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Perspective

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Thermoresponsive Nanocarriers Transduced by Inorganic Nanoparticles: Design Considerations and Applications in Drug Delivery

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Thermoresponsive polymers, which undergo phase transitions within physiologically tolerated temperatures, are key to developing drug delivery systems (DDS) with precise spatial and temporal control, potentially addressing challenges associated with the treatment of complex diseases. Inorganic nanoparticles with unique optical, electronic, and magnetic properties serve as efficient transducers, converting external stimuli into localized heat to trigger thermoresponsive nanocarriers. This review explores the design and application of thermoresponsive nanocarriers transduced by inorganic nanoparticles as DDS. Following a brief description of temperature-triggered phase transition of polymers and heat generation mechanisms by inorganic nanoparticles, strategies to integrate these components into hybrid systems are described. Examples demonstrating the utility of these hybrid systems as advanced DDS are discussed, highlighting their potential for precise drug release alongside theranostic capabilities by combining therapy with imaging. Despite the challenges in design, synthesis, and biological applications, thermoresponsive polymer-inorganic hybrids hold immense promise for transforming drug delivery and biomedical innovations.

Keywords: Thermoresponsive polymers, Inorganic nanoparticles, Heat transduction, Organic-inorganic hybrid assemblies, Drug delivery.

1. Introduction

There is a tremendous need in medicine to advance treatment solutions in a more controlled manner with time and space precision in order to cope with complex diseases, such as cancer. Of particular interest is to shift from traditional drug delivery systems (DDS) to stimuli-responsive ones as they are designed to favor the release of their cargo only in the presence of stimuli. Physical or chemical stimuli that are either induced externally or present in the milieu of the pathologic condition represent the triggering factors that control the cargo release. Stimuli-responsive, 'smart' polymeric carriers, which undergo fast and reversible physicochemical macroscopic changes in response to an internal (e.g. pH, redox potential, presence of a specific enzyme) or external stimulus (such as temperature, light, electric or magnetic field), have been explored for a broad range of applications including controlled drug delivery, tissue engineering, and biosensing.[1] Among those, thermoresponsive polymers that exhibit phase transition above or below

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Dr. Gül Kozalak holds a PhD in Molecular Biology and Genetics, with extensive expertise in cancer biology, focusing on drug resistance, apoptosis, and drug delivery systems. Her innovative research incorporates the use of nanoparticles and organ-on-chip systems to model and address complex biological challenges. She completed postdoctoral work at Sabancı University and earned a prestigious EMBO Fellowship at FHNW, contributing to advanced translational research. Currently a researcher at Sabancı University, Dr. Kozalak is committed to bridging molecular insights with therapeutic applications, driving forward innovative solutions in precision medicine and sustainable drug delivery technologies.

Prof. Dr. Cornelia G. Palivan received her Ph.D. degree in physics at the University of Bucharest, after a two years research stage at the University of Geneva. She is currently professor in physical chemistry of the University of Basel and member of the Steering Committee of the National Centre of Competence in Research "Molecular Systems Engineering." Her research team develops functional bio-artificial systems that interface biomolecules with supramolecular synthetic assemblies for complex reactions and communication at the nanoscale. Such bio-artificial systems support applications in domains such medicine, catalysis, food- or environmental-sciences. She received during her career several awards and fellowships.

Prof. Dr. Oya Tagit obtained her PhD at the MESA+ Institute for Nanotechnology, University of Twente, The Netherlands. Following a career in a highly international landscape (France, Singapore, Ireland), she is currently leading the Group of Biointerfaces at FHNW. She is also PI and member of the executive committee at the Swiss Nanoscience Institute. Utilizing an interdisciplinary approach, the group of BioInterfaces aims to address currently unmet biomedical needs in the diagnosis, monitoring, and treatment of complex diseases, such as cancer and resistant infections, with engineered nanoparticles tailored for the desired biological targets and functions.

a critical temperature have emerged as indispensable tools to obtain stimuli-responsive DDS due to their versatility, adaptability to physiological conditions, and straightforward application.

In biological systems, temperature changes that can be tolerated without sustaining damage to the cells spans a broad range between freezing temperature of water to around 42 °C.[2] On the contrary, cells can optimally function only within a narrow window of pH or ionic strength, and stimuli beyond these physiological limits can hamper cell viability. Consequently, unlike e.g. pH-responsive systems, the use of temperature-responsive polymers is not constrained by the need to maintain temperature changes within a narrow window to avoid damage to the cells. Interestingly, the most commonly used thermoresponsive polymers display phase transition temperatures within the physiologically tolerated range.[3] The transition temperature can be further adjusted by e.g. varying the polymer chain length and branching, carefully balancing the hydrophilic and hydrophobic components of amphiphilic block copolymers and functionalizing the chain ends with polar or charged groups. Utilizing thermoresponsive polymers with finely-tuned phase transition temperatures as building blocks serves for the development of nanocarriers triggered by temperature variations, that enables a controlled cargo release at target sites.

Indeed, temperature is a unique stimulus in the sense that it can be considered as both an internal and external trigger. As such, certain pathological tissues naturally exhibit hyperthermia, with temperatures reaching up to 42 °C, which can serve to trigger thermoresponsive nanocarriers specifically in diseased regions.[4] Alternatively, these nanocarriers can be triggered by externally increasing the temperature using various tools as heat sources. In this context, inorganic nanoparticles with unique optical, electrical, thermal, and magnetic properties stand out as promising transducers that can interact with several types of external stimuli and convert them into different physical, chemical, and mechanical forms of energy, including heat. The transduction mechanism for thermal conversion is induced and directly influenced by the physicochemical properties of the inorganic nanoparticles including their size, morphology, composition, aspect ratio, etc. The high versatility of inorganic nanoparticles allows for a precise control over the colloidal and optical properties to enhance their photothermal conversion efficiency. While photothermal conversion with plasmonic nanostructures and magnetic hyperthermia with magnetic nanoparticles are commonly explored, examples with high- and low-frequency electromagnetic waves are emerging.

Here we present an overview of thermoresponsive nanocarriers transduced by inorganic nanoparticles for drug delivery applications. We briefly introduce the concepts of temperature-triggered phase transition of thermoresponsive polymers and heat generation mechanisms of inorganic nanoparticles associated with the polymer supramolecular assemblies. Then we focus on various methods to construct temperature responsive polymer-inorganic nanoparticle nanohybrids and present their advantages and actual limitations. The main prerequisite to take advantage of localized heating with inorganic nanoparticles to trigger phase transition of thermoresponsive nanocarriers is to efficiently combine these two systems. The development of such polymer-inorganic nanohybrids poses several challenges from an adequate heat generation capacity also in deep tissue layers to precisely controlled phase transition temperatures without affecting the stability of encapsulated cargo, and therefore requires several design considerations. Finally, we discuss recent examples of polymer-inorganic nanoparticles hybrids and their application as advanced drug delivery systems. Although research on responsive polymer-inorganic hybrid nanoparticle assemblies is still in its early stages, these systems hold immense potential for delivering diverse payloads with precise spatial and temporal control over their release. Additionally, many inorganic nanoparticles used for heat generation to trigger payload release also serve as effective biomedical imaging probes. Therefore, combining thermoresponsive drug delivery systems with inorganic nanoparticles can facilitate the development of advanced theranostic agents that seamlessly combine therapy and imaging.

2. Thermoresponsive Polymer Carriers

2.1. Temperature-Triggered Phase Transition of Thermoresponsive Polymers

Thermoresponsive polymers are generally divided into two categories depending on how their solutions react to the changes in temperature. For a polymer solution binary system, the solubility changes with temperature and composition (polymer volume fraction) can be represented on a phase diagram. The phase boundary, binodal, indicates the temperature and composition at which the solution changes from a single phase to two separate phases. Polymers with a lower critical solution temperature (LCST) exhibit a concave binodal curve

(*Figure 1A*), being soluble below a critical temperature, and insoluble above it. On the contrary, polymers with an upper critical solution temperature (UCST) exhibit a convex binodal curve (*Figure 1B*), being soluble above a critical temperature, and insoluble below it. The critical temperatures (T_c) for LCST and UCST polymers are the extreme points on the binodal curve, below and above which the polymer and solvent are completely miscible in all compositions. Phase separation above LCST or below UCST allows for the determination of the critical temperature at which the visible phase separation occurs, the cloud point temperature (T_{cp}), through turbidity measurements. The terms T_{cp} and T_c (LCST/UCST) are often confused in the literature. While T_c is an intrinsic thermodynamic property, T_{cp} of a polymer solution depends on the measurement conditions such as concentration, heating/cooling rates, and measurement wavelength due to non-equilibrium effects and scattering, and approaches to T_c values in dilute solutions. The discussion in this review are based on the reported T_{cp} values as approximation of the LCST and UCST.[5–7]

While polymers exhibiting LCST behavior in aqueous solutions are considerably more common and extensively studied than those with UCST behavior, there are polymers well-known for their UCST behavior in organic solvents.[8] When LCST polymers are used for the construction of nanocarriers, polymer chains remain soluble below their LCST, while upon heating above this temperature, they undergo a hydrophilic-hydrophobic transition with a coil-to-globule change in morphology. During this process, polymer-polymer interactions prevail polymer-solvent interactions, resulting in shrinkage and the expulsion of internal water molecules, which triggers the release of entrapped cargo (*Figure 1C*). However, the cargo is usually not entirely released from the nanocarriers due to a residual miscibility of the hydrophobic core with the payload beyond the LCST, which limits the control of the release. On the contrary, nanocarriers based on UCST polymers can offer an advantage of complete drug release. UCST-type polymers undergo a hydrophobic-hydrophilic transition upon heating above their UCST, as the interactions between polymer chains (hydrogen bonding or electrostatic interactions) are destabilized at higher temperatures. Therefore, UCST-based nanoassemblies disintegrate at elevated temperatures, fully releasing encapsulated cargo (*Figure 1D*).[9]

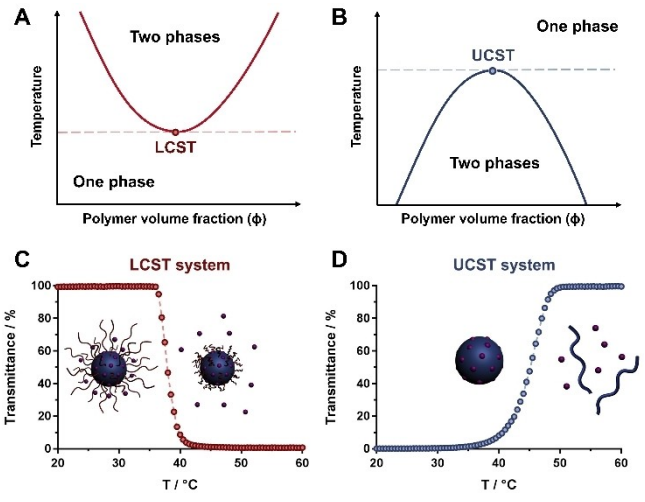
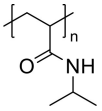
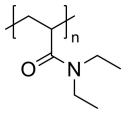
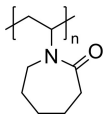
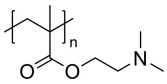
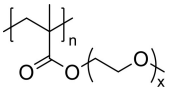
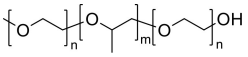
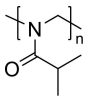
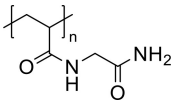
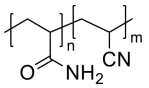
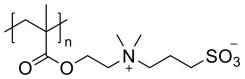
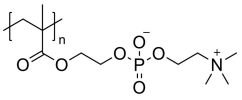


Figure 1. Phase diagrams for polymer solvent mixtures of (A) LCST and (B) UCST polymers. The temperature-triggered release from (C) LCST and (D) UCST polymeric nanocarriers. Adapted with permission from [5]. Copyright 2019, Elsevier.

