A BRIEF OVERVIEW

A hydrogel is a physically or chemically cross-linked natural or synthetic 3D network, which has the capacity to absorb a large fraction of water (up to thousands of times their dry weight), although typically of limited solubility in this media. The water retention capacity of hydrogels arises mainly from the presence of hydrophilic groups (amido, amino, carboxyl, hydroxyl, *etc.*) in the polymer chains and the degree of swelling can be modulated by the polymer composition and the density and nature of cross-links in the gel matrix. The water content of a hydrogel determines its unique physicochemical characteristics that can resemble those of living tissues more than any other class of synthetic biomaterials. These are largely attributed to their high water content, their soft and elastic consistency, and low interfacial tension when in contact with water or biological fluids. The porous structure of the hydrogel also allows drug loading into the gel matrix, and protects them from hostile environments, such as the presence of enzymes or low pH in the stomach.

Additionally, hydrogels can control drug release due to changes (swelling, dissolution or degradation) in the gel structure in response to internal or external stimuli. These types of environment-sensitive hydrogels are known as "intelligent" hydrogels.[10] The way the drug is incorporated into the hydrogel matrix has a great influence on controlling drug release.[11] When bioactive molecules are covalently bound to hydrogels,[12,13] their release requires the cleavage of the linking bond between the hydrogel and the drug. This chemical response is due to an enzymatic or chemical reaction, changes in pH, or an external stimulus such as light. However, in hydrogels containing the drug encapsulated by physical[14] or supramolecular interactions,[15] the release of the drug is due not only to a chemical response, but also to a physical change in the structure of the hydrogel, such as deswelling, which could be triggered by changes in pH, temperature, etc.

VOCABULARY: **Hydrogel** – 3D network which has the capacity to swell and retain a large fraction of water within its structure; **Nanocomposite** – material that incorporates nanosized particles into a matrix of standard material; **Intelligent hydrogel** – hydrogel that undergoes changes in the gel structure in response to internal or external stimuli; **Nanogel** – nanosized network of chemically or physically cross-linked polymers that swell in a good solvent; **Self-healing materials** – smart materials that have the capability of repairing themselves after being damaged;

The incorporation of stimulus sensitive components into hydrogels has allowed the design of systems that exclusively release their content on-demand. Glucose-sensitive hydrogels are an example of such stimuli-responsive systems. This type of intelligent systems can adjust the insulin release rate in response to the change of glucose concentration, to keep blood glucose level within the recommended range. Some hydrogel systems have been developed to modulate insulin levels, and all of them contain a glucose sensor built into the system.[16] Glucose-sensitive hydrogels are commonly based on enzymatic oxidation of glucose by glucose oxidase (GOx), binding of glucose with concanavalin A (Con A), or reversible covalent bond formation between glucose and boronic acids.

Despite the huge potential of stimuli-responsive hydrogels, in many cases these systems have limited use as drug delivery platforms today, since they exhibit poor mechanical properties, relatively rapid release of drugs from the gel (particularly in the case of hydrophilic drugs), and/or inefficient hydrophobic drug loading. Moreover, there are still problems associated with the control of the pulsatile delivery.[3,17]

NANOCOMPOSITE HYDROGELS: NEW SYNERGIES FOR ON-DEMAND DRUG DELIVERY

Over the last decades, nanotechnology has emerged as a potent tool to approach processes involving biological systems. In particular, nanocomposite hydrogels, *i.e.*, molecular networks physically or covalently cross-linked with nanoparticles or nanostructures, have been proposed as innovative means to overcome some of the challenges associated with the use of hydrogels in pulsatile drug delivery systems.

Figure 1. Nanoparticles such as carbon-based nanomaterials, polymeric nanoparticles, and metallic nanoparticles are combined with the polymeric network to create reinforced nanocomposite hydrogels.

Various types of nanoparticles such as inorganic/ceramic nanoparticles (hydroxyapatite, silica, silicates, calcium phosphate), polymeric nanoparticles (hyper-branched polyesters, cyclodextrins, *etc.*), metal/metal-oxide nanoparticles (gold, silver, iron-oxide), and carbon-based nanomaterials (carbon nanotubes (CNTs), graphene) are combined with the polymeric network to create reinforced polymeric hydrogels, developing nanocomposites with tailored physical properties and custom-made functionalities (Figure 1). The type of nanoparticle incorporated regulates the kind of stimuli that can be used to release the drug under the desired conditions, enhances the delivery in different parts of the body, allows the transport of hydrophobic drugs, or is responsible of multistimuli-response systems. There is a growing interest in this field, aiming to achieve rationally designed advanced hydrogels with tunable properties, which are not commonly found in polymers. We will see some examples of this in the following sections.

