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Stimuli-responsive drug delivery application of polymer and silica in biomedicine

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In the last decade, polymer and mesoporous silica materials as efficient drug delivery carriers have attracted great attention. Although the development and application of them involve some inevitable barriers, such as chronic toxicities, long-term stability, understanding of the biological fate and physiochemical properties, biodistribution, affection in biological environment, circulation properties and targeting efficacy *in vivo*. The construction of stimuli-responsive drug carriers with biological safety materials, followed by hydrophilic modification, bioconjugation, targeting functionalization, and detailed safety-analysis in small/large animal models may be the best way to overcome these barriers. And a huge progress in stimuli-responsive drug delivery systems based on polymer and mesoporous silica materials has been made, mainly including pH-, thermo-, light-, enzyme-, redox-, magnetic field- and ultrasound responsive drug delivery systems, which is also the highlight of this review.

1. Introduction

Nanoparticle-based drug delivery systems (DDS) have been used for the clinical applications ranging from oncologic to cardiovascular diseases. These nano medicines have the improved treatment abilities because of the altered pharma kinetics and bio distribution profiles. Especially environmental responsiveness of nanoparticles (NPs) was explored to have a desired and high therapeutic efficacy. When exposed to the external stimuli, the property changes of NPs favour the release of drug at target site of interest. These external stimuli may be a physical signal such as light, temperature, magnetic field and ultra sound, or a chemical signal such as pH, ionic strength, redox potential and enzymatic activity. Considerable efforts are currently being exerted to develop more efficient and safe DDS that provide therapeutic levels of drugs in specific organs, tissues, even cellular structures, where and when required.[1–3]

Traditional medicines devoted to reach the target by an immediate or progressive drug flooding of the body are no longer valid for most of the emergent synthetic and biotechnological therapeutic molecules, owing to the instability and toxicity problems or the hindrances to reach the target structure from the systemic circulation. Furthermore, drugs with long-term usage could benefit greatly from the development of a discontinuous (triggered) drug release in response to a specific stimulus. Thus, DDS, which can release an active molecule at the appropriate site with a fixed rate in response to the progression of the disease or to certain functions/biorhythms of the organisms, are particularly appealing.

To bring such a vision of the responsive DDS to clinical use, the majority of efforts are directed toward integrating the biomimetic methodologies into tailor-designed drug carriers, mainly based on molecule-selective agents, camouflage coatings / shells or stimuli-sensitive components. Although quite complex and diverse stimuli-responsive DDS are intended to mimic the events that occur when a cellular signal triggers a massive release of biochemical mediators from secretory granules or vesicles which serve as storage containers and undergo a reversible conformational change in response to an applied stimulus. DDS that modulate drug release as a function of the specific stimuli intensity are called "intelligent" and can work in open or closed circuit. Closed-loop or self-regulated systems detect certain changes in biological variables (*e.g.* pH, temperature or concentration of some substances) by activating or modulating the response, *i.e.* by switching drug release on and off or automatically adjusting the release rate. On the other hand, open-loop systems can respond to specific external stimuli by releasing the drug in a pulsatile manner, proportional to the intensity / duration of each stimulus. Such a release mode is advantageously independent of the conditions of biological environment, enabling a precise and explicit triggering of the release.

In this review, we focus on the recent development of stimuli-responsive drug delivery systems based on polymer and silica. Firstly, we give an overall introduction of commonly used materials of them, such as basic properties, classes, and conventional drug delivery applications, especially the multitudinous polymers. Secondly, we summarize the stimuli responsive drug delivery systems in detail, including pH-, thermo-, light-, enzyme-, redox-, magnetic field- and ultrasound responsive drug delivery systems. Notably, pH gradient is a

widely employed stimuli among all the environmental responses for the design of responsive NPs. And the nano-vehicle that responds to the pH gradient within the micro environment of organs, tissues and cell organelles may be useful for the therapeutic drug delivery.

2. Materials for drug delivery

2.1. Polymers

Polymers, as a kind of drug delivery material, a comprehensive understanding of the surface and the bulk properties to provide the intended chemical, interfacial, mechanical and biological functions is required. There are some criteria for the choice of polymer. Firstly, the physiological properties are dependent on the need for extensive biochemical characterization and specific preclinical tests to prove its safety. Secondly, the superficies features such as hydrophilicity, lubricity, smoothness and surface energy govern the biocompatibility with tissues and blood, besides, affect the physical properties such as durability, permeability and degradability. The superficies features also determine the water sorption capacity of the polymer, which can undergo hydrolytic degradation and swelling. Thirdly, the bulk properties need to be considered for the controlled delivery system, including molecular weight, bulk modulus, and solubility based on the release mechanism (diffusion or dissolution control), properties of its potential site of action, and the structural properties of its matrix. Moreover, its morphology and the pore size are important with respect to the mass transport (of water) into and (of drug) out of the polymer. Accordingly, polymeric NPs have been synthesized using various methods, which satisfy the requirement of

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Table 1 PLGA based biodegradable polymeric materials for drug delivery.

Synthesis method	Encapsulant	[a]EE	Therapeutic improvement	Release mechanism	Surface amendments	In vivo	[b]Ref.
Solvent evaporation /solvent extraction technique	Taxol	100%	Slow release of the drug up to 20days	Diffusion, matrix swelling and polymer erosion	D-α-tocopheryl polyethylene glycol succinate	–	4
Interfacial deposition	Paclitaxel	>95%	Improved antitumoral efficacy as compared to free drug	Dissolution and diffusion	–	30% decline in cell viability against NCL-H69 cells on incubating for 24h.	5
Nanoprecipi-tation	Taxol	70%	Greater tumor growth inhibition	Diffusion	Polyethylene glycol	More cytotoxic on Hela cells than taxol	6
Emulsion diffusion	Estradiol	48-75%	Enhanced bioavailibility	Diffusion and dissolution of polymer matrix	–	Smaller particles produced prolonged blood level	7
Nanoprecipi-tation	9-Nitrocampt-othecin	33%	Controlled release up to 160 h.	Diffusion	–	–	8
Solvent displacement technique	Xanthones	77%	Slow drug release up to 4 h.	Barrier amid oil core and external aqueous medium	–	–	9
Emulsion solvent diffusion	Docetaxel	87.3%	Superior cellular uptake over non-modified particles	Diffusion and matrix erosion	Polyethylene glycol	Greater extent of cellular uptake in folate receptor cancer cells	10
Solvent evaporation	2-Aminochromone	93%	Slow drug release up to 2 weeks	Diffusion	Dimethylamine borane	Enhanced arterial U-86 levels	11
Double emulsion solvent evaporation method	Thymopentin	31.03%	Enhanced intestinal boadhesion	–	Lectin	Highest amount of NPs in small intestines	12
Solvent evaporation method	Dexamethasone	6%	Slow drug release up to 50 h	Diffusion	Dipalmitoylphosphatidylcholine	–	13
Emulsification solvent evaporative method	SR-2508(Etanidazole)	20.06%	Drug retained its bioactivity and effectively sensitized two hypoxic tumor cell lines to radiation	Burst effect	–	Radiosensitisation of SR-2508 loaded particles was more significant than the free SR-2508. Colony count of hypoxic tumor cells was significantly lowered	14

[a]EE means encapsulation efficiency, [b]Ref. is the reference cited.

Table 2 PLA biodegradable polymeric NPs for drug delivery.

Synthetic method	Encapsulant	[a]EE	Therapeutic perfection	Release mechanism	Surface amendments	In vivo	[b]Ref.
Double emulsion method	Hemoglobin	87.9%	Less macrophage uptake	Diffusion	Polyethylene glycol	Reduced liver accumulation	15
Emulsion diffusion evaporation method	Ellagic acid	50%	Oral absorption was improved	Diffusion and degradation	–	NPs protected the cyclosporine induced nephrotoxicity in rats	16
Double emulsion method	Neurotoxin-I	35.5%	Brain delivery of NT-1 enhanced	Diffusion	Polyethylene glycol	Sustained plasma level after intramuscular and intravenous injection	17
Spray drying	Dexamethasone	6%	Slow drug release up to 50h	Diffusion	–		18
Solvent evaporation	Zidovudine	55%	Less phagocytosis	–	Polyethylene glycol	Avoids phagocytosis	19

[a]EE means encapsulation efficiency, [b]Ref. is the reference cited.

Table 3 PCL biodegradable NPs for drug delivery.

Synthesis method	Encapsulant	[a]EE	Therapeutic perfection	Release mechanism	Surface amendments	In vivo	[b]Ref.
Solvent displacement	tamoxifen	90%	Preferential tumor targeting and circulating drug reservoir		Pluronics	Increased level of accumulation of the drug with time and extended their presence in circulation	20
Solvent displacement method	Saquinavir	60%	Higher intracellular saqunavir concentration	Diffusion	Poly(ethylene oxide)	Rapid cellular uptake of rhodamine-123 encapsulated PEO-PCL was observed on THP-1 cells	21
	Insulin	96%	Preservation of insulin's biological activity	Diffusion	–		22
Nano precipitation method	Docetaxel	90%	Higher antitumor effect	Diffusion	Methoxy(polyethylene glycol)	Effectively kills B16 cells	23
Emulsion method	Vinblastine	48%	Slow drug release upto 20days	Diffusion	–	Breast cancer cell line (MCF-7) showed efficient intake	24

[a]EE means encapsulation efficiency, [b]Ref. is the reference cited.

their application and nature of drug to be encapsulated. These NPs are extensively used for the encapsulation of various useful bioactive molecules and medicinal drugs to develop nano-medicine. Biodegradable polymeric NPs are highly preferred because they show much more promise in drug delivery system. Such NPs provide controlled/sustained release properties, subcellular size and bio- compatibility with tissue and cells. In addition, these nano medicines are more stable in blood compared to conventional medicines and are very less toxic thrombogenic, immunogenic, inflamatory and do not activate the neutrophils, biodegradable, avoid reticuloendothelial system and applicable to various molecules such as drugs, proteins, peptides, or nucleic acids. A general layout for the synthesis of nano medicine is list in Fig. 1.