There are various LCST polymers that were synthesized to generate responsive carriers. Chemical structures of discussed thermoresponsive polymers are included in *Table 1*. LCST of thermoresponsive polymers can be adjusted through copolymerization, where adding hydrophilic comonomers tends to increase the LCST, while hydrophobic comonomers generally lower it. Poly(N-isopropylacrylamide) (PNIPAM) is the most extensively studied thermoresponsive homopolymer with an LCST around 32 °C, making it particularly relevant for biomedical applications due to its proximity to physiological temperature. In addition, LCST of PNIPAM is only slightly affected by environmental factors such as polymer concentration, pH or ionic strength, rendering it a robust platform for controlled release.[10] Other commonly investigated thermoresponsive polymers exhibiting LCST include poly(*N*-vinylcaprolactam) (PNVCL) with an LCST between 25 and 35 °C, poly(*N*,*N*-diethyl acrylamide) (PDEAAm) with an LCST between 25 and 32 °C, poly[2-(dimethylamino)ethyl methacrylate] (PDMAEMA) with an LCST of around 50 °C, and poly(2-isopropyl-2-oxazoline) with an LCST of around 36 °C.[11,12] In case of poly[oligo(ethylene glycol) methacrylate]s (POEGMA), the LCST of polymers varies depending on the number of ethylene glycol (EG) units in the monomer side chain, with LCST values ranging from about ~26 °C for 2 EG units to ~90 °C for 8–9 EG units.[11] In addition to varying the number of hydrophilic and hydrophobic comonomers, the LCST of thermoresponsive polymers can also be tuned by varying the molecular weight, end-groups, polymer architecture, and the degree of branching, offering a high versatility to obtain precisely-controlled DDS.[13]

Table 1. Chemical structures of commonly used thermoresponsive polymers.

Type	Name	Abbr.	Structure
LCST	poly(*N*-isopropyl acrylamide)	PNIPAM	
	poly(*N*,*N*-diethyl acrylamide)	PDEAAm	
	poly(*N*-vinylcaprolactam)	PNVCL	
	poly[2-(dimethylamino)ethyl methacrylate]	PDMAEMA	
	poly[oligo(ethylene glycol) methyl ether methacrylate]	POEGMA	
	poly(ethyleneoxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide)	Pluronic®	
	poly(2-isopropyl-2-oxazoline)	PiPrOx	
UCST	poly(*N*-acryloyl glycinamide)	PNAGA	
	poly(acrylamide-*co*-acrylonitrile)	P(AAm-*co*-AN)	
	poly(sulfobetaine methacrylate)	PSBMA	
	poly(phosphobetaine methacrylate)	PPBMA	

Temperature-sensitive polymers exhibiting UCST behavior are less commonly studied compared to the ones with LCST, largely due to their higher sensitivity to environmental factors such as ionic strength, pH and polymer concentration.[14,15] Poly(*N*-acryloyl glycinamide) (PNAGA) is the most widely investigated UCST polymer, and is often considered as the UCST counterpart of PNIPAM. PNAGA's thermoresponsive behavior originates from hydrogen bonds that can form between two H-donor sites on the nitrogen atoms and two H-acceptor sites on the oxygen atoms in the NAGA monomer side chain. However, UCST of

PNAGA is only observed if a purely non-ionic polymer is obtained without any traces of charged impurities, as the introduction of a few ionic groups is able to completely suppress its UCST behavior.[15] PNAGA exhibits a UCST of ~27 °C, which can be increased by copolymerization with a hydrophobic monomer, or decreased by copolymerization with a hydrophilic monomer.[5] Other UCST polymers relying on hydrogen bonding are poly(acrylamide-*co*-acrylonitrile) (P(AAm-*co*-AN)) copolymers, which demonstrate a broad range of critical temperatures (5–60 °C) that can be achieved by adjusting comonomer ratio.[9,16] Zwitterionic polymers which rely on electrostatic interactions are another class of thermoresponsive polymers with UCST behavior. Their monomers bear both positive and negative charges in the side chain, giving an overall neutral charge to the polymer. Examples include poly(sulfobetaine)s and poly(phosphobetaine)s. In addition to molecular weight and polymer concentration, the UCST behavior of these polymers is heavily influenced by the type of counterions present and the addition of salts.[17]

The choice of the polymerization technique for the synthesis of thermoresponsive polymers is governed by the intrinsic chemical properties of the monomers. The majority of polymers exhibiting LCST and UCST are synthesized from acrylates or acrylamides, making controlled free radical polymerizations (CFRPs), such as atom transfer radical polymerization (ATRP), reversible addition fragmentation chain-transfer (RAFT) polymerization, and nitroxide mediated polymerization (NMP) extensively used.[18] Copolymerization with other acrylic monomers can be used to tune the critical temperature, as in the case of P(AAm-*co*-AN).[16] A special consideration needs to be given to the polymerization conditions during the synthesis of polyzwitterions, such as the addition of salt to enhance the stability and solubility of the monomers.[19] Furthermore, CFRPs also allow for easy post-polymerization functionalization, often via click chemistry, through functional initiators or monomers.[20,21] On the other hand, thermoresponsive polyoxazolines are synthesized through cationic ring opening polymerization (cROP). The use of microwave reactors for cROP of 2-oxazolines has significantly streamlined the synthesis of these polymers, offering simplified reaction setups while maintaining excellent control over molecular weight distribution.[22,23] In contrast, Pluronics®, based on thermoresponsive poly(propylene oxide), are synthesized through an anionic ring-opening polymerization, although they are predominantly purchased as the synthesis is technically demanding.

2.2. Nanocarriers Generated by Thermoresponsive Polymers

By utilizing thermoresponsive polymers as building blocks, nanocarriers that respond to temperature changes can be produced, enabling on-demand release upon changes in environment temperature. Thermosensitive nanocarriers display diverse responses to temperature changes depending on their architecture. In a straightforward approach, thermoresponsive polymers can be used as coatings for core-shell nanoparticles, providing responsiveness while maintaining structural integrity. For polymers exhibiting LCST, the core-shell nanoparticles remain individually dispersed at temperatures below LCST as polymer chains are hydrated. However, at temperatures above LCST, polymer solubility decreases, leading to a reduction in shell thickness due to polymer chain collapse and, potentially, nanoparticle aggregation.[24] On the contrary, for core-shell nanoparticles with UCST, polymer chains extend with the increasing temperature, acting as gatekeepers that regulate the release of loaded cargo.[25]

More complex polymeric supramolecular architectures, such as micelles and polymersomes, are formed through self-assembly of amphiphilic block copolymers in aqueous solutions.[26] Polymeric micelles possess an inner hydrophobic core with hydrophilic blocks surrounding it as an outer shell. While the core can entrap hydrophobic cargo, the hydrophilic shell provides colloidal and structural stability in aqueous solutions.[26] Thermoresponsive micelles are obtained when at least one of the blocks of the amphiphilic block copolymer exhibit LCST or UCST. Most commonly, the hydrophilic block of the copolymer exhibits LCST behavior, where the increase of temperature above LCST triggers the collapse of micellar nanostructure, enabling cargo release. Based on this concept, thermoresponsive micelles were constructed from various classes of thermoresponsive polymers, such as PNIPAAm-*b*-PMMA,[27] PNIPAAm-*b*-PLA[28] and PDMAEMA-*b*-PCL-*b*-PDMAEMA[29] block copolymers. Polymers with UCST have also been used for the construction of thermoresponsive micelles, where hydrophobic blocks become hydrophilic above their UCST, resulting in disassembly upon heating. This approach was demonstrated with PEG-*b*-P(Aam-*co*-AN)[30] and PEG-*b*-P(NAGA-*co*-AN)[31] block copolymers for temperature-triggered cargo release.

Polymeric vesicles (polymersomes) are comprised of a bilayer of amphiphilic block copolymers, characterized by their ability to encapsulate both hydrophilic cargo within the inner aqueous cavity and hydrophobic cargo within the membrane.[32] Because of their hollow intrinsic compartmentalised architecture, polymeric vesicles are often found as carriers in drug delivery applications.[33] Compared to thermoresponsive micelles, there are only a few examples of thermoresponsive polymersomes in the literature. Triblock copolymers PVCL-*b*-PDMS-*b*-PVCL[34] and PNIPAM-*b*-PDMS-*b*-PNIPAM[35] were used to form thermoresponsive vesicles, whose vesicular structure collapses when heated above LCST. Polymersomes exhibiting UCST behavior were also developed, wherein the increase of temperature results in controlled disassembly.[36]

Nanogels are another class of nanocarriers that can be prepared using thermoresponsive polymers. These crosslinked hydrogel particles with nanoscale dimensions, typically ranging from 20 to 250 nm, feature high swelling ratios and water content.[37] Due to their predominantly hydrophilic nature, nanogels demonstrate excellent biocompatibility with a high loading capacity. Both hydrophobic and hydrophilic cargo, including small molecules, oligonucleotides, and proteins[38] can be encapsulated within the crosslinked networks of nanogels. Based on the polymer and crosslinker components, thermoresponsive nanogels with reversible shrinkage-swelling behavior in response to changes in temperature can be synthesized. This property enables controlled release of encapsulated cargo and is commonly achieved using LCST polymers, such as PNIPAM, PNIPMAM, PDEAAM, PVCL, POEGMA, and their respective copolymers.[39] In case of UCST polymers, nanogels undergo a volume phase transition and swell when the temperature rises above their UCSTs, unlike UCST micelles which tend to dissociate under similar conditions.[40,41]

While supramolecular assemblies were used for their thermo-responsibility in various DDS, here, we focus only on their combination with nanoparticles acting as transducers. Such hybrid systems have the unique advantage of a finer response to local temperature changes induced by the transducers present in the assemblies.