Stimuli-Responses Triggered/Enhanced by the Type of Nanoparticle. There are numerous reviews showing the different spectrum of stimuli-responsive hydrogels, detailing their mechanisms in controlling release.[18,19] Time controlled systems have been used in different administration routes such as oral, ocular or nasal. In these cases, drug release is controlled by diffusion or by the dissolution or degradation of the polymer, and environmental responses are specific to limited regions within the body. Thermo- and/or pH-sensitive hydrogels have been widely used in those situations, based on the elevated temperature and low pH found in the body. Specifically, the pH-sensitive ones are most frequently applied as controlled release systems for oral drug delivery.[10,20] The incorporation of nanosized materials has improved their response and their mechanical properties.[21,22] Moreover, the use of nanocomposite hydrogels gives access to new release systems allowing the delivery in different parts of the body. We will focus in this section on several representative examples of hydrogels whose responses are triggered or enhanced by nanoparticles under external stimulus (*e.g.*, electric and magnetic fields, near-IR light).

Electro-Responsive Hydrogels. Transdermal drug delivery provides a valuable alternative to the traditional dosage methods such as oral delivery and injections.[23] This approach not only avoids the gastric degradation and hepatic first-pass metabolism but also could greatly help in popular chronic treatments, eliminating the phobia and the pain associated with injections. Notwithstanding, the low permeability of the skin restricts the utility of this approach and major research is devoted to develop methodologies to increase the delivery of drug across this barrier. For example, Giri *et al.*[24] investigated the use of composites based on carboxymethyl guar gum and multiwalled carbon nanotubes (MWCNTs) as a transdermal system for sustained release of diclofenac sodium. In this case, the nanoparticle offers superior thermal stability, higher drug loading, and enhances drug retention efficiency within the hydrogel.

It has been found that electrical stimulation is an effective method to enhance and control the quantity of released drug from transdermal or subcutaneously implanted systems. Hydrogels sensitive to an electrical current are usually made of both synthetic and natural polyelectrolytes, separately or in combination. Under the influence of an electric field, electro-responsive hydrogels generally deswell or bend, depending on the shape and the orientation of the gel between the electrodes.[25] Electrically responsive drug release occurs *via* a number of different mechanisms, for example, a charged drug migrates toward the oppositely

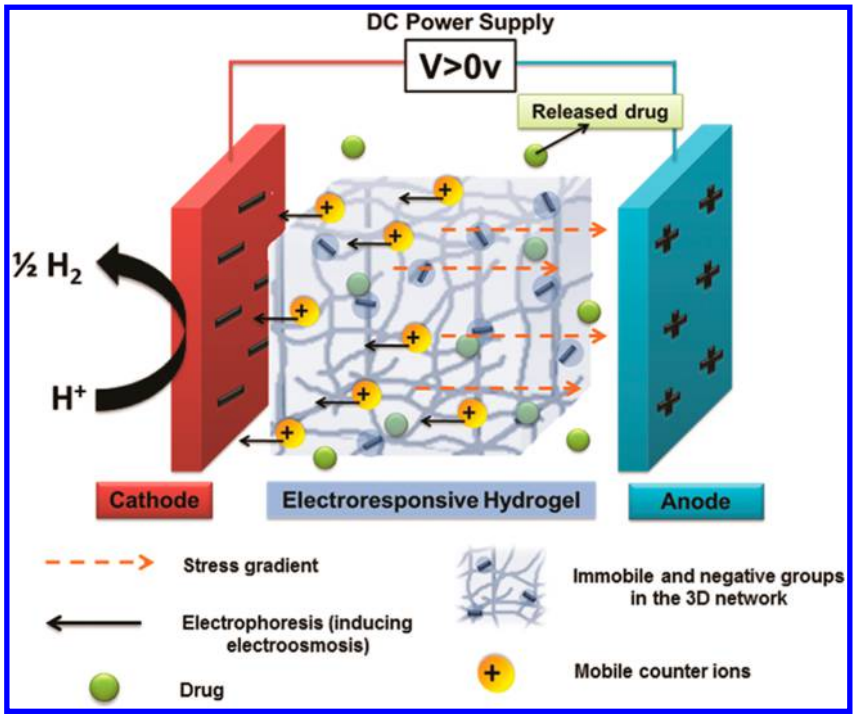


Figure 2. Schematic illustration showing the main mechanisms for electro-induced gel deswelling.

charged electrode or, more commonly, hydrogel contraction results in ejection of drugs out of the gels on electrical stimulation (Figure 2). Three main mechanisms have been proposed for electro-induced gel deswelling: (i) the development of a stress gradient in the hydrogel; (ii) changes in local pH around the electrodes as a result of the electrolysis of water (an increased pH in the cathode and a decreasing pH in the anode); and (iii) electro-osmosis of water coupled to electrophoresis. In practice, depending on the nature of the gel and on the experimental conditions used, anisotropic gel deswelling occurs by a combination of some or all of the mechanisms discussed above. However, the major limitations of these systems are slow response times, nonlinear control between stimulation and drug release,[26] and gel fatigue with time and electrical stimulations.[27]

The progress in nanocomposite hydrogels, although in its initial stages, could generate a step forward in applications for skin. We will discuss below some examples in which the incorporation of different nanoparticles (carbon nanotubes, graphene, nanoclays) were used to improve both mechanical and electrical properties of hybrid hydrogels.