Since preceding two decades, incalculable efforts have been put on to design most effective nano medicine with the biocompatible and biodegradable nano polymers. The role of nanostructures for drug delivery through oral, nasal and ocular has been reviewed by Alonso.[25] Pinto Reis *et al.* reviewed the numerous ways of synthesis and encapsulation of different bioactive molecules in NPs.[26] Utmost of the described methods are normally cast-off for the synthesis of the biodegradable nano medicine. Various frequently used nano polymers are concisely described in this review along with each section and their encapsulation efficiency. The administration, activity and therapeutic prominence of some medicinal drugs on different nano systems are unlike, for example anticancer drug taxol have 100% and 20% encapsulation efficiency on PLGA (poly-D, L-lactide-co-glycolide)[4] and PCL (poly-E- caprolactone)[27] nano devices, respectively. However, the therapeutic activity and stability of PCL nano medicine are rationally high than PLGA nanomedicine.[28] The therapeutic recompenses of the most frequently used polymeric NPs (ploy- D,

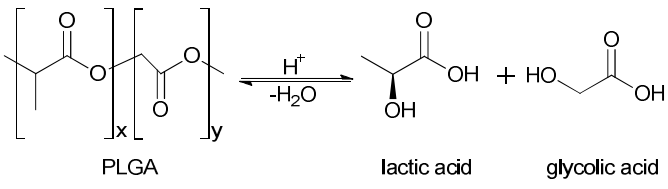

Fig. 1 Hydrolysis of Poly-D, L-Lactide-co-Glycolide (PLGA).

L-lactide–co-glycolide, polylactic acid, poly-ε-caprolactone and chitosan) have been defined in this portion of review.

2.1.1 Poly-D, L-Lactide-co-Glycolide (PLGA)

PGLA (poly-D, L-lactide -co-glycolide) is one of the most efficaciously used biodegradable systems to develop the nano medicines, because it endures hydrolysis in the body to yield the biodegradable metabolite monomers lactic acid and glycolic acid (**Fig. 1**). Since the body efficiently deals with these two monomers, there is marginal systemic toxicity associated by using PLGA for the drug delivery (**Table 1**).

2.1.2 Polylactic acid (PLA)

PLA (polylactic acid) polymer is a biocompatible and biodegradable material which undergoes scission in the body to monomeric units of lactic acid as natural transition in carbohydrate metabolism. PLA NPs have been prepared by solvent evaporation, solvent displacement,[29] salting out[26] and solvent diffusion (**Table 2**).

2.1.3 Poly-ε-caprolactone (PCL).

PCL can be degraded by hydrolysis of its ester linkage in physiological conditions (such as in human body), which provides a great deal of courtesy for use in the drug delivery. It is exclusively fascinating for the preparation of the implantable devices owing to its degradation slower than polylactide (**Table 3**).

2.1.4 Poly-L-lysine (PLL)

PLL is a kind of intrinsically biodegradable cell-adhesive polyelectrolyte, suitable for drug delivery application. Łukasiewicz and some other researchers have proved that PLL is a promising candidate for drug delivery.[30-32] Huang and co-workers used layer-by-layer polypeptide capsules as a carrier for platinum-based pro-drug delivery.[30] They firstly produced PLL-Pt(IV) polypeptide-drug conjugate by conjugating platinum(IV) to the side chains of poly(L-lysine) (PLL). Then PLL-Pt(IV) was assembled with poly(glutamic acid) (PGA) through an layer-by-layer technique on sacrificial template silica spheres. After dissolving the silica sphere, hollow $(PGA/PLL\text{-}Pt(IV))_3$ microcapsules was obtained. On the one hand, the hollow microcapsules showed enhanced Pt release under low pH and reductive conditions according to ICP-OES characterization. On the other hand, the microcapsules had higher cytotoxicity against CT-26 tumor cells than free cisplatin, which was explained as the enhanced cell internalization of Pt in the form of capsules.

To widen the application of PLL in drug delivery, the groups of Yan and Li developed a new class of protein-based drug delivery vectors.[33,34] They designed a HSA/PLL colloidal spheres by combining electrostatic assembly of binary components (disulfide-containing human serum albumin (HSA) proteins and oppositely charged PLL) and reversible covalent cross-linking for the first time.[33] The good pH and redox dual responsiveness drug delivery property of the material has been demonstrated in NIH 3T3 cell, making them facilitate the rapid release of payloads in an acidic and reductant-enriched ambient such as in lysosome. Significantly, more efforts have been spent on biomolecule-based materials due to their intrinsic biofunctionality, biodegradability, biocompatibility, and low toxicity. The research group of Li has devoted to the field for years, and got splendid achievement. They constructed different biomolecule-based materials, including autofluorescent protein coated mesoporous silica, dipeptide-based nanocarriers, and polysaccharide-based microcapsules, all exhibited unique advantages in biomedical applications.[35-39] Taking CDP-GA (cationic dipeptide-glutaraldehyde) dipeptide-based nanocarriers as an example, can encapsulate chemotherapeutic agents like doxorubicin hydrochloride (DOX) and the loading capacity can reach over 50%.[36] *In vitro* experiments show that the release kinetics of DOX in PBS (pH 7.2) is a remarkably faster with the existence of tyrisin, comparing to that without tyrisin, indicating the enzyme-responsive property. More important, DOX-loaded nanocarriers have much higher efficiency against tumor cell proliferation even at a very low concentration, compared with free DOX, possessing high promise in the treatment of cancer.

2.1.5 Chitosan

Chitosan is a modified natural carbohydrate polymer prepared from partial N-deacetylation of crustaceans derived natural biopolymer chitin. There are at least four methods reported for the synthesis of chitosan NPs. And chitosan based drug delivery materials for *in vivo* application is depicted in **Table 4**. The chitosan systems show a characteristic pH-sensitive swelling, being swollen in acid medium and shrunk in neutral and alkaline medium. Thus, non-interacting drugs are released quicker to media of acid pH value.

The chitosan based complexes can be prepared as bulk monoliths, and also as micro- or nano-gels in one or two steps. Chitosan films also have been prepared by crosslinking with different multivalent phosphates, namely pyrophosphate (Pyro) and tri-polyphosphate (TPP).[40] The films released quicker riboflavin and Coomassie Brilliant Blue R250 in acidic medium than at pH 7.5. These films, precisely the ones with pyrophosphate/chitosan, are potentially advantageous for stomach-specific drug delivery. Generally, the amalgamation of chitosan with neutral hydrophilic polymers enhances the responsiveness to pH value. In addition, films based on combinations of chitosan and polyethylene glycol can be obtained by a casting / solvent evaporation method that stimulates intermolecular hydrogen bonding.[41] The hydrogen bonds are broken in media of pH acid or with a high content of ions, ensuing a faster release of ciprofloxacin (Fig. 2).

The recent studies on mice by Dong *et al.* depicted the biodegradation ability of chitosan.[42] And the biodegradation of chitosan leads to the release of oligosaccharides which can be subsequently incorporated to glycosaminoglycan's and glycoproteins. However, the underlying mechanism is still unclear.

2.1.6 Gelatin

Besides the extensive applications in food and medical products, gelatin is attractive for the use in controlled release due to its nontoxic, biodegradable, bioactive and inexpensive properties. Gelatin is a polyampholyte having both cationic and anionic groups along with hydrophilic groups. It is known that the mechanical properties, swelling behaviour and thermal properties of gelatin depend on the degree of crosslinking gelatin. Gelatin based drug delivery materials for *in vivo* use are presented in Table 5. The elementary composition of gelatin is polypeptide with many carboxyl, amine, and amide functional groups, which could make gelatin negatively or positively charged upon the change of the pH value. By using such properties, numerous pH-responsive controlled drug release systems with gelation as carrier material were

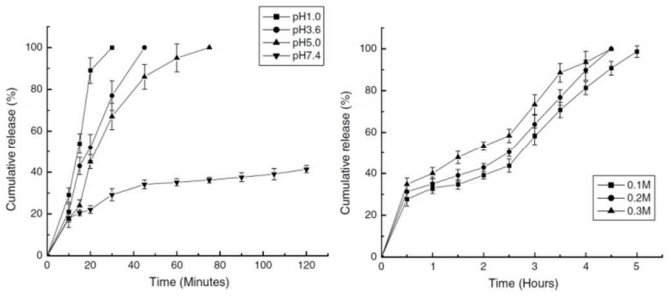

Fig. 2 Effect of the pH and the ionic strength (concentration of NaCl) of the release medium on ciprofloxacin release from chitosan/polyethylene glycol blend films. (Adapted from ref. 41, Copyright 2007, Elsevier Ltd. Reproduced with permission.)

Table 4 Chitosan based biodegradable NPs for drug delivery.

Synthesis method	Encapsulant	[a]EE	Therapeutic perfection	Release mechanism	Surface modification	*In vivo*	[b]Ref.
Ionic gelation method	Bovine serum albumin	92%	Slow drug release upto 4 weeks	Diffusion	Lactic acid		43
Ionic gelation method	Cyclosoprin A	73%	It was possible to achieve therapeutic concentration in extra ocular tissues	Dissolution		CyA concentration were high in cornea than conjunctiva	44
Ionic gelation method	Ammonium glycyrrhizinate	35%	Oral absorption of ammonium glycyrrhizinate increased	Diffusion and polymer degradation	Poly (ethylene glycol)		45

[a]EE means encapsulation efficiency, [b]Ref. is the reference cited.

Table 5 Gelatin based NPs for drug delivery.

Synthesis method	Encapsulant	[a]EE	Therapeutic perfection	Release mechanism	Surface modification	*In vivo*	[b]Ref.
Double dissolution technique	Didanosine	72.5%	Slow drug release up to 24h	Diffusion	Mannan	Higher accumulation of didanosine in brain	46
Ionotropic gelation method	Insulin	72.8%	Oral absorption and oral bioactivity improved	Diffusion	–	NPs adhere to intestinal epithelium and internalized by intestinal mucosa	47

[a]EE means encapsulation efficiency, [b]Ref. is the reference cited.

reported.[48] For instance, Li *et al.* recently synthesized pH responsive gelatin microgels replicating the structure of a porous $CaCO_3$ template. In such system, the internal charge repulsion force inside gelatin microgels increase with the increase of pH, resulting in the swelling of the gelatin microgels and the release of drugs. Additionally, some fresh investigations established that gelatin could adsorb onto the surface of the nanoparticles by complex interactions, such as van der Waals interactions, hydrophobic interactions, and electrostatic interactions, which make gelatin a beneficial contender for the pH sensitive coating layer. Recently, Kuntworbe *et al.* reported several *in vivo* chemosuppressive activities of cryptolepine hydrochloride-loaded gelatine nanoparticles (CHN) used for parenteral administration for the treatment of malaria in comparison to the drug free in solution.[49] In spite of these flourishing achievements, the use of gelatin for designing a drug release system is still an embryonic area of research.