3. Heat Generation by Inorganic Nanoparticles

Inorganic nanoparticles categorized as metal, ceramic, and semiconductor, display unique optical, electrical, thermal, magnetic, and biological properties at the nanoscale.[42,43] They are crucial in advancing nanosized devices for biomedical applications, holding a privileged position in the field.[44] The unique properties of these nanoparticles allow them to interact with various types of external stimuli and convert them to different physical, chemical, and mechanical forms, including heat. The shape of inorganic nanoparticles impacts their effectiveness as heat transducers, as the heat transfer of nanoparticles is increased with an increased surface-to-volume ratio.[45] While spherical nanoparticles are relatively easy to synthesize and provide a large surface area, their heat transfer efficiency is lower than non-spherical nanoparticles.[46] Anisotropic nanoparticles like nanorods and nanoplatelets can align with the polymer matrix and enhance thermal conductivity.[47] For example, gold nanorods display both longitudinal and transverse plasmon absorption peaks due to the difference in their length and diameter. Star-shaped nanoparticles with their multiple arms extending from the central core can increase the contact area with the polymer matrix, and their plasmonic properties make them suitable for optical heating.[48] The aggregated structure in nanoclusters can also enhance heat transfer due to the increased effective surface area. Various transduction mechanisms by inorganic nanoparticles to generate heat are discussed in the following sections. An overview of commonly used inorganic nanoparticles as heat transducers is given in *Figure 2*.

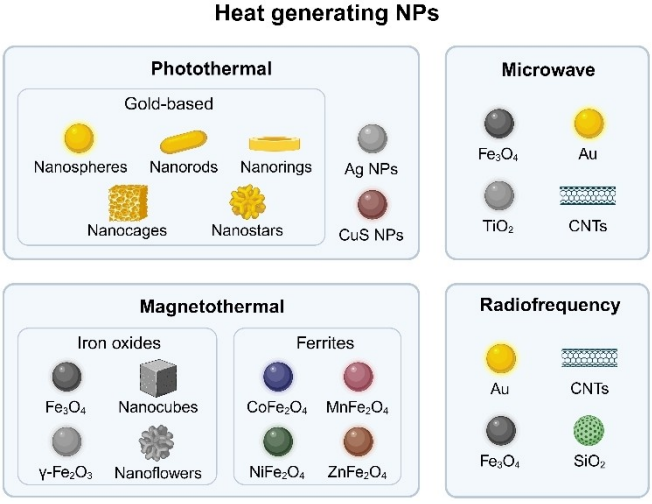


Figure 2. Nanoparticles commonly used as heat transducers categorized by their transduction mechanism.

3.1. Photothermal Conversion

Nanoparticles made from noble metals, such as gold (Au), can generate heat when exposed to certain wavelengths through a plasmonic photothermal conversion process. These nanoparticles absorb and scatter light at specific wavelengths due to Localized Surface Plasmon Resonance (LSPR).[49] LSPR phenomena occur when the frequency of incident photons is consistent with the collective oscillations of electrons in the conduction band. The resonance frequency, i.e., the wavelength at which LSPR occurs, strongly depends on the nanoparticle size, shape, and particularly the aspect ratio.[50] These metal nanoparticles, when subjected to LSPR, can absorb light energy and dissipate it through various mechanisms. In instances where the absorbed energy is non-radiatively dissipated, energetic 'hot' charge carriers are generated within the plasmonic nanostructure. These 'hot' electrons are transformed into metal lattice phonons via electron-lattice collisions, leading to a rise in metal lattice temperature. Eventually, this thermal energy diffuses into the surrounding environment within nanoseconds through phonon-phonon scattering.[51] The generated local hyperthermia, prominently observed in Au and Ag nanoparticles, is effectively utilized in various biomedical applications, particularly facilitated by the large absorption cross sections of plasmonic nanoparticles in the near-infrared (NIR) region, which is a suitable window for biological systems.[52]

In addition to noble metals, semiconductor nanoparticles have been explored in NIR photothermal conversion.[53] Particularly, CuS nanoparticles have attracted attention due to their low cost and low toxicity, and high photothermal conversion efficiency.[53] Unlike the optical absorption of noble metal nanoparticles that is affected by the dielectric constant of the surrounding medium, the NIR light absorption of CuS nanoparticles was hypothesized to be intrinsic and a result of intraband d–d transition of Cu^{2+}, which makes their optical absorption immune to the changes in the environment.[53] However, an efficient photothermal conversion with CuS nanoparticles is typically achieved using NIR irradiation at 980 nm (instead of 808 nm used for noble metals), which raises concerns due to absorption of this wavelength also by water. In this case, temperature elevation could occur in all exposed biological tissues even without ablation agents, and potentially cause unintended damage. Therefore, further investigations are needed before the practical application of CuS nanoparticles excited with 980 nm lasers in photothermal conversion.

3.2. Magnetothermal Heating

Materials comprising ferromagnetic metals (e.g. Fe, Co, or Ni), ferrimagnetic metal oxides (e.g. Fe_3O_4) and doped ferrites ($MnFe_2O_4$) display superparamagnetic behaviour at the nanoscale. The high magnetization exhibited in the presence of a magnetic field has been exploited in various biomedical applications including targeted drug delivery, magnetic hyperthermia, magnetic resonance imaging, and biosensing.[44,54,55] The heating effect is driven by the energy distribution mechanisms within the nanoparticles, namely Neel relaxation and Brownian relaxation.[56] Neel relaxation describes the fluctuations in the magnetization direction of the magnetic core within a nanoparticle, which occur as a result of thermal energy. When an external magnetic field is applied, these fluctuations can lead to heat generation. This phenomenon is particularly relevant for nanoparticles that are less than 10 nm in size. Heat is produced during the reorientation of magnetization, especially when the nanoparticle interacts with a cell. Furthermore, the relaxation time is temperature-dependent, thereby facilitating the controlled heating of magnetic nanoparticles.[57] Brownian relaxation describes the rotation of nanoparticles induced by an alternating magnetic field and the associated heat generation. The ability of these nanoparticles to rotate freely is significantly influenced by the viscosity of the surrounding medium.[58] Typically, Brownian relaxation becomes the dominant mechanism for nanoparticles exceeding 10 nm in size. Both relaxation mechanisms play a crucial role in the heating efficiency of magnetic nanoparticles. It is essential to note that the dominance of either mechanism is contingent upon the size of the nanoparticle and the viscosity of the medium in which it is situated.

Heating efficiency can be influenced by several factors, including the amplitude and frequency of external magnetic field, magnetic anisotropy, magnetization, interactions between particles, as well as the size, size distribution, and shape of magnetic nanoparticles.[59–61] Understanding these elements is essential for optimizing heating performance in relevant applications.

3.3. Microwave and Radiofrequency Hyperthermia

Microwaves are electromagnetic radiation (EMR) with frequencies typically between 300 MHz and 300 GHz.[62] In this frequency range, microwave energy is absorbed by water molecules and ions present in the tissues, and converted into heat.[63] Inorganic nanoparticles can serve as nano-antennas that effectively absorb incoming microwaves and convert this energy into thermal energy.[64] Importantly, the intensity of microwave hyperthermia can be adjusted according to the specific nanoparticles and microwave frequencies employed.[65] Microwave hyperthermia functions analogously to microwave ovens, relying on the interaction between microwaves and nanoparticles. Within a microwave field, electric dipoles undergo continuous rotational motion, leading to the absorption of microwave energy, which is subsequently released into the surrounding environment as heat.[66] Additionally, when microwaves encounter inorganic materials with magnetic properties, a portion of the microwave energy is absorbed by these materials.[67] This process, referred to as ferrite resonance, results in the conversion of microwave energy into heat through the vibrational motion of the magnetic dipoles present within the material.[67] Metallic nanoparticles demonstrate high electrical conductivity due to their significant electron content. Furthermore, the transparency exhibited by metal oxide and hybrid nanoparticles-attributable to their low relative permittivity and conductivity-further enhances their effectiveness in microwave heating applications.[68]

Radiofrequency energy comprises electromagnetic waves emitted at frequencies between 3 kHz to 300 GHz. When subjected to this energy field, inorganic nanoparticles can generate heat via different transduction mechanisms. For metal nanoparticles, heat generation takes place through resistive (ohmic) losses due to induced Eddy currents.[69] This resistance to the flow of induced electric currents causes the energy to be dissipated as heat. In the case of magnetic nanoparticles, they oscillate in response to the radiofrequency field, which leads to energy loss through Néel and Brownian relaxation, contributing to localized heating.[70] Ceramic nanoparticles exhibit polarization under the influence of the radiofrequency field, causing energy to be dissipated as heat due to dielectric losses.[71]

Several types of nanoparticles have been explored in radiofrequency-induced hyperthermia.[72] Among those, Fe_3O_4 nanoparticles are increasingly recognized for their ability to significantly enhance heat generation.[73] Au nanoparticles are often preferred in various applications due to their superior biocompatibility and their capacity for straightforward surface functionalization. These nanoparticles have the capacity to absorb radiofrequency waves, resulting in an increase in temperature within targeted tissues.[74] Moreover, carbon nanotubes (CNT) are being explored for their potential use in radiofrequency hyperthermia due to their exceptional thermal conductivity and biocompatibility.[75] Mesoporous silicon nanoparticles (MSNs) exhibit a remarkable capacity to enhance the efficacy of radiofrequency-assisted hyperthermia by generating heat in a controlled manner.[76]

Regardless of the energy source or transduction mechanism, hyperthermia generation by inorganic nanoparticles has proven efficient in various biomedical applications, particularly therapies involving tumor eradication. Indeed, inorganic nanoparticles serve as versatile theranostic nanosystems due to their ability to directly kill diseased cells, and function as imaging agents.[77–79] The heat generated by inorganic nanoparticles can also be used for triggering the release of payload from thermoresponsive nanocarriers, which requires an effective combination of these two systems. In the next section, we delve into designing such polymeric/inorganic hybrid assemblies, followed by their applications in drug delivery.