Numerous research groups have used carbon nanotubes as conductive additives to increase the electro-sensitivity of the hydrogels with special focus on the development of transdermal drug release.[28] For example, Servant *et al.*[29] prepared polymethacrylic acid (PMAA)/MWCNT hydrogel hybrids at different MWCNT concentrations. The incorporation of MWCNTs in the PMAA based hydrogels significantly enhanced the gel response to the applied electric field and allowed the *in vivo* delivery of radiolabeled (^{14}C) sucrose as a therapeutically hydrophilic drug under short stimulation times and low electrical voltage.

On the other hand, the addition of synthetic silicate nanoparticles, also known as nanoclays, significantly increases both the physical and mechanical properties of polymeric hydrogels.[30,31] In a recent study, an amphiphilic chitosan−silica hybrid hydrogel has been prepared for electrically modulated release of an anticonvulsant drug, ethosuximide. Drug release was controlled by applying voltage to the composite hydrogel. In this case, the electrical stimulus causes modulated drug release profiles *in vitro* ranging from burst-like to slow-elution patterns due to the combination of electrophoretic and electro-osmotic mechanisms.[32]

Graphene has also attracted attention due to its fascinating properties, such as high electron mobility, thermal conductivity and mechanical stability. Reduced graphene oxide (rGO) has been employed in the preparation of an electrically responsive drug release system. With the use of lidocaine hydrochloride as a model hydrophilic substance, the drug release behavior of the reduced graphene oxide−poly(vinyl alcohol) (rGO−PVA) hydrogels has been explored. When larger amounts of rGO were incorporated, the rGO−PVA polymeric network became more negatively charged, which enhanced the action of electro-osmosis and reduced the intermolecular interactions between rGO and lidocaine. As a result, the lidocaine release rate was increased.[33]

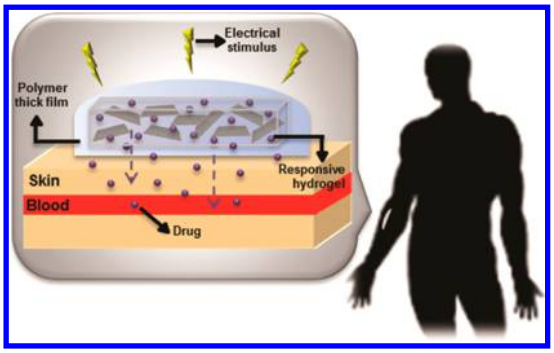


Figure 3. Schematic illustration of the pulsatile drug release upon application of electrical stimulus in an electro-responsive graphene based hydrogel.

Although pristine graphene has greater thermal, mechanical, and electrical properties than graphene oxide, only scarce examples of graphene-based hydrogels in drug delivery systems have been published. One of the major limitations of electro-responsive drug delivery systems is their potential temperature increase resulting from electrical stimulation, a process known as resistive heating. In a recent work by our groups,[34] it was demonstrated that the incorporation of graphene, at low concentrations, into an electro-responsive PMAA hydrogel almost completely eliminated the "resistive heating" from the hydrogel matrix, while significantly enhanced the mechanical properties of the hydrogels, compared to their carbon-nanotube-based hydrogel counterparts. This fact improved *in vivo* drug release under short stimulation times at low voltage, showing an excellent on−off switching capability. The graphene used in this study was obtained by ball-milling treatment[35] and contained significantly fewer defects than GO and rGO, retaining the electrical, mechanical, and thermal properties of the graphene structure. Ball-milled graphene material incorporation allowed the gels to be more responsive than their CNT counterparts at lower concentrations, using lower voltages, and displaying a reduced temperature increase upon electrical stimulation (Figure 3).

Magnetically Responsive Hydrogels. The application of magnetic micro- and nanoparticles in drug delivery was explored in the late 1970s as potential carriers for specific drug targeting. External magnetic fields can be used to transport the drugs, for example, to the tumor sites. Although apparently simple, the approach has some important issues, one being the potential accumulation of the nanoparticles, blocking the blood flow or concentrating in diverse organs. It is well-known that metal nanoparticles show the ability to generate heat when subjected to alternating magnetic fields. Consequently, nanocomposite hydrogels in which the hydrogel matrix is combined with metal or metal-oxide nanoparticles can be remotely heated by means of a magnetic field. This phenomenon has been used to control drug release in temperature responsive hydrogels.[36] Therefore, by incorporating magnetic nanoparticles within a hydrogel network, the nanocomposite network can rapidly respond to an external magnetic field, enabling their enhanced controllability and accelerating drug release. Some strategies to improve the delivery of drugs in magnetically responsive hydrogels are discussed below.

Liu *et al.*[37] prepared magnetic hydrogels by mixing PVA matrices and Fe_3O_4 nanoparticles. They found that the amount of drug release can be finely tuned by controlling the switching duration time. It was demonstrated that the magnetic field induces the metal nanoparticles to aggregate reducing the porosity of the hydrogel. In this state, the drug was confined in the network, leading to reduction in the diffusion of the drug through the hydrogel. On the contrary, when the field was turned off, a higher level of drug release was achieved (Figure 4). They also observed that the particle size had significant influence in the drug release behavior, showing that large nanoparticles offered the best magneto-sensitive effects.