2.1.7 Poly ethylene glycol (PEG)

As a polyhydroxy alcohol, PEG has good biocompatibility, thereby, has been widely used to enhance the dispersity of nanoparticles. Moreover, PEGylation could be further adopted to prevent the quick clearance by the reticuloendothelial system (RES), which could enhance the dose delivery efficiency in tumor *via* the EPR effect.[50-52] All the research groups of Shi, Zhang, Hyeon, Liu and Li have chosen PEG as hydrophilic group to modify different functional materials and achieved favorable dispersibility in aqueous solution.[53-58] Accordingly, all kinds of hydrophilic functional nanomaterials, such as $NaYF_4$:Yb,Er@PEG, $NaYF_4$:Yb,Er,Tm,Gd@SiO_2-Au@PEG and $Ba_{0.55}Y_{0.3}F_2$:Eu-PEG-COOH have been produced. According to the research, after PEG modification, all the nanomaterials were dispersed in water without any detectable degradation or aggregation.

In addition, Owing to the inimitable physical properties and ability to functionalize biological interactions at cellular and molecular level, magnetic nanoparticles have been enthusiastically investigated as the next generation of targeted drug delivery carriers for more than thirty years.[59,60] The importance of targeted drug delivery and targeted drug therapy is to carry drug molecules directly to the centre of the disease under numerous conditions and thereby treat it deliberately, with the fewest side effects on the body. The utmost therapeutic potential is undoubtedly allied with applications comprising "intelligent" particles with a magnetic core (to direct the particles to the vicinity of the target and also for hyperthermia or for temperature-enhanced release of the drug), a hydrophilic layer, a recognition layer (to which suitable receptors are attached), and a therapeutic load (adsorbed inside the pores or hosted within internal cavities of the particles). PEG is a good choice as hydrophilic layer. For example, with PEG coating, Liu *et al.* designed IONC@Au-PEG composite nanoparticles.[56] This type of composite nanoparticles display durable magnetic property and high near-infrared (NIR) optical absorbance, and thus offer pronounced disparities in both magnetic resonance imaging (MRI), a traditional imaging approach commonly employed in the clinic for whole-body imaging,[61] and photo acoustic (PA) imaging, a newly developed technique that permits higher-resolution imaging within a depth of few centimeters.[62] In this approach, both MRI and PA imaging are carried out, not only to visualize the tumor, but also to determine the efficiency of magnetic tumor-targeting in a time-dependent way for improved therapeutic development. Due to the strong magnetism of theranostic nanoparticles, extraordinarily enhanced tumor homing of those nanoparticles is witnessed under magnetic targeting, possibly due to the "magnetic targeting mediated EPR effect". Photothermal treatment of cancer is then judiciously scheduled and carried out. By finally tuning the laser power density and closely under treatment period, imaging is further executed for tumor prognosis to assess the therapeutic outcome (Fig. 4). This work purposely establishes the exceptional advantages of multimodal imaging guided therapeutic planning and post-treatment monitoring based on multifunctional theranostic nano-agents. Cheng *et al.* used a layer-by-layer assembly method to synthesize a new class of multifunctional nanoparticles

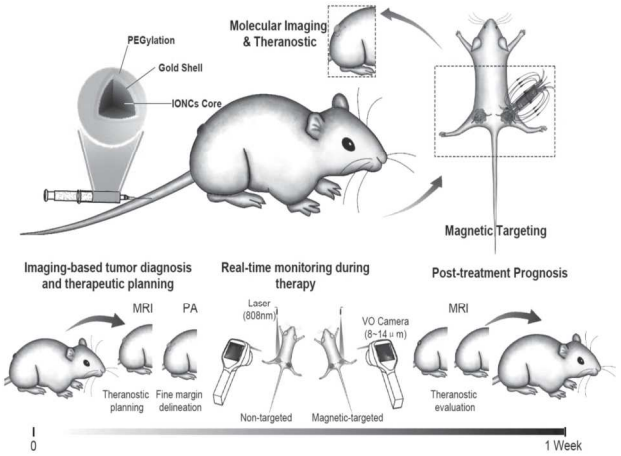

Fig. 4 The magnetic targeting enhanced theranostic strategy using IONC@Au-PEG nanoparticles under guidance by multimodal imaging. In our experiment, IONC@Au-PEG is intravenously injected into a mouse bearing two tumors, one of which is exposed to an external magnetic field while the other is not. As the theranostic nanoparticles circulate in bloodstream, they will be trapped into the magnetic field created by the nearby magnet, resulting in enhanced enrichment and prolonged retention in the targeted tumor. Dual modal MRI and photo acoustic imaging is carried out to track and understand the tumor homing of our theranostic nanoparticles for therapeutic planning. IR thermal imaging is conducted during NIR laser irradiation to real-time monitor the photothermal effect for better therapeutic control. MRI after PTT is finally performed for post-treatment prognosis. (Adapted from ref. 56, Copyright 2013, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Reproduced with permission.)

(MFNPs) comprising of upconversion nanoparticles as the cores, a layer of ultra-small iron oxide nanoparticles (IONPs) as the intermediate shell, and a thin layer of gold as the outer shell, the former bids MFNPs strong NIR optical absorption.[63] Those MFNPs were used for upconversion luminescence (UCL)/ MRI multimodal imaging as well as photothermal ablation of cancer cells *in vitro*. Additionally, they achieved highly efficient *in vivo* magnetically targeted photothermal therapy (PTT), which is guided by UCL/ MRI dual modal imaging (Fig. 5). This work is the first that the *in vivo* dual modal imaging along with PTT targeted by the magnetic field has been achieved in animal experiments, which promises the use of multifunctional nanostructures as cancer theranostic agents.

2.2. Mesoporous silica

Mesoporous silica NPs have attracted ample attention in recent years due to their advantageous superficial properties, such as

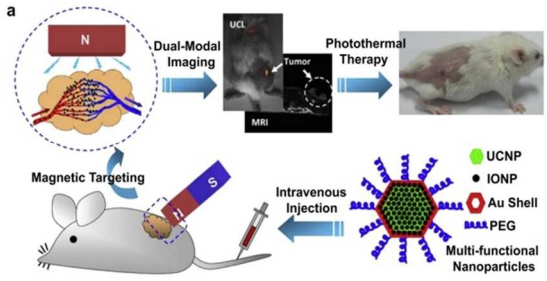

Fig. 5 A schematic illustration showing the composition of an MFNP-PEG and the concept of in vivo imaging-guided magnetically targeted PTT. The magnetic field around the tumor region induces local tumor accumulation of MFNPs. (Adapted from ref. 63, Copyright 2012, Elsevier Ltd. Reproduced with permission.)

high surface area and pore volume, tunable pore size, colloidal stability and the possibility to functionalize the inner core system. These highly attractive features make mesoporous NPs a promising and widely applicable platform for diverse biomedical applications including bio-imaging for diagnostics,[64,65] biosensing,[66,67] biocatalyst,[68,69] bone repair engineering[70,71] and drug delivery.[72-74] Caruso and co-workers discovered other important approach using mesoporous silica particles as the template to create submicron sized polymer capsule for anticancer drug delivery.[75,76] In particular, inorganic-organic core-shell nanomaterials based on mesoporous silica have received great attention as drug delivery carriers, where the ornamentation of the inner or the outer surface of the particles with organic molecules can impart important features for the successful drug delivery. The delivery of anti-cancer therapeutics into cancer cells by employing nanoparticle carriers has made significant progress in recent years. Herein, the intention is to overcome common issues of conventional systemic drug supply such as poor solubility, limited stability, rapid metabolization and excretion of the drug, undesired side effects, and the lack of selectivity towards specific cells types. The encapsulation of therapeutics within nanocarriers that selectively target certain cell types or tissues represents a promising strategy to address these problems.[77-80] In this perspective, we discuss recent research in the field of multifunctional mesoporous silica nanomaterials (MSNs size typically < 500 nm) designed as a multifunctional platform for different stimuli responsive trigger systems for a specific drug release.[72,73,81] Additionally, coating the NPs with different organic shells improves the biocompatibility, facilitates attachment of targeting ligands for specific cellular recognition, and can be utilized for the effective encapsulation of cancer drug.

MCM-41 with hexagonal arrangement of mesopores and SBA-15 with well-ordered hexagonal connected system of pores are two kinds of preeminent and recognized MSNs.[82] The MSNs, in contrast with xerogels, hold more homogenous assembly, lower polydispersity and higher surface area for adsorption of therapeutic or diagnostic agents.[83] The mechanism of drug loading into mesoporous silica material is chemical or physical adsorption. By using these MSNs, varied categories of drugs, including anticancer drugs,[83,84] antibiotics,[85] and heart disease drugs,[86] have been entrenched into them. Commonly, drug release is controlled by diffusion.[85] Moreover, silicalites and mesoporous silica NPs latent application in photodynamic therapy has been also studied.[87] Properties of MSNs make them a brilliant material for various pharmaceutical and biomedical solicitations. The assembly of MSNs enables the amalgamation of both small[83] and large molecules,[88] adsorption of DNA, and gene transfer.[89] This provides a leeway of using these nanomaterials in a combined therapy.[84] Certain data indicate that nano-sized silica particles (SNPs) are biocompatible and have a prodigious potential for a diversity of diagnostic and therapeutic applications in medicine. Especially the 2-10 nm sized mesoporous channels, suitable for stimuli-responsive drug delivery. Lin and co-workers developed a series of stimuli-responsive mesoporous silica drug delivery systems, in which the pores was capped with CdS nanoparticles,[90] Fe_3O_4 nanoparticles,[91] and poly(amido amine) dendrimers to keep the loaded drug molecules in the silica carriers.[92] Fig. 3 gives a typical structure of these systems. The CdS-capped MCM-41 controlled drug delivery system exhibits less than 1.0% of drug release over a period of 12 h without stimuli, while reaching 85% of drug release within 24 h with

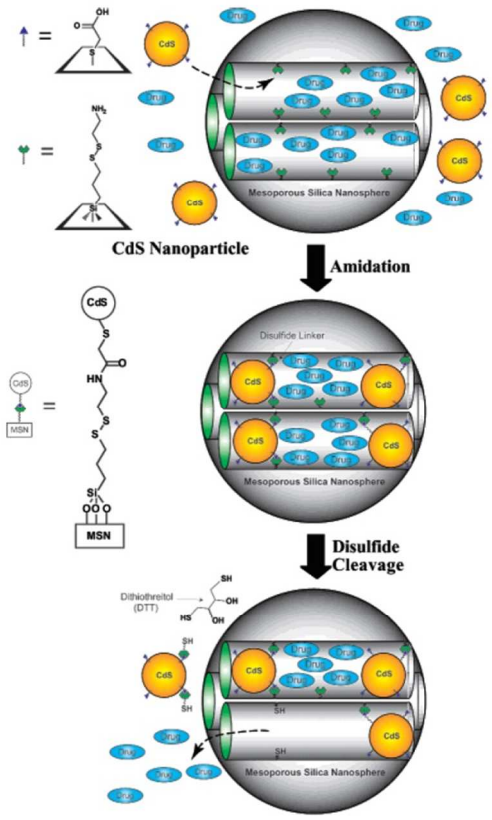

Fig. 3 Schematic representation of the CdS nanoparticle-capped MSN-based drug/neurotransmitter delivery system. The controlled-release mechanism of the system is based on chemical reduction of the disulfide linkage between the CdS caps and the MSN hosts. (Adapted from ref. 90, Copyright 2003, American Chemical Society. Reproduced with permission.)