4. Design Considerations for Thermoresponsive Polymer/Inorganic Nano hybrids

Careful consideration must be given not only to the selection of inorganic nanoparticles and thermoresponsive polymers and assemblies, but also to the way these constituents are combined to generate stimuli-responsive carriers. These factors critically influence the properties and performance of the resulting nanohybrids. Different strategies exist for the construction of hybrid nanostructures from polymers and inorganic nanoparticles. These methodologies can be broadly characterized based on whether the polymer and inorganic constituents are formed *in situ* (e.g. monomers are polymerized in the presence of inorganic constituent), or *ex situ*, where constituents are synthesized independently and combined afterwards.[80] Depending on the strategy used, different types of polymer-inorganic nanohybrids can be obtained (*Figure 3*).

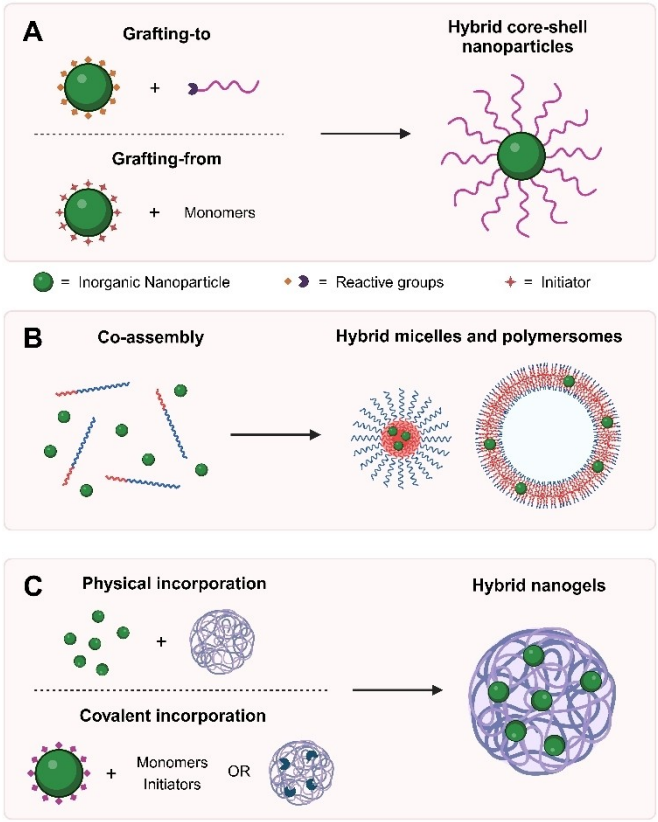


Figure 3. Different strategies for constructing polymer/inorganic nanohybrids: (A) grafting-to and grafting-from yielding core-shell nanoparticles, (B) co-assembly approach giving hybrid micelles and vesicles and (C) physical and covalent incorporation of inorganic nanoparticles into hybrid nanogels.

Common approaches include the covalent attachment of polymer chains to the surface of inorganic nanoparticles (*grafting-to*), growing a polymer chain *in situ* from the surface of inorganic nanoparticle (*grafting-from*), encapsulating inorganic nanoparticles within the polymer nanoparticles, and co-assembly of block copolymers and inorganic nanoparticles. The *grafting-to* and *grafting-from* methods typically yield core-shell nanoparticles, featuring an inorganic core surrounded by a polymer brush, while the encapsulation and co-assembly methods are suitable for incorporation of inorganic nanoparticles into more complex polymer architectures. Each approach not only defines the type of resulting nanohybrid but also imposes specific constraints on the selection of polymers and inorganic nanoparticles. Achieving a successful integration of these components requires either compatibility in terms of hydrophobicity and hydrophilicity or relies on the presence of specific functional groups. Regardless of the approach, either covalent modification of the inorganic nanoparticle surface or ligand exchange is required.

4.1. Polymer-Grafted Inorganic Nanoparticles

Covalent attachment of polymer chains to the surface of inorganic nanoparticles can be achieved through either a *grafting-from* or *grafting-to* approach (*Figure 3A*). Resulting nanostructures comprising an inorganic core and polymer brushes are among the most extensively studied inorganic/polymer nanohybrids. Here the term polymer brush typically refers to an extended conformation of densely grafted, non-crosslinked polymer chains directly conjugated to the inorganic nanoparticle surface by one chain-end. If polymer chains are crosslinked, they can be referred to as a polymer shell or a polymer coating, though these terms also apply to non-crosslinked polymer brushes.

In the *grafting-to* method, pre-formed polymer chains are covalently attached to the surface of inorganic nanoparticles, making this an *ex-situ* strategy for the nanohybrids preparation. This approach is based on the reaction between appropriately functionalized polymer chains and inorganic nanoparticles, mostly through click chemistry and condensation reactions. Alternatively, polymers and inorganic nanoparticles can be coupled through a bifunctional linker molecule. Polymers are typically synthesized using reversible-deactivation radical polymerizations like atom transfer radical polymerization (ATRP), reversible addition-fragmentation chain transfer (RAFT) polymerization and nitroxide mediated polymerization (NMP). These polymerization techniques offer precise control over molecular weight, dispersity and end-functionality of synthesized polymers, with the resulting end-groups easily modified in post-polymerization reactions.[81] Functional groups like carboxylic, amine, azide and alkyne can also be readily introduced onto the surface of inorganic nanoparticles through various post-functionalization methods.[82]

Click-chemistry has proven particularly effective for grafting end-functionalized polymer chains to appropriately functionalized surfaces via copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, due to its high efficiency and relatively mild conditions.[83] In the case of AuNPs, polymer chains can be directly covalently attached to the surface through gold-thiolate linkage, often eliminating the need for post-functionalization of gold surface. This strategy is widely used in the synthesis of gold-core-brush nanoparticles, with RAFT as the preferred polymerization choice, as the charge transfer agent (CTA) introduces

sulfur-containing end-group to the polymer chain that acts as a protected thiol. For instance, thiol terminated PNIPAM was successfully grafted to gold nanospheres and gold nanorods.[84,85] While the *grafting-to* method provides excellent control over the properties of pre-synthesized polymers, the high steric hindrance and slow diffusion of polymer chains to nanoparticle surface generally result in a low polymer grafting density.[86]

In the *grafting-from* method, polymer chains are grown via surface-initiated polymerization (SIP) from the surface of inorganic nanoparticles modified with functional groups capable of initiating polymerization, making this an *ex-situ* strategy. Surface-initiated reversible-deactivation radical polymerizations (SI-RDRP), specifically surface-initiated atom transfer radical polymerization (SI-ATRP) and surface-initiated reversible addition-fragmentation chain transfer polymerization (SI-RAFT), are commonly used in the *grafting-from* approach.[87–89] To promote grafting, inorganic nanoparticles should be properly functionalized, with an ATRP initiator (e.g. bromoisobutyryl group) in case of SI-ATRP, or an initiator or charge transfer agent in case of SI-RAFT. For example, Superparamagnetic Iron Oxide Nanoparticles (SPIONs) were functionalized with trimethoxysilanes bearing ATRP initiator moieties, enabling grafting of thermoresponsive PEGMA and PNIPAM from the SPIONs surface.[90,91] This method enables the simultaneous growth of all polymer chains directly from the nanoparticle surface, resulting in high grafting densities and precise control over the polymer architecture, composition, molecular weight and brush thickness.[92] The *grafting-from* method also benefits from low steric hindrance, allowing for the synthesis of polymer brushes with high grafting density. However, precise control over the molecular weight of the synthesized polymers is challenging, and standard polymer characterization techniques like size exclusion chromatography (SEC) and ^{1}H-NMR spectroscopy typically require the cleavage of grafted polymers.[86] Furthermore, inorganic nanoparticles need to be compatible with reaction conditions of polymerization. For example, semiconductor nanoparticles like quantum dots are incompatible with radicals generated during conventional radical polymerization, as they can degrade the nanoparticles and quench their photoluminescence. This further supports the use of techniques like SI-ATRP and SI-RAFT, where advancements in polymerization techniques allowed for the growth of polymers from the surface of quantum dots without compromising their integrity.[93]

4.2. Self-Assembly Strategies for Hybrid Assemblies

Hybrid polymersomes and micelles can be obtained by integrating inorganic nanoparticles during the self-assembly process (*Figure 3B*). The surface properties of inorganic nanoparticles, particularly their hydrophobicity, play a critical role in determining their localization within the assembled structures. Hydrophobic nanoparticles can effectively be incorporated into the hydrophobic core of micelles or the membrane of polymersomes, while hydrophilic nanoparticles can be encapsulated within the aqueous cavity of polymersomes. To achieve successful co-assembly with polymers, the surface of inorganic nanoparticles needs to be modified. Typically, unmodified inorganic nanoparticles possess surface hydroxyl groups that serve as surface-active sites for further modification, such as polymer grafting and ligand exchange. Alternatively, surface metals can be coordinated with polyphenols like dopamine, which have excellent biocompatibility.[94]

Inorganic nanoparticles can also be entrapped during the polymerization-induced self-assembly (PISA), where synthesis of amphiphilic copolymers and their self-assembly are carried out simultaneously in one-pot. By incorporating guest cargos, PISA facilitates efficient encapsulation of various guest species, providing a versatile platform for preparing hybrid nanomaterials at high concentrations.[95,96] Silica nanoparticles,[47,48] silver nanoparticles,[99] TiO_2 nanoparticles[100] and SPIONs[101] were efficiently loaded in block copolymer polymersomes during PISA process. Advancements in photoinitiated-RAFT PISA enabled the encapsulation of more sensitive cargo, with UV light-initiated RAFT PISA being utilized to synthesize Janus Au@P4VP-*b*-PS nanoparticles. This approach provides a promising alternative for the preparation of asymmetric hybrid nanoparticles with a controllable size and tunable morphology, and with both precisely controlled nanostructures and high yields.[102] The morphology of these nanohybrids can be tuned by adjusting parameters such as the size of the inorganic particles and the polymer/inorganic mass ratio.

Alternatively, nanohybrids can be formed by coupling pre-formed self-assemblies with inorganic nanoparticles, which can be synthetically more challenging. This approach requires the presence of complementary functional groups on both the surface of self-assemblies and the inorganic nanoparticles.[103] In particular, the end-groups of the hydrophilic polymer blocks, which are exposed on the surface of the self-

assemblies, must be functionalized to enable efficient and specific reactivity.