To avoid large cluster agglomeration, these magnetic nanoparticles should be stabilized by protective agents. Silica is one of the best studied protective agents, and a novel hydrogel based on chitosan cross-linked β-cyclodextrin grafted with silylated magnetic nanoparticles was synthesized as a drug delivery system for indomethacin.[38]

As mentioned previously, metal nanoparticles are also incorporated into thermosensitive or temperature-pH sensitive hydrogels with the aim of inducing changes in the hydrogel temperature and therefore achieve remotely controlled pulsatile release of drugs. When the temperature is increased above the lower critical solution temperature (LCST), the hydrogel structure collapses, resulting in the expulsion of the incorporated drug molecules. Specifically, a novel biodegradable and injectable thermosensitive hydrogel based on chitosan and Fe_3O_4 has been prepared, and its drug release under an applied magnetic field has been studied. This gel has been used to modulate the release of Bacillus-Calmete-Guérin (BCG) which increased the antitumor effect and caused a high local immune activity in bladder.[39]

In another study, alternating magnetic field (AMF) has been applied to control release from an injectable hydrogel containing both superparamagnetic iron oxide nanoparticles (SPIONs) and thermoresponsive microgels. Such combination permits optimal pulsatile release of small molecule drugs over several weeks, due to the relationship between the microgel volume phase transition temperature (VPTT) and the baseline incubation temperature. The heat generated by SPIONS under an AMF increases the temperature of the microgels over their VPTT, generating free volume inside the composite and, therefore, enhances drug diffusion across the hydrogel.[40]

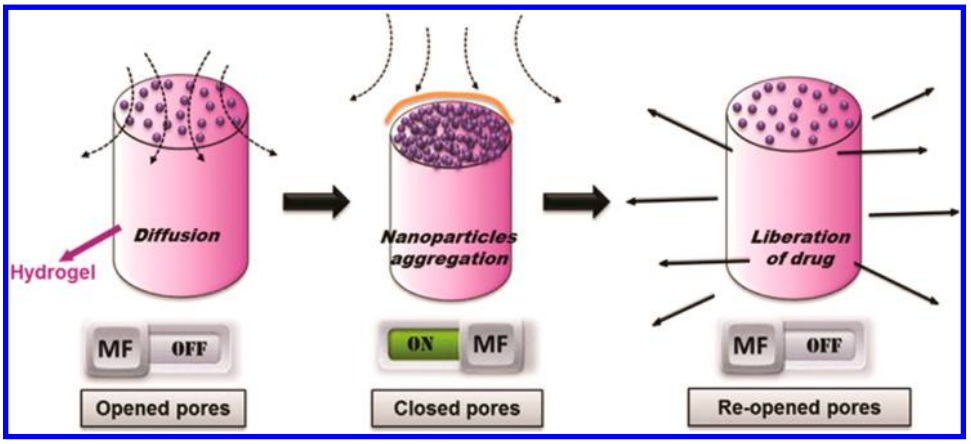


Figure 4. Schematic illustration of the mechanism of pulsatile drug release under magnetic fields. Adapted with permission from ref 37. Copyright 2006, American Chemical Society.

In addition, the introduction of magnetic nanoparticles into hydrogels contributes to the preparation of new materials with self-healing properties. In general, gels are exposed to stress-induced formation of fissures that may affect the integrity of the network structures, resulting in the loss of functionality. To address this challenge, self-healing gels which possess the ability to repair themselves have emerged as a novel class of soft materials.[41] The design of self-healing hydrogels is desirable, not only because it increases the lifetime of the material, but also because it can permit the preparation of injectable materials[42] which can be gelated *in situ* and stay at the target position. In this regard, Wei's group prepared magnetic and self-healing hydrogels by introduction of carboxy modified Fe_3O_4 nanoparticles into chitosan−PEG hydrogels. The fragments of the hydrogel could move under an external magnetic field and then merge together in an integral gel after several minutes. This research constitutes an innovative solution for the issues associated with ordinary injectable polymer-based materials.[43]

Light-Responsive Hydrogels. The stimulus of light is instantaneous and can be distributed with high accuracy in simple and available ways, which renders light-responsive materials very advantageous for different applications. The response of nanoparticles to electromagnetic stimulus has also been applied to the preparation of light responsive hydrogels which can be useful for drug delivery purposes. A photoresponsive hybrid hydrogel loaded with core−shell lanthanide doped upconverting nanoparticles (UCNPs) has been used to convert near-infrared (NIR) light into UV light. When the hydrogel is irradiated with 980 nm light, photodegradation and subsequent release of the embedded therapeutics occur.[44] (Figure 5)