the external stimuli of disulfide-reducing agents. The drug molecules cannot be released until the external stimuli was introduced to un-lock the gatekeepers. In this way, the drug release style, including start time, release rate and finish time can be well controlled. Therefore, when the stimuli-responsive drug delivery systems were applied to human body, the carried drugs will be "zero release" until the drug delivery systems arrived at the targeted cells and were exposure to external stimuli. This is an effective method to protect the healthy organs from the toxic drugs and prevent the decomposition / denaturing of the drugs. Besides the nanoparticles, polymers, such as poly (amido amine) dendrimers[92] and polycation poly (allylamine hydrochloride) / sodium polystyrene sulfonate (PAH/PSS)[93,94] polyelectrolyte multilayers also have been employed as gatekeepers. Because of the pH sensitivity and salt-induced responsive property of the PAH/PSS multilayers, hollow mesoporous silica was coated with them by Shi and co-workers to realize the pH-responsive drug delivery.[93,94] In addition, the large voids inside the mesoporous silica shells can store more drug molecules than that of the conventional mesoporous silica. Recently, some biomolecules, which are more suitable for human beings have been used as external stimuli to uncap the gatekeepers. For example, Shi *et al.* triggered glucose oxidase enzyme (GOD) and catalase (CAT) enzyme multilayer shells with glucose stimuli.[95] Above all, mesoporous silica materials have been considered to be excellent candidate as carriers for controlled drug delivery systems.

Although mesoporous silica materials were well applied for drug delivery study, low release efficiency is a drawback of the mesoporous silica carriers. Normally, for drug loaded pure mesoporous silica systems, the drug release efficiency is lower than 40% due to the strong adsorption capacity and a large number of hydrophilic groups on the surface. So far, modification of mesoporous silica with polymer or other functional groups is a good way to improve the drug release efficiency. Moreover, considering amorphous silica is an FDA-approved food additive, the mesoporous silica materials still a promising carrier material.

3. Stimuli responsive drug delivery

3.1. pH responsive drug delivery

Amid the environmental incitements, pH gradient have been commonly used to design peculiar, responsive NPs. The pH perceptive NPs based on delivery have been gauged at three levels, namely, at organ, tissue and subcellular level. It's striking to take explicit examples from the oral drug delivery, tumor targeting and intracellular delivery to acme the conceptually interesting pH responsive nanoparticle design. Hence nanoparticle preparations that respond to the pH gradient within the micro environment of organ, tissue and cell organelle may be useful to the spectrum of NPs-based existing therapeutic drug delivery.

3.1.1 ORAL DRUD DELIVERY

Each partition of the gastrointestinal tract upholds its own idiosyncrasy of pH level from pH of (1–3)[96] in acidic stomach to pH of (6.6–7.5)[97] in alkaline lumen for the neutralization of acidic chime (Fig. 6). Oral delivery is a salient route for drug delivery due to its expediency and patient compliance and cost effectiveness. However orally administered drugs are wide-open to the strong gastric and presystemic enzymatic degradation resulting in the reduced systemic exposure. It has been proven to be a challenge to achieve adequate and consistent bioavailability levels for the orally administered drugs.[98] Until now, NPs formulated with biodegradable biopolymers have been used to enhance the bioavailability of easily degraded peptide drugs such as insulin,[99] calcitonin[100] and elcotonin.[101] Very recently, innovative nano medicines have included pH-responsive mechanism to advance systemic

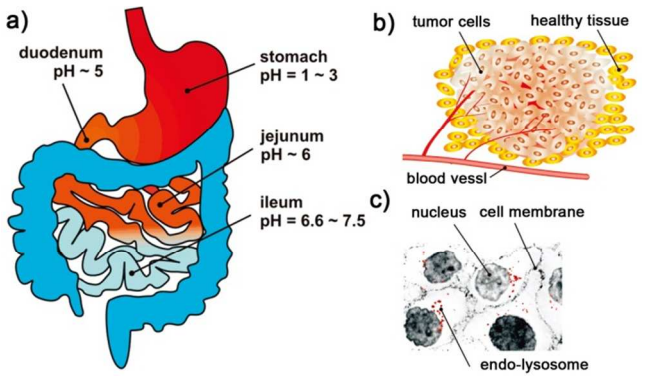

Fig. 6 Sketch of acid-responsive NPs for choosy drug release. (a) Targeting at the organ level: the gastrointestinal is categorized by a pH gradient. (b) Targeting at the tissue level: solid tumors have a characteristic acidic extracellular environment different from healthy tissues. (c) Targeting at the cellular level: endolysosomes are more acidic in comparison to the cytoplasm (shown in red). (Adapted from ref. 96, Copyright 2003, American Chemical Society. Reproduced with permission.)

exposure *via* a greater gastric retention, trans epithelial transport and cellular targeting with surface functionalized ligands.[102] One mostly acknowledged approach to accomplish organ specific drug release is to formulate NPs that display the pH-dependent swelling. For example, when acrylic based polymers such as poly (meth acrylic acid) (PMAA) were used, NPs can sustained a hydrophobic, collapsed state in the stomach due to protonation of carboxyl groups. The gastric passage an increase in the pH leads to NPs swelling due to carboxyl ionization and hydrogen bond breakage.[103] Founded on these properties, PMAA-PEG diblock copolymers were capable to reach swelling ratios (mass of swollen polymer/mass of dry polymer) of 40-90-fold reliant on copolymer composition and PEG graft length.[104] When NPs were loaded with insulin, about 90% of the insulin was released at pH 7.4 within two hours in their swollen state, whereas only a small fraction (approximately 10%) of the insulin was released at pH 1.2 in their collapsed state. Researchers have designed NPs that endure a surface charge reversal after gastric passage to promote drug release in the alkaline intestinal tract. Using inorganic materials such as mesoporous silica, NPs were surface-functionalized with different densities of positively charged trimethyl ammonium (TA) functional groups. The positively charged TA facilitated loading of anionic drugs such as sulfasalazine (an anti-inflammatory prodrug for bowel disease) in acidic environments (pH < 3). When the drug-loaded NPs were placed in physiological buffers (pH 7.4), a partial negative surface charge on the NPs was generated from the deprotonation of silanol group. The electrostatic repulsion triggered the sustained release of loaded molecules.

3.1.2 TISSUE LEVEL: TUMOR TARGETING

Human tumor has been revealed to show pH states that range from 5.7 to 7.8,[105] there is a considerable variation within different regions of the same tumor. In general tumors are more acidic than normal tissue with median pH value of about 7.0 in tumor and 7.5 in normal tissue.[106] The acidity of tumor microenvironments is caused in part by lactic acid which is built up in rapidly growing tumor cells owing to their elevated rates of glucose uptake but reduced rates of oxidative phosphorylation.[107] This persistence of high lactate production by tumors in the presence of oxygen, termed Warburg's effect, provides a growth advantage for tumor cells *in vivo*.[108] In addition, insufficient blood supply and poor lymphatic drainage, which are the characteristics of most tumors, also contribute to the acidity of tumor microenvironment.[109] Increasingly, researchers have exploited the acidic tumor pH to achieve high local drug concentrations and to minimize overall systemic exposure.[110] NPs have been formulated for pH dependent drug release by using polymers that change their physical and chemical properties, such as by swelling and an increase in solubility, based on local pH levels. To achieve NPs swelling, Griset *et al.* cross-linked NPs using acrylate-based hydrophobic polymers with hydroxyl groups that were masked by pH-labile protecting groups (*e.g.* 2,4,6-trimethoxybenzaldehyde).[111] The NPs were stable at neutral pH, but the protecting groups were cleaved and the hydroxyl groups were exposed at mildly acidic pH (pH ~5). This hydrophobic-to-hydrophilic transformation caused the swelling of NPs and subsequent drug release. Paclitaxel release was shown to be minimal at pH 7.4 (< 10%), whereas nearly all of the paclitaxel was released within 24 h at pH 5. These acrylate-based, pH-sensitive NPs were shown to inhibit the rapid growth of Lewis lung carcinoma (LLC) tumors in C57Bl/6 mice compared to nonresponsive NPs or paclitaxel in solution, suggesting that pH-responsive drug release may be beneficial for drug delivery to tumors.

The pH dependent hydrophobic to hydrophilic transitions may also be used to control polymer dissolution, in which the polymer matrix collapses for drug release. Wu *et al.* formulated NPs (AP-PEG-PLA/MPEG-PAE micelles (AP-pH-PMs) with an average size of 150 nm) using PEG-poly(-amino ester) polymers that have a pKb of ~6.5.[112] At pH 6.4-6.8, amine protonation increases polymer solubility and induces a sharp micellization-demicellization transition for drug release. In another study, Criscione *et al.* showed that self-assembly of poly(amidoamine) dendrimers occurred at a physiological pH, followed by drug release from NPs dissolution at pH < 6.[113] Drug molecules have been conjugated to polymer chains *via* (amidoamine) dendrimers at physiological pH, followed by drug release pH-labile cross-linkers for pH-responsive drug release. Recently, Aryal *et al.* developed cisplatin-polymer conjugated NPs using hydrazone cross-linkers to achieve low pH drug release.[114] Cisplatin release occurred at pH < 6 due to hydrazone hydrolysis as opposed to poly(lactic acid) (PLA) degradation. NPs uptake and subsequent cisplatin release contributed to the enhanced cellular cytotoxicity over free cisplatin *in vitro*.[115] In another study, chromone conjugated to magnetic Fe_3O_4 NPs *via* a Schiff-base bond led to a 4-fold improvement in chromone release at pH 5 versus at pH 7.4, an improvement in chromone solubility in buffer solutions from 2.5 to 633 μg/mL, and an enhancement of cytotoxicity *in vitro*. For dual-drug delivery, Shen *et al.* formed liposome-like NPs by conjugating camptothecin to short PEG chains *via* an ester bond, followed by encapsulating hydrophilic DOX.[116] When loaded with DOX, rapid release of both DOX and camptothecin drug molecules occurred at pH < 5 or esterase was added. Likewise, Bruyère *et al.* synthesized a series of orthoester model compounds which had different hydrolysis rates at pH ranging from pH 4.5 to 7.4.[117] To increase the time for NPs retention in tumors, NPs have been designed to reverse their surface charge from neutral/negative to positive at the tumor site. In one study, quantum dots and adenovirus-based NPs were surface-functionalized with pH sensitive poly (L-lysine) (PLL).[118] PLL with amine groups were conjugated with biotin-PEG and citraconic anhydride (a pH sensitive primary amine blocker) to generate carboxylate groups. Under acidic conditions (pH < 6.6), the citraconylated amide linkages were cleaved, resulting in the recovery of positively charged amine groups. This surface charge reversal in turn led to enhanced NPs uptake by HeLa cells. The pH-responsive mechanisms described here draw upon a general phenomenon which is the acidity of tumor microenvironments. Here, NPs maintain stability in circulation and undergo physicochemical changes that favour localized drug release.