4.3. Hybrids by Incorporation of Nanoparticles Into Nanogels

Hybrid nanogels are constructed by either physically or covalently incorporating inorganic nanoparticles into the crosslinked polymer matrix of nanogels (*Figure 3C*). Nanoparticles based on gold, silver, silica, magnetic oxides and quantum dots were introduced to nanogels, providing an array of functionalities to resulting nanohybrids.[89] Most of the hybrid nanogels are simply prepared by physically incorporating the inorganic nanoparticles within the nanogels matrix before or after gelation.[104] Physical hybrid nanogels are prepared *in situ* by performing polymerization in the presence of formed inorganic nanoparticles or nanoparticle precursors, or *ex situ* by physically mixing polymer matrix and inorganic nanoparticles after polymerization. While physical methods for hybrid nanogels formation offer the advantage of synthetic simplicity, they are associated with the potential drawback of inorganic nanoparticle leakage, hindering their biomedical applications.

There are only a few examples of hybrid nanogels formed by covalently incorporating inorganic nanoparticles into polymer matrix. One of the strategies is the so-called grafting-through approach, where the surface of inorganic nanoparticles is modified with monomers that can participate in polymerization. When added to the pre-polymer mixture, monomers on the surface of nanoparticles can copolymerize with monomers fabricating nanogels, therefore acting as cross-linkers. This way, functionalized magnetic nanoparticles were used to crosslink PNIPAM-Fe_3O_4 hybrid nanogels.[105] Alternatively, covalent hybrid nanogels can be prepared through coupling between functional groups present on the surface of inorganic nanoparticles and in the polymer matrix.[89]

5. Applications of Thermoresponsive Polymer-Inorganic Nanohybrids in Drug Delivery

The combination of thermoresponsive polymers with inorganic transducing nanoparticles has created new opportunities for the development of advanced drug delivery systems. *Table 2* provides a comprehensive overview of these hybrid assemblies.

5.1. Optically Transduced Drug Delivery

Light has been used as a biocompatible external stimulus for activating drug delivery systems due to its several easily controllable properties, e.g. wavelength, power, spatial exposure and exposure duration. While most polymers possess good thermomechanical properties, they often lack optical response as they are transparent in the visible light range.[106] However, the phase transition in stimuli-responsive polymers can be triggered by the energy transduced by nanoparticles (NPs) like gold, silver, platinum or quantum dots (QDs). When such optically active nanoparticles are treated with a suitable optical stimulation, they have the potential to produce heat, fluorescence, or light scattering[107] (see Section 3). For optical stimulation of deep biological tissues, the NIR window is preferred as it offers deeper penetration (lower absorption by tissue chromophores) and lower phototoxicity in living tissues.[108,109] Therefore, utilization of NIR-absorbing inorganic nanoparticles can allow for localized heat generation and facilitate triggered release from thermoresponsive drug carriers in deep tissues layers.

Gold nanorods (AuNRs) are among the most commonly used photo-responsive transducers. They have high optical stability, adjustable biochemical properties, good biocompatibility, and a high extinction coefficient, making them strong absorbers in NIR window.[145–147] Stimuli-responsive amphiphilic polymers are often used as drug carriers in combination with AuNRs.[94,133] Representative examples illustrating different types of nanohybrids, including core-shell structures, micelles, polymersomes and nanogels made from thermoresponsive polymers, are shown in *Figure 4*.

For instance, biodegradable, doxorubicin (DOX)-loaded, lipoylated poly(ethylene glycol)-block-poly(ε-caprolactone) (PEG-*b*-PCL-LA) micelles with AuNR cores have been prepared for NIR-triggered release of DOX and effective killing of drug-sensitive and multidrug-resistant cancer cells.[111] Notably, the cytotoxic effects of DOX were observed only upon NIR-irradiation, which photothermally induced phase transition of PCL and facilitated DOX release (*Figure 4A*). These biodegradable micelles with AuNR cores displayed high stability, photo-triggered drug release, and effective reversal of multidrug resistance in cancer cells. In another study, chitosan micelles functionalized with thermosensitive poly(N-isopropyl acrylamide) (PNIPAM) and poly(acrylamide) (PAAm) with an average micelle size of 14 nm were attached to AuNRs (65 nm×19 nm, *length*×*width*) via gold-thiolate com-

Table 2. Examples of thermoresponsive polymer-inorganic nanohybrids in drug delivery.

Transduction mechanism	Heat generating nanoparticle	Thermoresponsive polymer	Nanocarrier type	Cargo	Reference
Photothermal	Gold nanorods	P(AAm-*co*-AN-*co*-TPP)-*b*-PEG	Core-shell	TPP porphyrin	[110]
	Gold nanorods	PEG-*b*-PCL	Core-shell	DOX	[111]
	Gold nanorods	PAA-*b*-PNIPAM-*b*-PCL	Core-shell	DOX	[112]
	Gold nanocages and hollow nanostars	PAA-*b*-PNIPAM-*b*-PCL	Core-shell	DOX	[113]
	Gold nanocages	PNIPAM-*co*-PAAm	Core-shell	Alizarin-PEG	[114]
	CuS nanoparticles	PEG–P(AAm-*co*-AN)	Core-shell	DOX	[25]
	Gold nanorods	Chitosan-PLA-*g*-P(NIPAM-*co*-Aam)	Micelles attached to INPs	Paclitaxel	[115]
	Gold nanoparticles	PNIPAM-*b*-PLGA	Polymersomes with INPs in the membrane	Pyranine	[116]
	Gold nanorods	PEG-*b*-PDEAEM	Polymersomes with INPs in aqueous core	DOX	[117]
	Gold nanoparticles	PDEGMA-*co*-POEGMA	Nanogels loaded with INPs	Temozolomide	[118]
	Hollow gold nanoparticles	PNIPAM	Nanogels loaded with INPs	Bupivacaine	[119]
	Fe_3O_4 nanoparticles	PNIPAM-*co*-PMAA	Nanogels loaded with INPs	DOX	[120]
	Gold nanorods	PNIPAM-*co*-PAA	Nanogels with INP core	ICG	[121]
	Gold nanorods	PNIPAM-*co*-PAA	Nanogels with INP core	DOX	[122]
	Silver-gold nanoparticles	PDEGMA-*co*-POEGMA	Nanogels with INP core	Temozolomide	[123]
Photothermal & Magnetothermal	Fe_3O_4 nanocrystals	PNIPAM-*co*-PAAm	Nanogels with INP/carbon core	Curcumin	[124]
Magnetothermal	Fe_3O_4 nanoparticles	Dextran-*g*-P(NIPAAm-*co*-DMAAm)	Core-shell	DOX	[125]
	Fe_3O_4 nanoparticles	Pluronic P123-*g*-PEI	Core-shell	Ibuprofen and Eosin Y	[126]
	Fe_3O_4 nanoparticles	PNIPAM-*co*-PNHMA	Core-shell	DOX	[127]
	Fe_3O_4 nanoparticles	PNIPAM	Core-shell	Apotransferrin and Wnt3a	[128]
	Fe_3O_4 nanoparticles	P(DEGMA-*co*-PEGMA-*b*-[TMSPMA-*co*-VBA])	Core-shell	DOX	[129,130]
	Fe_3O_4 nanocubes	P(DEGMA-*co*-OEGMA)	Core-shell	DOX	[131]
	$CoFe_2O_4$ nanoparticles	PNIPAM	Core-shell	Methotrexate	[132]
	$La_{1-x}Sr_xMnO_3$ nanoparticles	P(EO-*co*-PO)-*b*-PLL	Core-shell	DOX	[133]
	Fe_3O_4 nanoparticles	Pluronic F127	Micelles encapsulating INPs	DOX	[134]
	Fe_3O_4 nanoparticles	P(NIPAM-*co*-AAm)-*b*-PCL	Micelles encapsulating INPs	DOX	[135]
	Fe_3O_4 nanoparticles	P(PI-1-*co*-PI-2)	Micelles encapsulating INPs	DOX	[136]
	$MnFe_2O_4$ nanoparticles	PCL-*b*-p(NIPAM-*co*-DMAAm)	Micelles encapsulating INPs	DOX	[137]
	Fe_3O_4 nanoparticles	PI-*b*-PNIPAM	Polymersomes with INPs in the membrane	Calcein	[138]
	Fe_2O_3 nanoparticles	P(DEGMA-*co*-OEGMA-*co*-MAA)	Nanogels loaded with INPs	DOX	[139]
	Fe_2O_3 nanoparticles	PVA-*b*-PNVCL	Nanogels loaded with INPs	Tamoxifen	[140]
	Fe_3O_4 nanoparticles	Chitosan-*g*-PNVCL	Nanogels loaded with INPs	DOX	[141]
	Fe_3O_4 nanoparticles	PNIPAM	Hollow nanogels with INPs in gel	DOX	[142]
Microwave	Fe_3O_4 nanoparticles	PEG-*g*-P((AAm-*co*-AN)	Micelles encapsulating INPs	DOX	[143]

Table 2. (cont.)