Following a different approach, carbon nanotubes have been used for the preparation of light responsive gels. These nanomaterials are ideal candidates for photothermal therapy because of their strong optical absorbance in the NIR region, which could release significant heat and enhance thermal destruction of cells. For this purpose, multiwalled carbon nanotubes (MWCNTs) were employed as molecular antennae for NIR light combined with thermal-responsive PNIPAm to enhance the photothermal conversion effect in hydrogels.[45]

Graphene oxide is also considered a NIR responsive nanomaterial.[46] It can absorb NIR light and convert it into heat efficiently. In a recent example, Wu *et al.*[47] have prepared a supramolecular gel for pulsatile drug release *in vivo*. Since these soft materials are formed through noncovalent interactions, it is difficult to regulate the drug release properly (physical diffusion or degradation of the hydrogel). To overcome this limitation, the authors incorporated graphene oxide sheets (GOS) into the gel. The obtained hydrogel possesses high mechanical stability, syringe-injectability, and low erosion rate, and the release of the drug is remotely controlled by NIR irradiation.

Gold nanoparticles are also able to absorb visible to NIR light and this fact can be used to generate a local heat. Recently, Strong *et al.*[48] reported the incorporation of NIR absorbing silica−gold nanoparticles onto poly(*N*-isopropylacrylamide-*co*-acrylamide) (NIPAAm-*co*-AAm) hydrogel with potential application in cancer therapy. The local heating, produced by the nanoparticles after light stimulation, is capitalized to cause tissue necrosis, together with controlled delivery of the entangled chemotherapeutic molecules.

Delivery of Hydrophobic Drugs. As already discussed in the introduction, conventional hydrogels are 3D networks of hydrophilic polymers, which typically tend to absorb hydrophilic drugs. In this regard, nanocomposite hydrogels have been designed as innovative solutions to overcome limitations as inefficient hydrophobic drug loading.

For example, hydroxyapatite (HA) nanoparticles were used as drug delivery systems for a water-insoluble anticancer drug, paclitaxel (Tax). The Tax-loaded

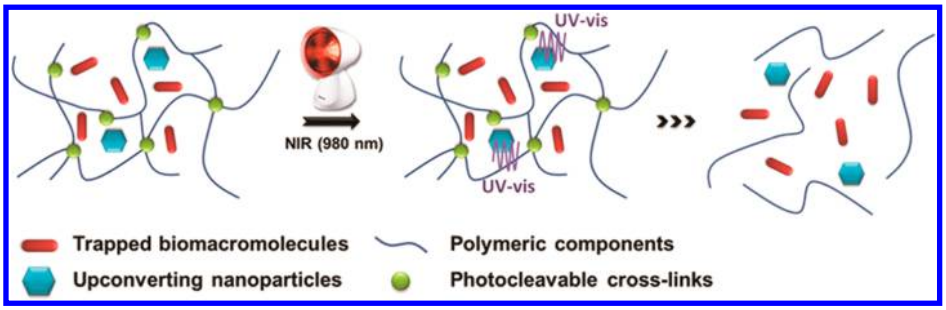


Figure 5. NIR-light-triggered degradation of a photosensitive hydrogel using the UV light generated by encapsulated upconverting nanoparticles. Adapted with permission from ref 44. Copyright 2012, American Chemical Society.

HA was embedded in a collagen gel to result in a Tax/HA/Col gel, which exhibited higher levels of cytotoxic activity than the Tax-containing collagen gel, particularly in highly metastatic MDA-MB-231 cells than the poorly metastatic MCF-7 cells.[49]

Other types of organic–inorganic hybrid materials consisting of layered metal hydroxides (LMHs) have been used. LMHs are widely studied as drug delivery nanocarriers, as they can accommodate various kinds of anionic drugs and transport them into cellular systems efficiently. For example, Gwak *et al.* prepared a hydrogel–inorganic hybrid material, in which agarose and zinc basic salt (ZBS), a type of layered metal hydroxide, were combined to exhibit sustained release of loaded anionic molecules, such as ferulic acid.[50]

Polymeric nanoparticles such as hyper-branched polymers, liposomes, micelles, microspheres, and cyclodextrins, which are widely used as drug delivery systems, have also been incorporated into hydrogels to utilize their drug releasing ability, as well as to improve their mechanical properties.[9] For example, Zhong *et al.*[51] first prepared a dual-drug delivery system of poly(D,L-lactic) microspheres embedded in an alginate hydrogel. In this system, glycyrrhetinic acid (a hydrophobic drug) was encapsulated in the microspheres, while bovine serum albumin (a hydrophilic drug) was loaded in the hydrogel. In another example, Liu *et al.*[52] encapsulated erythromycin (EM) in micelles formed by Pluronic F-127 and then obtained an EM/PF127 hydrogel under a low-intensity UV light, in order to extend EM release and prevent side effects of the drug. One of the main drawbacks of some chemotherapeutic agents is their high hydrophobicity which can be related with dangerous side effects. For this reason, and to increase their water solubility, Paclitaxel (TAX) was loaded in an injectable micelle–hydrogel hybrid system based on Polaxamer 407 and chitosan. *In vivo* studies revealed a reduction in the progression rate of the tumor and diminution in side effects compared with TAX.[53]

A sophisticated example has been recently developed by Nagahama *et al.*[54] in order to control drug release in a novel way. They prepared a new injectable gel through the self-assembly of copolymer micelles, clay nanodisks (CNDs), and doxorubicin (DOX). The drug incorporated into the hydrogel not only serves as cross-linker for gel networks formation, but also controls its own release.