Our group introduced rare earth luminescent phosphor into stimuli-responsive drug delivery system, and designed a pH-responsive drug delivery system by photo polymerization poly (acrylic acid) (PAA) inside $CaF_2:Ce^{3+}/Tb^{3+}$ hollow phosphor spheres.[119] The hollow structure exhibits a high storage capacity of drug, and Tb^{3+} shows strong and green luminescence. The luminescence intensity is changed greatly with the drug loading and release process, which has potential for the tracking and monitoring applications. The drug release rate of DOX from the prepared $CaF_2:Ce^{3+}/Tb^{3+}$-PAA hollow composites was obviously pH-dependent and increased with the decrease of pH, for example, only 6.5% of DOX was released after 48 h at pH = 7.4, while 52.5% was released after 48 h at pH =4.0, and more than 70% was released within 4 h at pH =

2.0. The pH-responsive drug delivery profile was dependent on two factors related to PAA. The first one is the electrostatic interaction between the carboxylic acid groups on PAA chains and the amino group of DOX. The other one is the electrostatic repulsion between the negative-charged carboxylic acid groups of PAA. When pH was decreased, the carboxylic acid groups on PAA will be protonated and no electrostatic interaction between PAA and DOX occurred. And the PAA network swells with protonating of carboxylic acid groups to liberate the DOX molecules. Above all, the carrier system presents an alternately pH switch-on / off effect of drug release.

3.1.3 CELLULAR LEVEL TARGETING

Ensuing endocytosis, speedy endosomal acidification (~2-3 min) happens owing to a vacuolar proton ATPase mediated proton influx. As a result, the pH levels of early endosomes, sorting endosomes, and multivesicular bodies drop promptly to pH < 6.0.[120] The passage of endosomal acidification can be detrimental to the therapeutic molecule being delivered, especially for macromolecules such as DNA, small interfering RNA (siRNA), and proteins. However, endosomal acidification may also be used as a trigger for endosomal escape and payload release, a mechanism conjectured to occur *via* a "proton sponge" effect.[121] Here, NPs absorb protons at endosomal pH, leading to an increase in osmotic pressure inside the endosomal compartment, followed by plasma membrane disruption and NPs release into the cytoplasm. pH-sensitive polymers that buffer endosomal compartments have been grafted with other functional segments for intracellular delivery. For example, a nanoparticle platform designated Dynamic Poly Conjugates (Mirus Bio LLC) have an amphipathic endosomolytic poly (vinyl ether) backbone composed of butyl and amino vinyl ethers. The NPs were used to conjugate and deliver siRNA through a reversible disulphide linkage, including functional components such as PEG and targeting ligands. The Dynamic Poly Conjugates provided effective knockdown of two endogenous liver genes, apolipoproteinB and peroxisome proliferator-activated receptor alpha (PPARα) *in vivo*.[122,123]

Copolymers made from pH-sensitive monomers and nonionic monomers allow fine-tuning of polymer pKa to improve endosomal escape. For example, using copolymers made from monomers with different pKa such as (dimethyl amino ethyl methacrylate and nonionic monomer 2-hydroxyethylmethacrylate), it is possible to adjust the pH sensitivity of NPs, DNA encapsulation efficiency, and monomer toxicity to optimize transfection efficiency.[124] Biodegradable poly (-amino ester) (PbAE) polymers contain tertiary amines that have been used for pH buffering. A combinatorial family of PbAE compounds was prepared by parallel synthesis using amine- and acrylate-terminated monomers in a Michael addition reaction, without the use of specialized monomers or protection steps.[125] In this study, PbAE NPs were shown to undergo rapid dissolution in acidic microenvironments (pH 6.5) which facilitated drug release. And NPs based on PbAE have been applied to deliver small molecule drugs,[126] DNA[127] and siRNA.[128,129] Finally, nanoparticle designs may comprise protein transduction domains, which are cationic, amino acid sequences hypothesized to endosomal membranes upon endosomal acidification.[130] The mechanism of protein transduction domain membrane penetration is an active research topic, and protein transduction domains have been widely used to improve intracellular delivery in oncologic-based applications.[131,132] In one study, the co-administration of a free tumor-penetrating peptide (*e.g.*, iRGD sequence) was shown to enhance the efficacy of doxorubicin (doxorubicin liposomes), paclitaxel (nab-paclitaxel), and monoclonal antibody (trastuzumab) treatments.[133] Still, attentiveness must be reserved when targeting is used to advance intracellular delivery, because the magnitude of endosomal acidification is influenced by the choice of targeting ligand and hence the endocytic pathway taken. For example, surface modification with folate was shown to lead endocytosis through recycling centre's characterized by near neutral pH of 6-7, which may make it less appropriate for pH-based mechanisms.[134] Therefore, pH-sensitive mechanisms are also important at the stages after NPs internalized by the target cell, especially for cytoplasmic release of a payload. These mechanisms are even more crucial for payloads such as siRNA, DNA, and proteins, where denaturation in the acidic lysosomal compartment may result in a significant loss of efficacy.

3.2. Thermo responsive drug delivery

Treatment of the body tissue by exposing it to a high temperature is called hyperthermia therapy. In hyperthermia therapy, the body tissue is exposed to high temperatures (up to 43 °C) to mutilate and kill cancer cells, or to make the cancer cells superfluous sensitive to the special effects of radiation and chemotherapeutic agents. Indigenous heating is one of the utmost common forms of hyperthermia therapy in which heat is applied to a small area by means of microwave, radiofrequency, or ultrasound. It is often used with chemotherapy to increase its effectiveness because mild hyperthermia not only damages tumor cells directly but also enhances the effects of certain anticancer drugs.[135–137] Unluckily, the combination of hyperthermia therapy with chemotherapy is far from perfection because many chemotherapeutic drugs are toxic to normal cells and can cause serious side effects at excessive doses.[138] As a

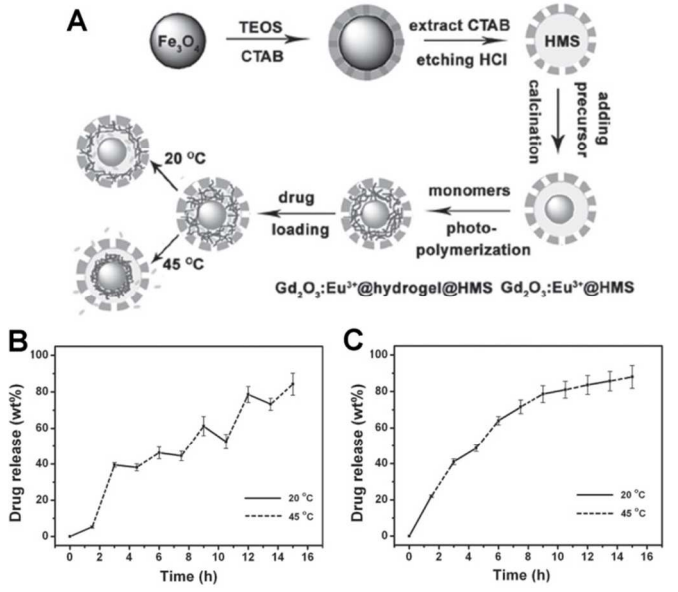

Fig. 7 Schematic illustration for the synthetic process for P(NIPAM-co-AAm) hydrogel modified luminescent rattle-type mesoporous silica microspheres and subsequent loading and temperature-controlled release of indomethacin (IMC) drug molecules (A), controlled release of IMC from Gd_2O_3:Eu^{3+}@P(NIPAm-co-AAm)@HMS (B) and Gd_2O_3:Eu^{3+}@HMS (C) in response to temperature changes in 10 mM PBS (pH = 7.4). (Adapted from ref. 149, Copyright 2012, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. Reproduced with permission.)

result, a apposite drug delivery system that can minimize side effects is required in chemotherapy. However, the release behaviour of diverse drug delivery systems is also a main concern because the antitumor efficacy of loaded drugs has often been limited by slow release of bioavailable drug within the tumor site. Therefore, a superlative drug delivery system which can both confine the range of amalgamated agents in human tissues and release drugs in response to an increased temperature is necessary in combined chemotherapy and hyperthermia cancer treatment. There has been a prodigious research on thermo sensitive drug carriers which could be used in tumor local hyperthermia therapy. Poly(N-isopropylacrylamide) (PNIPAM), a sort of temperature responsive polymer, is frequently employed as a component of thermo sensitive drug carriers. Chung and his colleagues successfully amalgamated adriamycin into polymeric micelles constructed from PNIPAM and poly(butylmethacrylate) block copolymers in 1999.[139] Since then, various PNIPAM block copolymers have been studied as a kind of thermo sensitive drug delivery system, including hetero bifunctional block copolymers of poly(ethyleneglycol) and PNIPAM,[140] poly block-PNIPAM,[135] and a temperature-pH-sensitive block copolymer of PNIPAM-block-poly(4-vinylpyridine).[141]