Transduction mechanism	Heat generating nanoparticle	Thermoresponsive polymer	Nanocarrier type	Cargo	Reference
Radiofrequency	Dual-valent gold nano-clusters	P(NIPAM-*co*-AAm)	Core-shell	RFA and TAE	[144]

PAA: poly(acrylic acid), PAAm: poly(acrylamide), PAN: poly(acrylonitrile), PCL: poly(ε-caprolactone), PDEAEM: poly(*N,N*-diethylaminoethyl methacrylate), PDEGMA: poly(di(ethylene glycol) methyl ether methacrylate), PDMAAm: poly(*N,N*-dimethylacrylamide), PEG (PEO): polyethylene glycol, PEGMA: poly((ethylene glycol) methyl ether methacrylate), PEI: poly(ethyleneimine), PI: poly(isoprene), PLA: poly(l-lactide)/poly(l-lysine), PLGA: poly(lactic-*co*-glycolic acid), Pluronic (PEO-*b*-PPO-*b*-PEO): poly(ethylene oxide)-*b*-poly(propylene oxide)-*b*-poly(ethylene oxide), PMAA: poly(methacrylic acid), PNHMA: poly(*N*-(hydroxymethyl)acrylamide), PNIPAM: poly(*N*-isopropylacrylamide), PNVCL: poly(*N*-vinylcaprolactam), POEGMA: poly(oligo(ethylene glycol)methyl ether methacrylate), PPI: poly(phenyl isocyanide), PPO: poly(propylene oxide), PTMSPMA: poly(3-(trimethoxysilyl)propyl methacrylate), PVA: poly(vinyl alcohol), PVBA: poly(3-vinylbenzaldehyde)

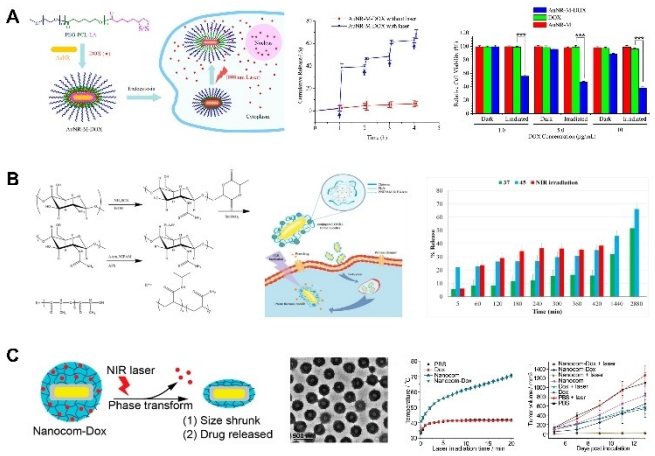


Figure 4. Gold nanorods can be combined with thermoresponsive polymers to construct different types of nanohybrids for NIR-light triggered drug release. (A) AuNRs grafted with thermosensitive triblock copolymer releasing DOX. NIR-light irradiation enhances drug release and boosts antitumor activity to drug resistant MCF-7 cells. Reproduced with permission from [111]. Copyright 2013, American Chemical Society. (B) AuNRs coated with thermoresponsive polymeric micelles for Paclitaxel release. Reproduced with permission from [115]. Copyright 2020, Elsevier. (C) Hybrid nanogels with AuNRs for NIR-light triggered DOX release. Nanohybrids showed good photothermal effect *in vivo* and antitumor activity against murine 4T1 breast tumor. Reproduced with permission from [122]. Copyright 2014, American Chemical Society.

plex formation.[115] The collapse of thermoresponsive polymers and subsequent release of Paclitaxel was achieved by exposing the complex to NIR irradiation. Interestingly, AuNR-facilitated heating resulted in higher drug release in comparison to direct heating at 45 °C (*Figure 4B*), highlighting the benefits of such hybrid systems.

Polymersomes have been also developed as thermoresponsive carriers and combined with inorganic nanoparticles for stimuli-responsive drug delivery applications.[149] For example, polymersomes consisting of thermosensitive and inert bilayers of amphiphiles poly(ethylene glycol)-*b*-poly(lactic acid) (PEG-*b*-PLA) and poly(*N*-isopropylacrylamide)-*b*-poly(lactic-*co*-glycolic acid) (PNIPAM-*b*-PLGA) in their hydrophobic portion contained gold nanoparticles that induced heating upon laser irradiation. When the temperature was increased above the lower critical solution temperature (LCST) of the thermoresponsive blocks, the polymersomes released their payload.[116]

Thanks to their inherent porosity, hydrogels can be used for the entrapment of various payloads including transducing inorganic nanoparticles and drugs. Hybrid nanogels with AuNRs for NIR-light triggered DOX release has shown good photothermal effect *in vivo* and antitumor activity against murine 4T1 breast tumor (*Figure 4C*).[122] In another example, AuNRs incorporated into thermoresponsive PNIPAM hydrogel were activated via irradiating with a NIR light source (650–900 nm).[150] NIR-irradiated PNIPAM-AuNR assemblies demonstrated photothermal phase transition and accumulation in local targeted sites which were irradiated. An implantable nanogel composite device supported drug release which was controlled by timing the intensity of the NIR irradiation.[151] The copolymer nanogel particles, synthesized from thermo-responsive N-isopropyl acrylamide, N-isopropylmethacrylamide, and acrylamide, were incorporated into impermeable membrane which became porous upon temperature increase. When exposed to 808 nm laser, hollow Au nanoshells loaded into the membrane, heated up from room temperature to approximately 42.5 °C, causing the collapse of the polymeric nanogel, thus inducing drug release.

The light-absorbing nanostructures can also generate reactive oxygen species (ROS), which can induce cancer cell apoptosis through the so-called photodynamic therapy (PDT). For example, a combination of

photodynamic therapy and photothermal therapy was achieved by mesoporous silica-coated gold nanorods encapsulated in a thermo- and pH-responsive polymer (*Figure 5*).[121] Gold nanorods were coated with a 15 nm thick porous silica layer and encapsulated within poly(*N*-isopropylacrylamide-*co*-acrylic acid) nanocarriers. In addition, photosensitive indocyanine green (ICG) was added to the hybrid to couple the photodynamic properties with the photothermal properties of AuNRs. The dual-responsive polymer layer increased the drug loading capacity and its stability. Upon 808 nm laser irradiation, both gold NRs and ICG contributed to the local heat generation, which induced the shrinkage of PNIPAM layer and enhanced the drug release rate (*Figure 5A*).[121] Furthermore, the presence of ICG and AuNRs in the hybrid facilitated *in vivo* fluorescence (*Figure 5B*) and photoacoustic imaging (*Figure 5C*), respectively, in tumor-bearing mice. Upon intravenous administration, the hybrid nanosystem was mainly distributed in the liver at the early time points and the fluorescence signal gradually appeared at the tumor site. The photoacoustic signals also confirmed a gradual increase at the tumor site, indicating efficient tumor accumulation that is highly needed for an efficient therapy.

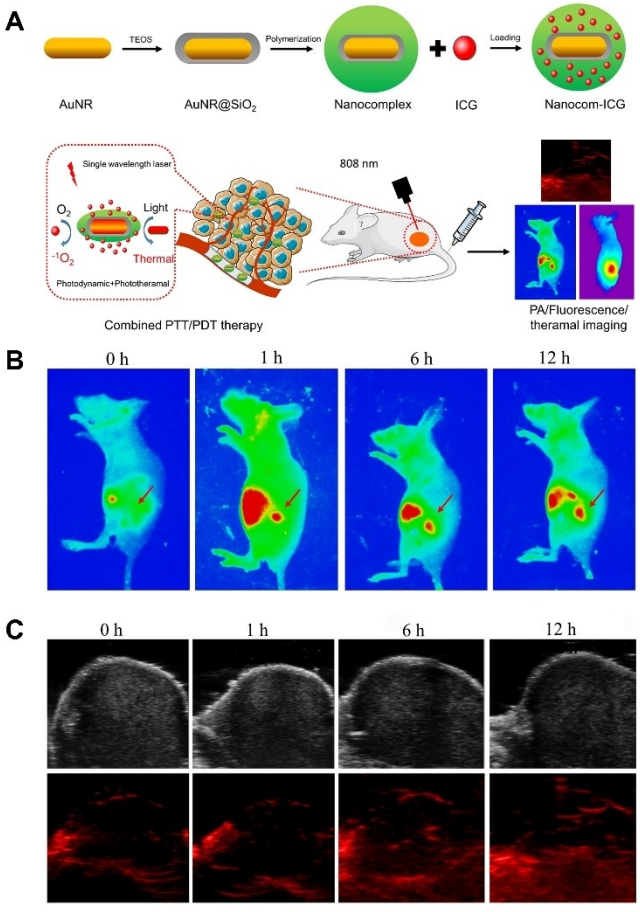


Figure 5. Dual-responsive, ICG and AuNR-loaded poly(*N*-isopropylacrylamide-*co*-acrylic acid) nanocomplexes. (A) Synthesis and application of hybrid nanocomplexes for simultaneous PTT and PDT. (B) Real-time fluorescence imaging of A549 tumor-bearing mice injected with nanocarriers. The red arrows indicate the region of the tumor. (C) Photoacoustic images of A549 tumour-bearing mice upon nanocarrier administration. Reproduced under terms of the CC BY license.[121] Copyright 2021, Springer Nature.

Indeed, the majority of hybrid DDS combining inorganic nanoparticles and thermoresponsive polymers involve AuNRs. Although rare, examples utilizing other inorganic nanoparticles also exist. For instance, silver NPs with shape-dependent plasmon resonance peaks[152] were embedded within a UCST-based poly(butyl methacrylate-*co*-acrylamide-*co*-methacrylic acid) ([P(BMA-*co*-AAm-*co*-MAA) to develop DDS. This system utilized spherical silver NPs to trigger the drug release upon irradiation with a 405 nm laser.[153] The comparison of thermal and optical switching in the nanohybrids revealed a faster transmittance drop upon light exposure possibly due to an efficient heat conduction of the silver NPs. Although *in vitro* drug release experiments triggered by irradiation were successful, the applicability of this system to *in vivo* models is challenging due to poor penetration depth of excitation laser. Nevertheless, this example highlights the broader utility of inorganic nanoparticles for optically-induced heat generation.

5.2. Magnetically Transduced Drug Delivery

Magnetic fields and magnetically responsive nanoparticles offer a promising exogenous strategy for controlled drug delivery. Apart from their ability to improve the accumulation of drugs in a desired region through magnetic targeting, several inorganic magnetic nanoparticles can generate high temperatures locally.[154] When combined with drug carriers made from thermoresponsive polymers, the locally generated magnetic hyperthermia can be advantageously used to trigger the drug release upon application of an alternating magnetic field (AMF).[155,156] In one such example, superparamagnetic Fe_3O_4 core and dextran grafted with a poly(*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide) [dextran-*g*-poly(NIPAM-*co*-DMAAm)] shell served for triggered DOX release. Copolymerization of PNIPAM with hydrophilic PDMAAm increased the LCST to ~38 °C, making it desirable for controlled drug release.[125]

Thermoresponsive nanoparticle coatings based on Pluronics (PEO-*b*-PPO-*b*-PEO),[126,134,157] PNIPAM and its copolymers,[127,128] PDEGMA and its copolymers,[129,130,158] polyoxazolines,[159] have been reported for magnetically-induced drug release. For example, the protein growth factor Wnt3a was entrapped within the thermoresponsive PNIPAM coated on SPIONs. Upon exposure to AMF, magnetic heating triggered the collapse of the PNIPAM shell, while the release of Wnt3a was promoted by the presence of nonspecifically binding competing proteins that are naturally present in human tissues. Released protein growth factor enhanced mesenchymal stem cell proliferation, demonstrating how the applications of such magnetic nanohybrids are beyond small-molecule drugs delivery.[128]