Cyclodextrins (CDs) have also been widely studied as drug delivery systems.[55] As a result of their molecular structure and shape, they are usually used to complex poorly water-soluble drugs, increasing their aqueous solubility. Therefore, incorporation of CDs into hydrogel systems is appropriate for maintaining the swelling properties of the hydrogel, and their hydrophobic interior can facilitate the capture and controlled release of hydrophobic drugs. Cyclodextrin-containing hydrogels can be prepared in many ways.[56] The main strategies can be classified in three broad groups: (i) direct cross-linking of CDs that can be obtained directly using cross-linkers such as ethylene glycol diglycidylether to release cyclosporine A; (ii) copolymerization of CDs with vinyl- or acrylic-*co*-monomers; and (iii) grafting of CDs to preformed polymer networks. Most simply, preformed cyclodextrin–drug complexes can be added into the hydrogel during or after gel cross-linking. The driving forces leading to inclusion complexes are hydrophobic and van der Waals interactions, hydrogen bonding, and changes in surface tension. Recently, Kuang *et al.*[57] prepared an injectable and biodegradable supramolecular hydrogel, using a nucleobase (adenine/thymine)-terminated poly(ethylene oxide)s (A-PEG-A/T-PEG-T) and α-CD. *In vitro* evaluation indicated that the supramolecular hydrogels have adequate biocompatibility, and are appropriate for developing sustained and controlled-release systems of antitumor drugs. Furthermore, these nanocomposite hydrogels showed significant efficacy in inhibition of tumor growth *in vivo*.

Graphene oxide (GO), the "hydrophilic" derivative of graphene, contains a range of reactive functional groups, including hydroxyl, epoxy and carboxylic acid groups. GO and its derivatives as well as composites have been considered ideal materials for the preparation of drug scaffolds by taking advantage of its water-solubility, high specific surface area and good biocompatibility. Moreover, the 2D plane of GO sheets provides large specific surface area to carry drugs *via*

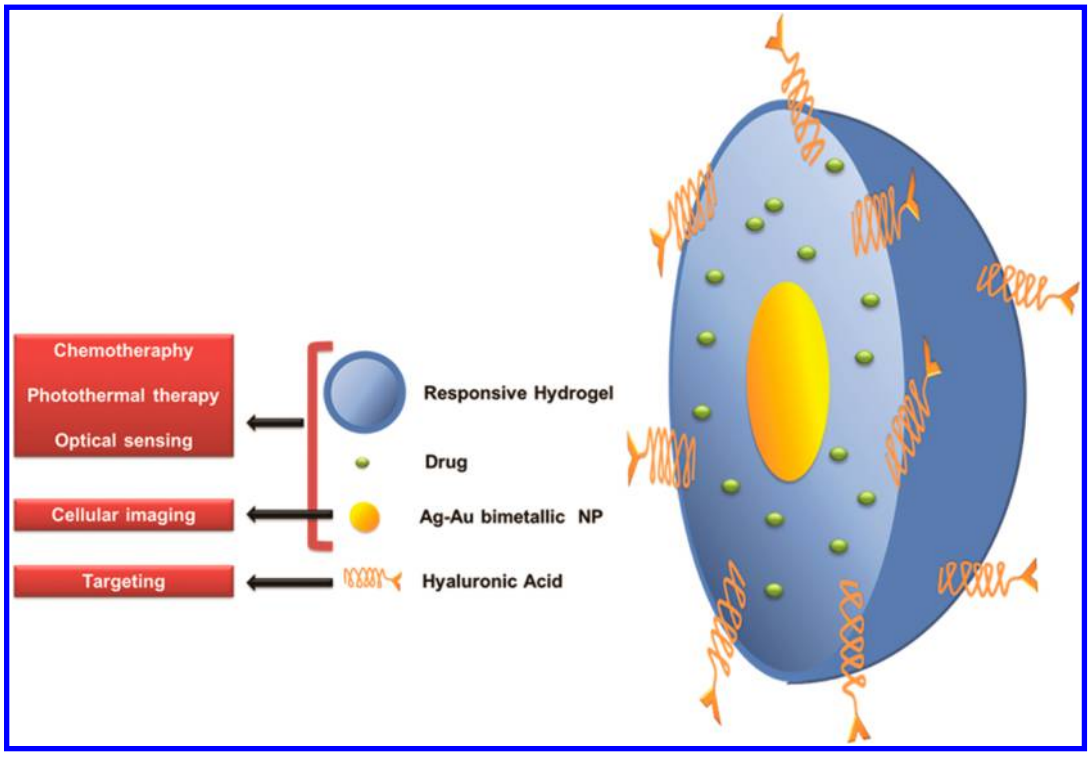


Figure 6. Schematic illustration of multifunctional core−shell nanogel. Adapted with permission from ref 61. Copyright 2010, Elsevier.