Thermo-responsive PNIPAAm-PEG-DA hydrogel was applied for the extended release of the drug delivery to the posterior segment. And proteins (bevacizumab and ranibizumab) were encapsulated into the hydrogels, including BSA and immunoglobulin G (IgG). On the one hand, PEG wss cross-linked with PNIPAAm to get a hydrogel having a homogenous structure.[142] For the above synthesis, PEG was chosen because of its pore-forming property. On the other hand, an ideal hydrogel must retain its thermos-responsive characteristic and should retain homogeneous pores throughout. For achieving the said property, PEG-DA is hosted to PNIPAAm. Here, PEG-DA (cross-linker) was used as a tuner for controlling the pore size of the hydrogel. In addition, altering the degree of cross-linker density, the protein release rate can be regulated. Thermo-responsive hydrogels formed by such crosslinking have shown faster and reversible phase transition with altered temperature. Hydrogels with less cross-linking agents exhibit fast release and better syringeability, when injected by intravitreal route *via* small-gauge needles. Hydrogels formed by PNIPAAm-PEG-DA exhibited a significant improved mechanical strength. Use of PEG-DA as a cross-linker did not alter the lower critical solution temperature (LCST), it was observed that below the LCST, the hydrogel swells and above the LCST, the hydrogel collapse. Pure PNIPAAm hydrogel altered its phase (LCST) at ~31 °C while PNIPAAm-PEG-DA hydrogel altered at ~ 32 °C, due to the increased hydrophilicity.[143] Moreover, this hydrogel system shows ideal syringe ability and injectability. Rodent model was used to study the injectability of the hydrogel for the vitreous chamber. PNIPAAm-PEG-DA hydrogel is biocompatible and has a unique polymerization characterization, as acrylates are used as end groups due to rapid polymerization. To extend the work, authors developed another intravitreal injection of a poly(ethylene glycol) diacrylate (PEG-DA) crosslinked PNIPAAm hydrogel for injectable drug delivery on retinal function. Crosslinked PNIPAAms showed the thermos-response behavior at approximately 32 °C exhibiting a VPTT,[144] above which the swelling behavior decreases with subsequent burst release. One of the advantages associated with the PNIPAAm was seen with its highly swollen nature of crosslinked PNIPAAm. At this stage (room temperature), the crosslinked PNIPAAm shows better syringeability.[145] Finally, thermo-responsive hydrogels were prepared by dissolving PEG-DA solution followed by N-isopropylacrylamide. OCT was used for measuring the retinal thickness confirming a small decrease in retinal thickness after one week post-injection, which was returned to initial levels in later weeks. As soon as the injection is applied, no significant change was observed in the IOP immediately but in subsequent weeks, a significant change was observed when compared to control IOP value. The PEG-DA crosslinked PNIPAAm hydrogel for intra vitreal injection thus had minimal impact on IOP. PEG-DA crosslinked PNIPAAm hydrogels were proved to be a potential drug delivery system for the posterior segment of the eye.[146]

However, the utilization of PNIPAM in biomedical applications is restricted because it is toxic and non-biodegradability.[147] Therefore, an innovative biocompatible and biodegradable thermo sensitive material is awaited to replace PNIPAM in drug delivery for tumor local hyperthermia therapy. Hydroxybutyl chitosan (HBC), manufactured by conjugation of hydroxybutyl groups to the backbone of chitosan, is a type of unique thermo responsive polymer which owns satisfactory biocompatibility and minimal cytotoxicity.[140] It is water soluble at a temperature below its LCST, while becomes insoluble due to the hydrophobic alteration at a temperature higher than its LCST. HBC has been widely utilized in areas of tissue engineering,[148] post-operative treatment,[140] and therapeutics delivery[135] as a biodegradable and thermal sensitive biomaterial. Nevertheless, there is rarely any article published about its solicitations on the nanoscale.

Our group developed a luminescent rattle-type mesoporous silica microsphere (Gd_2O_3:Eu^{3+}@P(NIPAm-co-AAm)@HMS), which is prepared by filling temperature-responsive poly[(N-isopropylacrylamide)-co-(acrylic acid amide)] (P(NIPAM-co-AAm)) hydrogel in mesoporous silica coated Gd_2O_3:Eu^{3+} hollow sphere (Fig. 7A).[149] The thermo-sensitive hydrogel is used as controlled switch to realize thermally controlled drug release. At low temperature, such as 20 °C, the drug molecules are confined in the pores due to the swollen of hydrogel (Fig. 7B and C). When the temperature was raised to 45 °C, the shrinking of the hydrogel opens the pores, driving the drug molecules to be released. Therefore, the control of drug release was regulated *via* the change of temperature.

3.3. Light responsive drug delivery

3.3.1 Conventional ligh responsive grug delivery

Light-responsiveness is in receipt of increasing attention owing to the opportunity of developing materials sensitive to innocuous electromagnetic radiation (mainly in the UV, visible and near-infrared range), which can be applied on demand at well delimited sites of the body. Some light-responsive DDS are of a single use (*i.e.* the light triggers an irreversible structural change that provokes the delivery of the entire dose), while others able to undergo reversible structural changes when cycles of light / dark are applied, behave as multi switchable carriers (releasing the drug in a pulsatile manner). Light-responsive systems possess a potential to become truly biomimetic sensors or actuators.[141] Photo induced self-healing polymers can mimic the biological systems in which damage triggers a self-healing response. These materials can be used to repair fibre fracture, delamination or propagation of micro cracks of polymeric components used in a variety of applications, extending the functional life and safety of the polymeric components.[147,150] On the other hand, some polymers such as segmented polyurethanes that are able to undergo light-induced shape changes can imitate the movement of artificial

muscles, and the shape-memory polymers being useful for medical devices that can recover a certain form by a remote light activation.[151,152] Another example of light responsive systems is "gated" membranes controlling the transport of ions or the flow of gases or liquids through micro channels.[153–155] The development of biocompatible materials for *in vivo* applications and the improved understanding of the photo regulated solute transport opened the prospects of photo responsive materials in drug delivery. Electromagnetic radiation in the range of 2500–380 nm can be externally applied to the body to switch drug release on and off at a specific site, offering a potential for controlling the release that is otherwise difficult to achieve using other stimuli and reducing the effect of radiation on the adjacent tissues to a minimum.[151] UV or blue light can serve as a triggering agent for topical treatments applied to the skin or the mucosa.[156,157] Radiation of wavelength below 700 nm cannot penetrate more than 1 cm deep into the tissue, because of scattering and a high level of endogenous absorbers, such as oxy and deoxy haemoglobin, lipids and water.[158] Thus, the interest in light irradiation below 700 nm is limited to the treatment of pathological processes on or under the skin or on the external layers of some internal organs. One of the key strategies for a deeper (more than a few millimetres) light penetration into living tissues has been the use of NIR light within the range of wavelengths from 650 to 900 nm. This is because haemoglobin (the principal absorber of visible light) and water and lipids (the main absorbers of infrared light) have their lowest absorption coefficient in the NIR light region. Thereby, NIR imaging techniques are currently being used for non-invasive *in vivo* imaging of physiological, metabolic and molecular function. For instance, light with a wavelength of 830 nm is used for measurement of oxidation of haemoglobin in many organs, including the brain.[159] NIR light is innocuous and does not cause a significant heating in the area of its application. Therefore, such light can be useful for triggering a drug release in the difficult to access areas of the body.[159–161] In addition, photopolymerizable materials used for preparing dental composites or implants such as UV curable precursors adopting the shape of the implantation zone are applied without the use of injections or other invasive techniques. This approach has great potential for achieving prolonged delivery (yet not stimuli-responsive) of dental antiseptics or peptides and hormones.[162] Research on light-responsive DDS have been focused on self-assembled colloids such as copolymer micelles and liposomes, although other photo responsive supramolecular architectures are also under study.[161,162–166] Modern laser systems enable a precise control of light wavelength, duration, intensity and diameter of the beam, hence offer a wide range of possibilities for biomedical applications.[167]

Recently, we develop a multifunctional drug delivery system combining NIR-activated platinum(IV) pro-drug delivery and tri-modality imaging (up-conversion luminescence imaging, magnetic resonance imaging and computer tomography).[168] The multifunctional nanomaterial of UCNP-DPP-PEG was fabricated by conjugating *trans*-platinum(IV) pro-drug (*trans, trans,trans*-$[Pt(N_3)_2(NH_3)(py)(O_2CCH_2CH_2COOH)_2]$, denoted as DPP) on the surface of $NaYF_4$:Yb/Tm@$NaGdF_4$:Yb nanoparticle (denoted as UCNP), then coating a monolayer of PEG. The platinum (IV) pro-drug is stable in dark and can be activated by the UV light emission of UCNPs (Fig. 8A). As shown in Fig. 8B, 980 nm NIR light (or 365 nm UV) can enhance the drug release effectively because the platinum(IV) pro-drug DPP has been activated and changed to platinum(II)

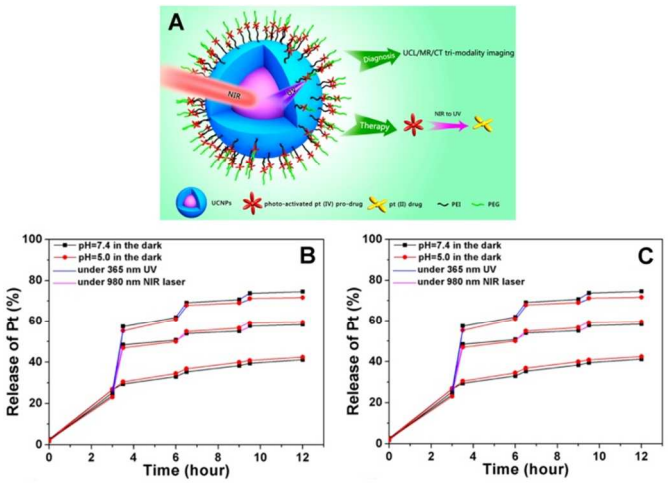

Fig. 8 (A) Schematic illustration of the characterization of UCNP-DPP-PEG nanoparticles. (B) Release profile of UCNP-DPP-PEG nanoparticles under different pH values (7.4 and 5.0) alternately changing the illumination conditions between 980 nm NIR irradiation (or 365 nm UV) and in the dark conditions. (C) In vivo tumor volume changes of Balb/c mice on different groups after various treatments, 980 nm laser irradiation for 30 min (2.5 W/cm^{-2}, 5 min break after 5 min irradiation), UV (365 nm) irradiation for 30 min, or without any irradiation. (Adapted from ref. 168, Copyright 2013, American Chemical Society. Reproduced with permission.)

complexes under the irradiation of the converted UV emission from UCNPs or UV directly. Therefore, the UCNPs can not only release the drug from the nanoparticles under 980 nm NIR irradiation but also activate the pro-drug to gain a high toxicity platinum(II) drug to kill the cancer cells. Moreover, the cell viability proves the effective tumor growth inhibition efficacy of [UCNP-DPP-PEG + 980 nm laser] system (Fig. 8C).

An interest in combining light-sensitive polymers and inorganic substrates in a single system has been recently highlighted, which can achieve improved mechanical properties and control the loading and release of guest substances.[169–171] Silica NPs are biocompatible and readily modifiable with new functionalities useful for application in drug delivery devices.[172] Light-responsive silica NPs (70 nm) were prepared by covalent conjugation of photoactive o-nitro benzyl bromide molecules with amino groups on the particle surface.[173] Drugs with carboxylic, phosphate or hydroxy groups were covalently attached to the o-nitrobenzyl bromide groups. When the resulting particles are irradiated at 310 nm, the o-nitrobenzyl bromide groups transform into o-nitrobenzaldehyde, which causes an irreversible cleavage of the particle-bonded drug, leading to drug release. And these particles are small enough to penetrate into cells, enabling an external control of the intracellular drug release.