In addition to spherical nanoparticles, iron oxide nanocubes have also been used to construct core-shell nanohybrids for magnetothermal delivery of DOX (*Figure 6*). The surface of nanocubes was functionalized with catechol-based initiators to facilitate surface-initiated photoinduced copper-mediated radical polymerization (*Figure 6A*), producing a thin polymer shell based on poly(di-and-poly(oligoethylene glycol methyl ether methacrylate) P(DEGMA-*co*-OEGMA) (*Figure 6B*). When exposed to AMF, the thermoresponsive polymer shell underwent shrinkage, triggering the release of DOX (*Figure 6C*). *In vivo* efficacy studies demonstrated complete tumor suppression (*Figure 6D*) and the highest survival rate (*Figure 6E*) for animals treated with DOX-loaded-nanocubes, provided the treatment was accompanied by AMF exposure.[131]

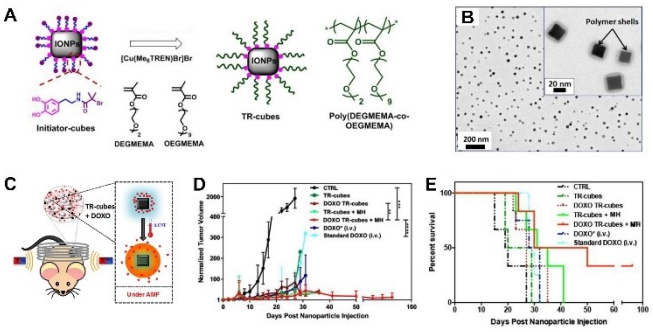


Figure 6. Thermoresponsive iron oxide nanocubes for magnetic hyperthermia (MH) and heat-mediated DOX delivery. (A) Schematic illustrating synthesis of nanohybrids by surface-initiated polymerization. (B) TEM image of nanocubes with thermoresponsive polymer shell. (C) Schematic illustrating the *in vivo* efficacy study. Application of AMF causes magnetic hyperthermia, faciliating drug release. (D) The DOX-loaded-nanocubes + MH group in the tumor growth curve showed significant improvement in tumor suppression in comparison to the control group (with $p = 0.0002$ (***)), the standard DOX group ($p < 0.0001$ (****)), and the DOX-nanocube group ($p = 0.0035$ (**)). (E) Survival plot showing that the animals treated with DOX-loaded-nanocubes + MH had the longest survival rate. Reproduced under terms of the ACS AuthorChoice License from [131]. Copyright 2019, American Chemical Society.

Besides iron oxide nanoparticles, nanoparticles of spinel ferrites such as $MnFe_2O_4$ are often used for their magnetothermal properties, offering strong magnetizations comparable to Fe_3O_4.[160] Amphiphilic block copolymer polycaprolactone-*b*-poly(*N*-isopropylacrylamide-*co*-*N*,*N*-dimethylacrylamide) [PCL-*b*-p(NIPAM-*co*-DMA)] was used to develop thermoresponsive micelles, where $MnFe_2O_4$ and DOX were loaded during the self-assembly process. These nanohybrids exhibited excellent magnetothermal-dependent DOX release and endocytosis, inhibiting tumor growth by 84% in tumor-bearing mice, with excellent biosafety and without any weight loss.[137] In another study, micelles based on amphiphilic block copolymer poly(*N*-isopropylacrylamide-*co*-acrylamide)-*block*-poly(ε-caprolactone) P(NIPAM-*co*-AAm)-*b*-PCL were loaded with SPIONs and DOX. A complete release of encapsulated DOX was observed within 10 h with heating cycles in a water bath, while magnetically induced heating to the same temperatures accelerated DOX release by three-fold. The end functionalization of the polymer with cancer-specific integrin β4 antibodies also facilitated *in vivo* MR-based detection of cancer cells, highlighting the suitability of the system for theranostic applications.[135]

Thermoresponsive polymersome-magnetic nanoparticles hybrids were also studied for the loading and release of both hydrophilic and hydrophobic cargo.[138,161] SPIONs were entrapped within the hydrophobic membrane of the polymersomes based on poly(isoprene-*b*-*N*-isopropylacrylamide) (PI-*b*-PNIPAM), while calcein, a model hydrophilic cargo, was loaded in their cavity. This system showed the release of 25% of encapsulated calcein after one 10 min AMF pulse. However, the release was limited to 50% for calcein, probably due to uneven distribution of SPIONs between different polymersomes.[138]

Magnetic nanohybrids based on thermoresponsive nanogels were also reported in the literature.[105,124,139–142,162–165] They are usually constructed in a similar approach to polymer coatings, with an additional crosslinking step. In a peculiar example, maghemite nanoparticles (γ-Fe_2O_3 NPs) were decorated with phenylboronic acid moieties and used as dynamic crosslinkers. Nanogels were formed by crosslinking poly(vinyl alcohol)-*b*-poly(*N*-vinylcaprolactam) (PVA-*b*-PNVCL) micelles with magnetic cross-

linkers by forming boronate/diol bonds, making resulting nanohybrids thermo-, pH- as well as glucose-responsive.[140] In another study, a hybrid nanoplatform comprising γ-Fe_2O_3 NPs and nanogels (MagNanoGels) based on oligo(ethylene glycol) methyl ether methacrylate (OEGMA) monomers were used for the magnetothermal delivery of DOX (*Figure 7A*). Methacrylic acid (MAA) was used as a comonomer, making these nanogels pH-responsive as well. AMF pulses (335 kHz, 9 mT, 12.0 kA·m^{-1}, 30 min) significantly enhanced DOX release, increasing it from 24% to 47% at pH 7.5, and from 96% to 100% at pH 5.0 (*Figure 7B*). Nevertheless, the pH-responsive behavior of MagNanoGels had a higher impact on the release. It's also important to note that no macroscopic heating was detected. Furthermore, MagNanoGels were efficiently internalized inside the PC-3 human prostatic cancer cell line, and AMF served for intracellularly and remotely triggering the DOX release. The most significant reduction in cancer cell viability was observed for DOX- MagNanoGels-treated cells under an applied AMF (*Figure 7C*).[139]

While beyond the scope of this review, it is worth noting that applying an AMF can enhance cargo release from nanohybrids, even when the polymer is not thermoresponsive. This effect can occur through mechanisms such as pore formation or increased permeability of the polymeric DDS.[166,167]

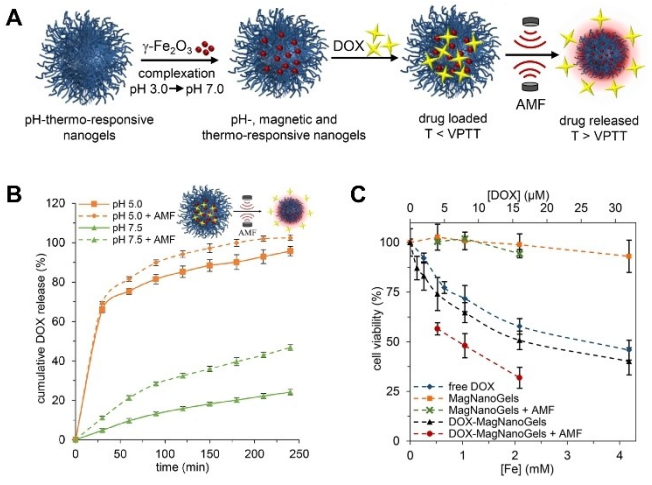


Figure 7. Magnetic nanogels for magnetothermal delivery of DOX. (A) Schematic illustrating synthesis, loading and release of DOX under an AMF. (B) Cumulative DOX release over time of DOX- MagNanoGels in physiological (pH 7.5) and acidic (pH 5.0) conditions with and without an AMF (335 kHz, 9 mT, 12.0 kA·m^{-1}, 30 min). (C) Cell viability of PC-3 cells incubated for 2 h with free DOX, MagNanoGels and DOX-MagNanoGels with and without an AMF (471 kHz, 18 mT, 14.4 kA·m^{-1}, 2 h). Reproduced with permission from [139]. Copyright 2017, American Chemical Society.

Apart from magnetic fields, magnetic nanoparticles have been shown to generate heat as a response to other exogenous stimuli, including NIR excitation,[168] radiofrequency (RF) fields,[169] microwave irradiation[170] and high-intensity focused ultrasound.[171] Although all these could be used for triggering nanohybrids of magnetic nanoparticles and temperature-sensitive polymers, examples in literature still mostly include magnetic fields-triggered systems.

5.3. Radiofrequency and Microwave Transduced Drug Delivery

Metallic nanoparticles, such as gold, iron oxide, cobalt, carbon-based materials and QDs, show responsive RF heating through Joule or magnetic heating. The concept of RF-assisted "cooking" of the cancer cells was first introduced using tumor targeting antibody-conjugated Au-NPs, which produce optimum heat and induce apoptosis or necrosis in cancer cells upon applying an RF source.[172,173] The stimuli-responsive polymer shell around RF transducers offers a higher drug loading capacity and control of the release upon modulation of RF-responsive nanoparticles.[174] RF-responsive dual-valent gold nanoclusters were incorporated into thermoresponsive poly(N-isopropylamide-*co*-acrylic acid) (PNAs) (*dv*GC@PNAs), as shown in *Figure 8A* and *8B*.[144] dvGC@PNA was composed of a core-shell nanostructure of Au(0) atoms surrounded by a high content of Au(I) ions in the template of PNAs. It was observed that the RF-induced heating effect might have originated from the friction heat by Au(I) ion oscillation under RF currents (100 W), thus reaching 65 °C (*Figure 8C*). *dv*GC@PNAs nanocluster greatly improved tumor hypoxic microenvironment post-trans-arterial embolization procedure and enhanced the antitumor effect of radiofrequency ablation, resulting in significant tumor cell apoptosis (*Figure 8D*).