surface adsorption, hydrogen bonding, and other types of interactions.[58] Covalent attachment of folic acid, polyethylene glycol, and chitosan to GO provides a potential platform for delivering anti-inflammatory and water-insoluble anticancer drugs such as doxorubicin (DOX), and SN38 (a camptothecin analogue).[59]

Multiresponsive and Multifunctional Systems. Sometimes the swelling kinetics of the smart hydrogels are not as fast as desirable for some applications. The design of hybrid materials, which can deliver their cargo in response of multiple stimuli, allows the preparation of faster responding systems compared to the ones acting in response of a single stimuli. Moreover, to improve the temporal control over drug release, a stimulating solution is the preparation of nanogels, nanoscale networks that provide several advantages inherent in their nanoscale size. In addition, the introduction of nanoparticles in these materials can introduce new functionalities and applicability to the structure.

Targeted drug delivery systems have captivated increased attention in cancer therapy. Active targeting requires the attaching of a ligand which recognizes a specific receptor. The nanoscale size of nanogels, with their high specific surface area, makes it feasible the conjugation of active targeting agents. In addition, due to the higher temperature and lower pH of cancer tissues related to normal tissues, nanogels which structure changes at small pH ranges are very useful to deliver drugs to tumor sites. Hence thermo- and pH-responsive nanogels, with bovine serum albumin encapsulated gold nanoparticles conjugated onto their surface, have been synthesized and further functionalized with a tumor targeting peptide. Chemotherapeutic drug DOX was introduced by electrostatic absorption and cytotoxicity studies proved that the system could deliver the drug, specifically to the tumor with enhanced efficacy and controlled release. Moreover, the red fluorescence emission from gold nanoclusters was used to identify and follow the nanogel *in vitro*.[60]

Wu *et al.*[61] have also reported the preparation of multifunctional core−shell nanogels for simultaneous optical temperature sensing, targeted tumor and combined chemical and photothermal treatment. The thermoresponsive PEG based nanogels had an Ag−Au bimetallic nanoparticle core and hyaluronic acid chains as targeting ligands. The fluorescence intensity of the Ag−Au core can be used for imaging, but also to trigger the release of the anticancer drug under the local temperature increase of targeted zones, induced by NIR irradiation (Figure 6).

In a recent report, the combination of pH sensitive nanogels, a hydrophobic dendrimer, and folic acid as target agent has been used for the delivery of paclitaxel. The incorporation of hydrophobic segments into the nanogel core through cross-coupling of H-40-poly-(ε-caprolactone) (H40-PCL) dendrimer allows hydrophobic drugs loading.[62]

In another example, the covalent attachment of cyclodextrin particles to nanogels gives them the ability to form inclusion complexes, providing in this way a new drug loading and release mechanism based

TABLE 1. Examples of Nanocomposite Hydrogels Whose Properties Are Triggered or Enhanced by Nanoparticles

NANOCOMPOSITE HYDROGELS				
Benefits		**Nanoparticles**		**Ref.**
Controlled Drug Release Under External Stimulus	Electrical	Carbon NPs	MWCNTs	29, 34
			Graphene	33, 34
		Nanoclays		32
	Magnetic	Iron Oxide	Fe_3O_4	37, 43
			Fe_3O_4 and Fe_2O_3	40
	Near-IR Light	Lanthanide UCNPs		44
		Carbon NPs	MWCNTs	45
			Graphene	47
		Gold		48, 61
Controlled Hydrophobic Drug Release		Polymeric NPs	Microspheres	51
			Micelles	52, 54
			Cyclodextrins	57, 63
			Dendrimers	62
		Inorganic NPs	Hydroxyapatite	49
			Layer Metal Hydroxides	50
		Carbon NPs		59
Enhancements in mechanical properties and stability		Carbon NPs	MWCNTs	24, 34
			Graphene	34
		Nanoclays		32
		Polymeric NPs		9
Self-healing		Carbon NPs	SWCNTs and Graphene	70
		Iron Oxides	Fe_3O_4	43
Imaging		Gold		60
		Silver-Gold		61
Targeting		Iron Oxides	Fe_3O_4	38, 39

on these complexes and thus preventing drug release upon media dilution.[63]

CONCLUSIONS AND PERSPECTIVES

On the basis of all the results described in this review, we can conclude that the introduction of nanoparticles in hydrogels can be an innovative means for creating multicomponent systems aiming to achieve a rational design of advanced delivery systems with tunable properties.