Another approach toward nanocomposite-based DDS is to use azobenzene chains as both impellers and nanovalves when they are tethered within and onto mesoporous silica NPs. The pores in silica materials can be designed with templating agents such as surfactants who can be removed when the structure is complete. To control the diffusion of solute within the pores, the pore walls can be derivatized with molecules acting as nanovalves by reversibly changing their conformation. Derivatization of the pores with azobenzene chains is of interest because of the reversibility of azobenzene isomerization. Within the framework of this concept, zeolite membranes modified with azobenzene were shown to possess photo

switchable gas permeation properties regulated by the trans-to-cis isomerization of the azobenzene moieties.[175] Similarly, azobenzene-modified cubic-structured silica films enabled the control of the transport of ferrocene derivatives to an electrode surface.[176] Angelos *et al.*[174] explored the possibility of a continuous excitation of spherical silica NPs with a small azobenzene derivative (AzoH) attached to the pore interiors at 457 nm, and a larger azobenzene derivative (AzoG1) attached to the pore openings (Fig. 9). Both the *cis*- and *trans*- derivative conformers absorb light at 457 nm, which causes isomerization and results in a dynamic wagging of the moving parts of azobenzene derivative. Prior to the excitation, the guest molecules (Rhodamine 6G and coumarin 540A) hosted in the pores cannot diffuse out because of the high density of the azobenzene chains. Excitation caused azobenzene chains to wag in predominant directions, opening diffusion pathways and expelling the guest molecules out of the pores. The concentration of azobenzene chains determines the diffusivity inside the pores and enables the on–off switching of the solute transport. Further advances along this research line enabled the preparation of nanoimpellers-controlled and mesostructured silica NPs to deliver and release anticancer drugs into living cells on demand.[177] Experiments carried out with human cancer cell lines showed that once the NPs were taken up by the cells, the anticancer drug camptothecin was only released inside of cells that were illuminated at 413 nm to activate the impellers. The nanoimpellers are azobenzene moieties positioned in the pore interiors with one end attached to the walls and the other end free to undergo photoisomerization. As *cis*- and *trans*-azobenzene isomers have almost the same extinction coefficient at 413 nm, irradiation at this wavelength causes the azobenzene moieties to move back and forward, driving the drug molecules out of the silica pores. Applying this mechanism, we envision that intracellular release and, consequently, cell apoptosis can be controlled by light intensity, irradiation time and wavelength. The intermolecular reversible photodimerization and photo cleavage of coumarin derivatives have also been tested for regulating the passage of guest molecules through the narrow pores (ca 2–4 nm diameter) of silica particles. A photo responsive coumarin derivative was grafted on the pore outlet of particles acting as an 'open-close double doors' system. Irradiation with UV light longer than 310 nm wavelengths induced the photodimerization of coumarin to close the pore outlet with cyclobutane dimer.[178] Guest molecules such as phenanthrene neither can enter nor escape from the individual pores of the particles. On the other hand, irradiation with shorter wavelength UV light (250 nm) regenerates the coumarin monomer, the pores are opened and the guest molecules can be released.[162]

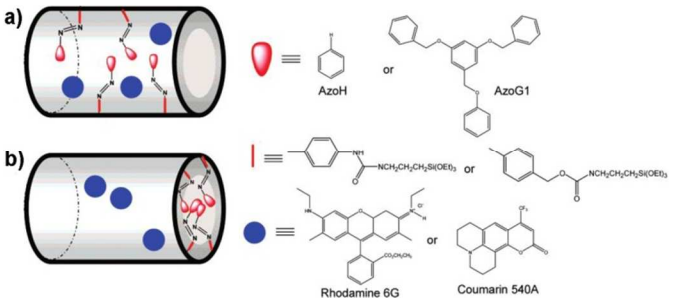

Fig. 9 Photo responsive materials based on silica particles functionalized with azobenzene derivatives for creating impellers (a; attaching small azobenzene derivatives AzoH to the pore interiors) or nanovalves (b; attaching large azobenzene derivatives AzoG1 to the pore openings). For each system, the moveable phenyl ring of the azobenzene machine is illustrated by the red inverse tear drop, the tethered phenyl ring of the azobenzene machine by the red vertical bar and the impelled molecule by the blue circle. (Adapted from ref. 174, Copyright 2007, American Chemical Society. Reproduced with permission.)

3.3.2 PHOTOTHERMAL RESPONSIVE NANO-CARRIERS

Recent years, photothermal effect was widely used in cancer therapy, namely, PTT. In PTT, a photoabsorber is applied to absorb and transform optical irradiation into heat. Then the elevated temperature causes denaturation of intracellular protein or disruption of membrane, leading to thermal ablation of cancer cells. Up to date, NIR light-absorbing nano-agents including gold nanorods/nanostars/nanocages, graphene nanosheets, carbon nanotubes, Cu_xS_y nanoparticles, and polypyrrole polymer have been served as photothermal therapeutic agents due to the strong optical absorption in NIR region.[179-196] To further improve the therapy efficiency and safety, these photoabsorbers were combined with drug delivery systems, forming photothermal responsible nano-carriers. In the past ten years, our group comblined light-absorbing nano-agents of Cu_xS_y nanoparticles and Au nanoclusters with upconversion nanoparticles, forming numbers of multifunctional cancer therapy platforms, such as $NaGdF_4$:Yb,Er@$NaGdF_4$:Yb@$NaNdF_4$:Yb@$m$$SiO_2$-$Au_{25}$, Y_2O_3:Yb,Er@Y_2O_3:Yb@$m$$SiO_2$-$Au_{25}$-P(NIPAm-MAA) and $NaYF_4$:Yb,Er@Au–Pt(IV)-FA nanocomposite spheres and Y_2O_3:Yb,Er@$m$$SiO_2$-$Cu_xS$ double-shelled hollow spheres.[197-202] Firstly, the upconversion luminescence process in these platforms were utilized as a taken advantage of strengthen of photothermal effects by fluorescence resonance energy transfer effect. And all the results showed than the therapy platforms have considerable thermal effect to kill tumor directly. Secondly, if loading drugs, the systems exhibited higher anti-cancer efficacy due to the synergistic PTT induced by the attached Cu_xS_y/Au and the enhanced chemotherapy promoted by the heat when irradiated by 980 nm near-infrared light. Finally, upconversion nanoparticles provide the functions of CT, MRI and upconversion luminescence multimodal bioimaging, realizing a true sense of light-induced imaging-guided cancer therapy. Liu and co-workers developed a multifunctional nanocomposite by coating magnetic iron oxide nanoclusters with a near-infrared light-absorbing polymer polypyrrole and PEG, obtaining Fe_3O_4@polypyrrole-PEG core-shell nanoparticles.[38] Then the core-shell nanoparticles were binded with aromatic drug molecules of DOX due to the hydrophobic structure with delocalized π-electrons in polypyrrole, forming a new therapy system. The therapy system exhibits a strong photothermal effect to kill cancer cells directly by hyperthermia, at the same time, enhances chemotherapeutic efficiency by promoting cross-membrane drug delivery and triggering intracellular drug release. So, their work may offer great opportunities in the development of new cancer therapeutic approaches.

The research groups of Zhao, Yoo and Qu *etc*. constructed Au nanocages/nanorods with mesoporous silica, arginine-glycineaspartic acid (RGD) peptides, chitosan, poly(Nisopropylacrylamide) (PNIPAM) and other materials to form near-infrared controlled photothermal drug delivery systems.[203-210] On the one hand, upon NIR 808 nm diode laser irradiation, the gold nanorods/nanostars/nanocages in these photothermal drug delivery systems can produce heat to kill cancer cells effective. On the other hand, more loaded drugs can be released upon NIR 808 nm diode laser irradiation due to the heat and some other reasons. Accordingly, photothermal

drug delivery systems were commonly used to combine PTT and chemotherapy to provide highly effective synergistic effect and kill more cancer cells.

The sp^2 carbon nanomaterials, including graphene, carbon nanotubes and fullerenes have been developed as nanocarriers for recent years. Especially graphene and carbon nanotubes with strong NIR optical absorbance, have been considered as good photothermal agents.[179] Kim and co-workers developed a functionalized reduced graphene oxide (PEG-BPEI-rGO) (BPEI, branched polyethylenimine) composite who has the ability to load DOX.[211] And the system was also an excellent nanoplatform for photothermally controlled drug delivery. With the increasing of NIR irradiation and GSH concentration, the drug release was accelerated due to (i) the change of binding energy between PEG-BPEI-rGO and DOX by NIR-mediated heat generation and (ii) the disruption of noncovalent hydrophobic interactions and π-π stacking of the aromatic regions of the graphene oxide sheets, respectively. Chen *et al*. prepared a new nanoformula of CAHA-sSWCNT-DOX by wrapping single-walled carbon nanotube (sSWCNT) with cholanic acid-derivatized hyaluronic acid (CAHA) biopolymer and then loading DOX.[212] Study showed that CAHA-sSWCNT-DOX nanoformula can act as a self-targetable nanoprobe with proper apoptotic temperature, enhanced drug delivery efficiency, high cancer cell specificity, and long-term physiological stability. Liu *et al*. turned graphite sheets to a special graphene oxide nanoparticles (GON), then modified them with PEG and comblined with poly(methacrylic acid) (PMAA) brushes or grafting the biocompatible PEGylated alginate (ALG-PEG) brushes, forming $PMAA_2$-GON-PEG or GON-Cy-ALG-PEG nanocarriers.[213,214] After loading drug molecules, the system showed good response of glutathione (stimulated tumor tissues), the former system even showed a 6-fold faster releasing rate at pH 5.0 than at pH 7.4.