Another class of promising RF-responsive nanomaterials consists of iron oxide nanoparticles (IONPs). IONPs are highly bio-compatible, bioresorbable and easy to modify.[175,176] For example, thermoresponsive poly(ethylene glycol)-g-poly(acrylamide-*co*-acrylonitrile PEG-*g*-p(AAm-*co*-AN) micelles decorated with hepatic tumor cell targeting peptide-A54 were used to encapsulate DOX and magnetic nanoparticles.[143] A54-PEG-*g*-p(AAm-*co*-AN) micelles with 80 nm diameter displayed UCST at 43 °C. While the A54 ligand navigated the nanoparticle to the tumor site, exposure

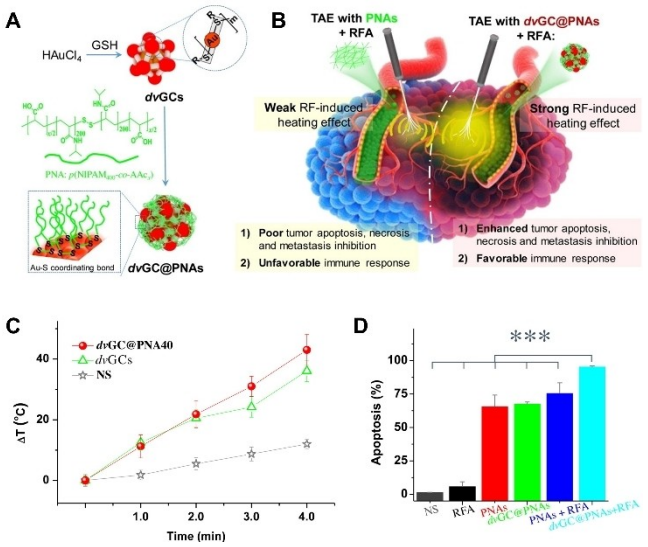


Figure 8. Radiofrequency responsive dvGC@PNAs for enhancing synergistic therapy of RFA and TAE.[144] (A) Schematic illustration of the preparation of dvGC@PNAs. Temperature-sensitive PNA polymers are covalently attached onto dvGCs by Au–S bonds. (B) Schematics demonstrating synergistic antitumor efficacy of TAE and RFA by RF-induced heating effect. (C) RF-induced heating effect of dvGC@PNAs. The elevated temperatures are quantified with the thermal images. (D) The synergistic antitumor evaluation of the combined therapies with TAE and RFA on VX2 tumor-bearing rabbits. There is a highly significant difference (*** $P < 0.001$) between PNA@dvGCs + RFA and the other groups on tumor cell apoptosis. Reproduced with permission from [144]. Copyright 2020, Elsevier.

to a mild microwave power (8 W) facilitated the drug release via hyperthermia generation.

Among the carbon-based materials, carbon nanotubes (CNTs) possess physical and chemical properties suitable for biomedical applications.[177] Their surface can be further modified to enhance their optoelectrical properties and improve microwave and radiofrequency absorption.[178] Although applications in triggering thermoresponsive polymers via hyperthermia generation are not documented, examples with thermal ablation of tumor cells under a non-invasive radiofrequency field are noteworthy.[179]

6. Challenges and Perspectives

Hybrid DDS comprising thermoresponsive polymers and inorganic nanoparticles can potentially replace conventional therapeutic approaches by providing spatial and temporal control over drug release and simultaneous imaging capabilities. Several promising approaches that have been highlighted in this review achieved success *in vitro* and in preclinical settings. There is great potential for the creation of tailored DDS by carefully designing each component of these modular systems, and integrating them into robust, stable assemblies. However, several key challenges must be addressed to fully realize this potential.

One key challenge is to achieve adequate heat generation efficiency in the biological systems. In this context, photothermal and magnetothermal approaches are commonly applied. The localized heat generation by inorganic nanoparticles via transducing different forms of energy is essential to trigger the drug release. Consequently, external energy sources must be carefully selected to ensure they can effectively penetrate and interact with nanoparticles located in deep tissues. This also directly affects the selection of the inorganic nanoparticle type. For instance, external stimuli such as light or ultrasound, while effective in superficial layers, are usually attenuated due to their interaction and absorption by biological tissues, which can limit their deep-tissue applications.[155,180] In contrast, biological tissues demonstrate minimal interaction with magnetic energy, making them effectively transparent to its influence. As a result, thermoresponsive hybrid assemblies with magnetic inorganic components can provide better heating efficiency and therapeutic efficacy in deep tissue layers upon exposure to AMF. However, the safety profiles of these assemblies should also be carefully evaluated. For instance, AuNRs that are commonly used for photothermal conversion are regarded as highly biocompatible,[181] while iron overload generated by magnetic nanoparticles may trigger oxidative stress and unintended cytotoxicity.[182] Addressing such safety concerns is essential for the successful application of these hybrid systems, which can be achieved by surface protection strategies with inert coatings, such as a silica shell.

A precise control of the phase transition temperature of hybrid assemblies is another key challenge that needs to be addressed. Indeed, the most commonly used thermoresponsive polymers display phase transition temperatures within the physiologically relevant range. This temperature can be finely tuned by several chemical modifications as outlined in Section 2. However, while precisely tailoring the phase transition temperatures, such chemical modifications may alter other material properties. This issue becomes particularly relevant for designing thermoresponsive polymersomes, where the length and volume fraction of the thermoresponsive block directly affect

the phase transition temperature and the assembly type.[33] For instance, the thermoresponsive block lengths suitable for self-assembly into polymersomes may be too short to display a clear stimuli response, compromising the overall functionality of the polymersomes. Consequently, thermoresponsive polymersomes are less common compared to other types of self-assembled architectures, such as micelles. Overall, the complexity in balancing phase transition temperature with other nanomaterial properties, such as architecture, stability, and cargo loading capacity makes the development of thermoresponsive nanocarriers an intricate task. The challenges grow further when integrating these nanocarriers with inorganic nanoparticles to develop hybrid nanosystems.

One of the most promising aspects of thermoresponsive polymer-inorganic nanoparticle hybrids is their dual functionality for drug delivery and imaging. Combining thermoresponsive polymers with inorganic nanoparticles into stable hybrids without compromising the functionality of either component is a complex challenge. The integration of these two distinct elements requires efficient methods to ensure the stability of the hybrid system, while also preserving the thermoresponsive behaviour of the polymer. In addition, a homogeneous distribution of inorganic nanoparticles through the polymer matrix is essential to homogeneously trigger and efficiently release the cargo.[138] In this respect, chemical incorporation through grafting methods can provide stable hybrid nanostructures with well-defined architectures, composition, and controlled distribution of inorganic components. By chemically incorporating the inorganic nanoparticles to the thermoresponsive polymer matrix, grafting methods minimize the risk of nanoparticle release during the polymer phase transition, ensuring the structural integrity and stability of the hybrid system under physiological conditions. However, this method has certain trade-offs. Tethering inorganic nanoparticles within the polymer matrix can limit the available free volume within the hybrid nanostructure, which can reduce the capacity for encapsulating therapeutic cargo. Combining chemical grafting with physical encapsulation techniques may help balance the stability and cargo-loading capacity. The stability of the loaded cargo is also crucial to retain. The type, duration, and intensity of applied stimulus should be carefully controlled to ensure that the stability and therapeutic efficacy of the of drug are not compromised due to generated heat.

Despite the significant promise of thermoresponsive nanocarriers as DDS, no such system has yet received FDA approval primarily due to challenges related to material toxicity, biodegradability, and the complexity of synthesis. For instance, PNIPAM, while extensively studied for its thermoresponsive properties, raises concerns about non-biodegradability and potential cytotoxicity, limiting its suitability for *in vivo* applications. To address this issue, researchers have developed biodegradable NIPAM-based copolymers.[183,184] However, degradation of these materials often produces high molecular weight fragments and small molecules, necessitating thorough toxicity evaluations to ensure the safety of the resulting byproducts. Without such assessments, even biodegradable nanocarriers may fall short of clinical applicability. Poloxamers, on the other hand, are FDA-approved thermoresponsive block copolymers widely used as excipients in solid, semi-solid, and liquid formulations, primarily as surfactants and stabilizers in products such as Luxturna®, Mircera®, and Orencia®.[185] However, these applications do not exploit poloxamers' thermoresponsive properties for temperature-triggered drug release. The only thermoresponsive nanoformulation to reach clinical trials is ThermoDox®, a liposomal doxorubicin formulation incorporating thermosensitive lipids.[186–188] In these trials, ThermoDox® was administered alongside radiofrequency ablation (RFA) to treat hepatocellular carcinoma, leveraging the localized temperature increase from RFA to trigger drug release. Despite its innovative design, the trials were discontinued because the primary endpoint of progression-free survival was not achieved. Variability in RFA techniques and inconsistent heat distribution likely contributed to the suboptimal outcomes.[186] In this respect, as highlighted in this review, inorganic nanoparticle-mediated heating can provide more localized and homogeneous heating profile. Inorganic components such as gold and iron oxide nanoparticles are closer to clinical translation due to their established safety profiles in other biomedical applications, but long-term accumulation and off-target effects remain concerns. Materials such as carbon nanotubes and titanium dioxide face even greater regulatory hurdles due to their known toxicity risks. Additionally, the multicomponent nature of these systems complicates the scale-up manufacturing and reproducibility, which are critical for regulatory approval.[189,190] Addressing these challenges through material innovations, scalable manufacturing technologies, and comprehensive safety studies will be crucial for advancing thermoresponsive nanocarrier-inorganic nanoparticle hybrids toward clinical use.

7. Conclusions and Outlook

Overall, thermoresponsive polymer-inorganic nanoparticle hybrid systems represent a transformative approach in drug delivery, offering precise control over spatial and temporal release of therapeutic agents while enabling integration with imaging. By leveraging the unique properties of inorganic nanoparticles and the stimuli-responsive nature of polymers, these hybrid systems can potentially address key challenges in treating complex diseases. Despite the significant obstacles associated with the development of such hybrid DDS, there are several promising avenues for overcoming these hurdles. Advances in nanotechnology combined with macromolecular design has facilitated the development of engineered nanoparticles with precisely defined structures, compositions, and functions, and brought the technology thus far. Recently, computational tools have been introduced as complementary strategies that can provide invaluable insights into functional materials design and guided synthesis,[191] including stimuli responsive polymer networks[192] and nanoparticles.[193] As early stage in research, it is important to note that there are various novel concepts in combining transducer nanoparticles with responsive polymers that are expected to advance DDS by a fine control of space and time delivery upon the presence of specific stimuli. In addition, these advancements should be evaluated as functionality, biocompatibility and biodistribution by *in vivo* assays as a critical step for further medical applications. Such assays are still limited, and their progress will support the selection of leads that will be promoted for further development. Ultimately, insights gained from advancements in nanotechnology, macromolecular chemistry, and computational methods can collectively provide a strong driving force for further evolution of this field to create hybrid systems with enhanced functionality, precision, and efficiency. With joint multi-disciplinary efforts, these innovative systems could make a substantial impact on advancing personalized medicine and theranostic technologies.

Author Contribution Statement

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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