Nanoparticles can not only enhance the mechanical properties of the gels but also modulate efficiently its response to different stimuli. We have shown examples of electric, magnetic, and light responsive hydrogels (Table 1). However, with the preparation of new or modified nanoparticles, further stimuli can be studied, like ultrasonication or pressure in responsive systems. As an example, microwaves have been employed recently in thermotherapy, producing diathermia (heating up to 41 °C), hyperthermia (heating into the interval of 41−45 °C), and thermoablation (over 45 °C). Carbon nanostructures are excellent microwave absorbent, and thus, in thermoresponsive gels, the electromagnetic-induced hyperthermia from carbon nanomaterials could cause the volumetric change in the hydrogel, inducing the release of the drug. In this sense, a volume change in a smart hydrogel/conductive polymer nanocomposite induced by microwave irradiation has recently been reported.[64]

Moreover, the introduction of nanoparticles transfers new functionalities to the system. Some further examples could be the formation of polymeric networks with quantum dots (QDs), which has already been used for the development of materials with photoluminescent properties and thus for sensing and drug delivery applications.[65] Likewise, novel silver nanocomposite hydrogels based on acrylamide have been reported.[66] These structures are potentially useful in treating infections due to the antibacterial properties of silver.

Considering the possibility of functionalization/modification of nanoparticles, the development of hydrogels incorporating these modified structures can be also considered in order to further introduce new functionalities and applicability to the system, paving the way for the development of hybrid hydrogels with specific molecular responses, for example, to glucose. Some examples have been already discussed about the synthesis of gels with targeting and imaging agents, but the advancement in hydrogel technology will produce new systems that enhance diagnostics and controlled drug release. Carbon-based nanoparticles, such as carbon nanotubes and graphene, have attracted much attention in recent years owing to their excellent properties (*i.e.*, mechanical strength, flexibility, thermal, electrical, and optical conductivity). Therefore, these structures are considered highly promising materials to incorporate multifunctionality in stimuli-responsive hydrogels. Carbon nanostructures can interact physically or covalently with the polymeric chains, and although they have usually a hydrophobic nature, different techniques have been developed to enhance their dispersions within the composite network. Moreover, carbon nanomaterials can be functionalized in order to introduce polar groups in their structure, and these chemical modifications can provide new possibilities for precise molecular recognition events. Composite materials based on carbon nanotubes and polymeric hydrogels have been applied as innovative drug delivery devices combining properties of both hydrogels and CNTs.[67]

In recent years, there has been noticeable progress in the development of clinically applied hydrogels, while clinical uses of nanoparticles are rare. The combination nanoparticle−hydrogel could overcome the limitations and drawbacks associated with the use of nanoparticles as drug delivery systems. Additionally, there is still a need for studies focusing on the interactions between nanoparticles and polymers inside the hydrogel in order to tailor their properties to special drug delivery requirements.

The preparation of nanogels has also been described. Compared to macroscopic hydrogels, nanogels show faster responsiveness, and due to their nanometric size, they have been proposed as ideal drug delivery systems for various organs including brain and lungs.[3] It has been postulated that the swellable nanogels have limited clearance by the lungs, allowing a longer term release of the drug, by slow degradation, once these particles are inhalated.

Nanogels have also shown good potential to safely transport macromolecules across the blood brain barrier. Progress in this field would have impact in new clinical treatments. Recently, some authors have described an efficient nanocarrier scaffold with sequential intraintercellular delivery as an innovative mechanism for deep tumor penetration. It consists of a reversible pH-responsive nanogel that can be internalized by the cancer cells. At the endosomal or lysosomal pH, the gel protonates, producing an electrostatic repulsion which triggers the swelling of the gel along with the release of the drug. The large volume of the positively charged hydrogel produces the bursting of the endolysosomes and the nanogel is transported into the cytosol where it returns to its original size, due to higher pH in that region. The shrunk gel escapes from the dead cell, and it reproduces the process infecting a new cell.[68] The layer by layer assembly technique has also been used in the preparation of multilayer ultrathin films, obtaining hydrogel nanocomposite films with higher loading capacity.[69]

The development of self-healing hydrogels has also been discussed in this review. Self-healing materials are commonly found in living organisms, but this behavior is unusual in artificial systems. Interestingly, some authors have recently shown that the self-recovery time of some gels is shortened by the introduction of carbon nanotubes or reduced graphene oxide within the gel.[70] The hybrid gels also exhibited semiconducting behavior what facilitates new functionalities.

Finally, the use of hydrogels for delivering therapeutic cells is another interesting aspect to consider in regenerative medication. In this case, the objective is to use hydrogels as platforms where cells can reorganize into more sophisticated tissues.[71] This strategy together with the use of carbon nanotubes could be applied, for example, to neuronal growth. Carbon nanotubes have already shown to have a remarkable affinity for neurons,[72] and their integration in 3D networks could contribute to the developing of these cells. The combination of new approaches using microengineering and 3D hydrogels will be a potent tool in the design and tailoring of these materials.[73]

Conflict of Interest: The authors declare no competing financial interest.

Acknowledgment. Part of the work described in this article has been supported, by the Spanish Ministerio de Economía y Competitividad (project CTQ2011-22410 and project IPT-2012-0429-420000), the University of Trieste and the Italian Ministry of Education MIUR (cofin Prot. 2010N3T9M4 and FIRB prot. RBAP11ETKA) and the EU FP7-ICT-2013-FET-F GRAPHENE Flagship project (No. 604391).

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