3.4. Enzyme responsive drug delivery

Enzymes are vital constituents of bio-nanotechnology toolbox that owns exceptional bio-recognition competencies and exceptional catalytic properties. When pooled with the distinctive properties of nanomaterial's the follow-on enzyme responsive nanoparticle can be aimed to perform function efficiently and with high specificity for the triggering stimulus. This authoritative idea has been effectively applied to the fabrication of drug delivery system where the tissue of interest is targeted *via* release of cargo triggered by the bio catalytic action of enzyme. An evolving arena in the nanomaterial's is design of nanoparticles whose physical properties are responsive to the bio catalytic action of enzymes.[215–217] Enzymes play a dominant role in cell regulation and hence are key target for drug delivery development and in therapeutics. When enzyme is found at a higher concentration at the target site the nanomaterial can be calibrated to deliver drug *via* enzymatic conversion of carrier.[218] Besides detection of enzyme activity can be beneficial tool in diagnostics, since dysregulation of enzyme activity is root of numerous diseases.[219] Also the unique capability of enzymes in catalysing a chemical reaction can be harnessed to amplify the signal produced by some analyte. This predominant role of enzymes in biomedical applications such as diagnostics and therapeutics has driven to the mounting curiosity in developing enzyme responsive nanomaterial as transducers of enzymatic activity. In some circumstances, the nanoparticle is made of material which is responsive to the enzymatic transformation either because it encloses a chemical structure that is known to the biocatalyst or

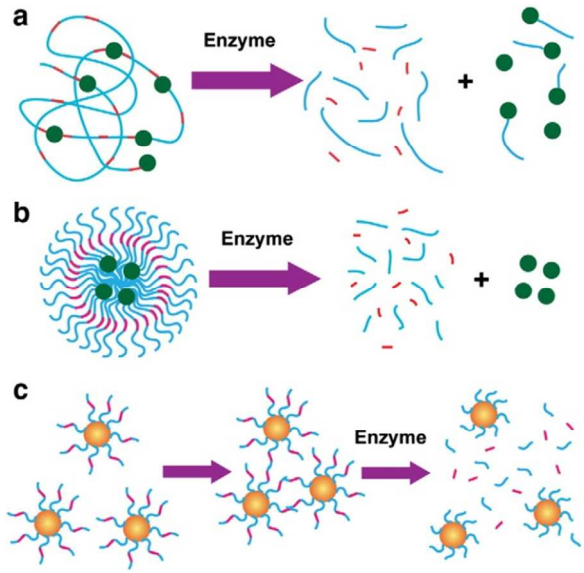

Fig. 10 Enzyme-responsive nanomaterials for drug delivery and diagnostics (a) polymer centred nanoparticles can be covalently altered with drugs through an enzyme cleavable linker so that the enzyme activity triggers drug delivery in the tissue of interest; (i) proteases can trigger drug delivery when the drug is linked to the carrier by a peptide; (ii) glycosidases can trigger drug delivery when the carrier is a polysaccharide; (b) polymer stabilized liposomes can be loaded with drugs, whose degradation can be programmed to be triggered by an enzyme; (i) proteases can trigger drug delivery when the stabilizing polymer is linked to the unstable liposome via peptide connections; (ii) lipases can trigger drug delivery when they hydrolyze the phospholipid building blocks; (c) Inorganic nanoparticles can be used for diagnostics when the activity of the target hydrolase controls the assembly or disassembly of the nanoparticles, which in turn changes the physical properties of the nanoparticle solution. (Adapted from ref. 220, Copyright 2012, Elsevier B.V. Reproduced with permission.)

it can be transformed by the product of enzymatic reaction. This is the condition of some polymeric nanoparticles that integrate biological motifs that can be cleaved *via* enzymatic digestion. Under these conditions, it is probable to plan the nanomaterial to release their cargo (*e.g.* a drug) by prompting the degradation of polymeric shell when nanomaterial confronts an enzyme. As for Fig. 10a, this approach can also be applied to self-assembled nanoparticles (Fig. 10b) in other cases the biomaterial is not responsive to biocatalyst but its surface can be amended with a molecule that breeds a modification in its physical properties of nanoparticle solution upon enzymatic action (Fig. 10c). This method had been broadly used for the design of enzyme responsive inorganic nanoparticles and permits one to advantage from exceptional optical properties of these Nano utilization of vigorous immobilization scheme for amending the surface of nanoparticles[221] as well as the design of ligands that transduce the enzymatic action into a physical change of the nanoparticle solution.[222,223] Conversely the consumption of inorganic materials *in vivo* is not devoid of toxicological concerns as the hold hazardous heavy metals and organic solvents since there synthesis.[224–227] Therefore their utilization as drug delivery carrier is not as developed as in case of polymeric nanomaterials.

Still they are outstanding structures to study the assembly and disassembly of nanoparticles because their physical properties change with their state of aggregation and therefore they are appreciated materials for prototyping enzyme responsive systems.[228]

3.4.1 Enzyme responsive nanomaterials

The numerous methods that exploit the bio catalytic action of an enzyme for drug delivery are summarized in Table 6. Hydrolases, including proteases, lipases and glycosidases, are most extensively used for drug delivery possibly due to their simplistic design involving the attachment of bioactive moieties to the carrier *via* cleavable units, as shown in Fig. 10a and 10b. Likewise, the dispersion of inorganic nanoparticle can be prompted by a hydrolase when the nanoparticles are accumulated by biomolecules presenting cleavable units in Fig. 10c. However some hydrolase responsive nanomaterials are already being used in clinical trials, the use of oxidoreductases is still in proof of concept stage, and some pioneering examples on their utilization for drug delivery and diagnostics are highlighted. Other enzymes such as kinases,[240,241] closely related to cancer or acetyltransferases,[242] crucial in epigenetics, have only been explored by biosensing.

Most of these enzyme responsiveness systems are normally prepared by employing a covalent approach, which is followed by covalently linking the enzyme-responsive moiety to the polymers. In 2011, Heise's group made a biohybrid block copolymers of poly(n -butyl acrylate) (PBA) and (block co)-polypeptides of PGlu and P(Glu- co -Ala) using N carboxyanhydride ring opening polymerization and nitroxide-mediated radical polymerization.[243] The unprotected polypeptide block was used as the hydrophilic constituent to make the membrane of the vesicle. The designed vesicular assemblies of the block copolymers can be degraded selectively when exposed to elastase and thermolysin, depending on the composition of the hydrophilic peptide block and the composition of the hydrophobic non degradable block. Alternative illustration was an enzyme-triggered cargo release from methionine sulfoxide-containing copolypeptide vesicles. Deming and co-workers designed and prepared a hydrophobic precursor diblock copolypeptide, poly(L-methionine)$_{65}$-b-poly(L-leucine$_{0.5}$-stat-L-pheny lalanine$_{0.5}$)$_{20}$, followed by its direct oxidation to gain water soluble methionine sulfoxide (M^O) derivative, $M^O{}_{65}(L_{0.5}/F_{0.5})_{20}$.[244] Self-assembly of $M^O{}_{65}(L_{0.5}/F_{0.5})_{20}$ in water gave vesicular structures and the M^O reductases A and B (MSR) enzymes-catalysed reduction of M^O-based vesicles was researched. Alteration of disarrayed, hydrophilic M^O segments on the vesicle surface to α-helical, hydrophobic methionine-rich segments directed to the vesicle membrane curvature come to be progressively disfavoured, ultimately triggering membrane falling-out once a critical level of M^O reduction is reached, resulted in an ensuing supramolecular change from spherical to a crumpled sheet-like morphology. Since the MSR enzymes could be found within cells all over the human body, meanwhile the materials of M^O possessed good solubility, structural simplicity, and degradable into natural metabolites, these systems may offer ways for increasing cell uptake and targeted cargo release in tissues.

Of late, the noncovalent methodology to fabricating enzyme-responsive systems has bagged more and more courtesy. In 2012, the overexpression of cholinesterase has been associated for Alzheimer's disease. Liu and co-workers described a cholinesterase-responsive supramolecular vesicle using p-sulfonatocalix[4]-arene (SC4A) as the macro cyclic host and

Table 6 Some vital examples of enzyme responsive nanomaterials.

Class	Subclass	Enzyme	Nanomaterial	Application	[b]Ref.
Hydrolases	Proteases	Cathepsin B	N-(2-hydroxypropyl)methacrylamide (HPMA)	Intracellular drug delivery	229
				Extracellular drug delivery	230
		CAPs	polymer {cholesterol-anchored, protease-sensitive, graft copolymer containing poly(acrylic acid)} stabilized liposome	Targeted drug delivery	231
		Caspase1 thrombin-	Semiconductor nanoparticle	Biosensing via FRET	232
		Collagenase chymotrypsin	(Quantum dot)		
		PSA	Gold nanoparticle	Prostate cancer diagnosis	233
	Lipase	PLA_2	polymer stabilised	Synergistic drug delivery	234
			Liposome	Phospholipase sensor	235
	Glycosidases	α-amilase	Polymeric nanoparticle (Dextran)	Targeted drug delivery	236
	Others	Urease	Gold nanoparticles	ELISA	237
Oxidoreductases		Glucose oxidase	Liposomes	Drug delivery triggered by glucose	238
		Peroxidase	Gold nanoparticles	ELISA	239

[b]Ref. is the reference cited.

natural enzyme-cleavable myristoylcholine as the guest molecule,[245] possibly for the delivery of Alzheimer's disease drugs. First of all, both myristoylcholine and myristic acid form micelles with critical aggregation concentrations (CAC) of 2.5 and 4.5 × 10^{-3} M, while the hydrophobic drugs cannot be released from the micelles because hydrophilic–hydrophobic balance is not lost. Upon addition of SC4A with the top mixing ratio (SC4A:myristoylcholine) of 1:10 for the amphiphilic assembly, the complexation of SC4A with myristoylcholine directs the formation of a supramolecular binary vesicle (Fig. 11).

It is noteworthy that myristoylcholine cannot aggregate in the concentration of 0.1×10^{-3} M , but introducing SC4A led to self-assembles into a binary vesicle, which means the complexation lowers its CAC by 2 orders of magnitude to a low concentration ($<0.1\times10^{-3}$ M). The disassembly progression brought by enzyme was monitored using optical transmittance and mass spectrum measurements, indicating the enzymatic cleavage of the ester bonds of myristoylcholine in the supramolecular vesicles. Then, a characteristic tacrine-loaded vesicle was prepared and it can partially disassemble in the presence of BChE, leading to the release of the entrapped water-soluble drugs. Though, the reasonably challenging synthesis of SC4A may limit the inclusive application of this system to some extent. Almost at the same time, on the basis of surfactant-cyclodextrin (CD) host-guest complexes and α-amylase, Huang and co-workers made another enzyme-triggered assembly system. In the system, CDs can form host–guest complexes with surfactants in high binding constants by including hydrophobic moieties of surfactants into CD cavities, rendering the resultant complexes hydrophilic in their outer surface.[246]The addition of α-amylase to surfactant-CD mixtures cleaved a 1,4-linkages between glucose units of CDs and degraded CDs in two steps of ring-opening and chain scission. Hence, the enzyme-released surfactant molecules from CD cavities, and consequently trigger the self-assembly of the surfactant molecules into vesicles.

Recent studies reported use of short peptide sequence, cleavable by matrix metalloproteinases, as linkers between surface PEG chains and either TAT functionalised liposomes (Fig. 12) or CPP-decorated and dextran-coated iron oxide nanoparticle.[247,248] After cleavage of the PEG shell in the tumor

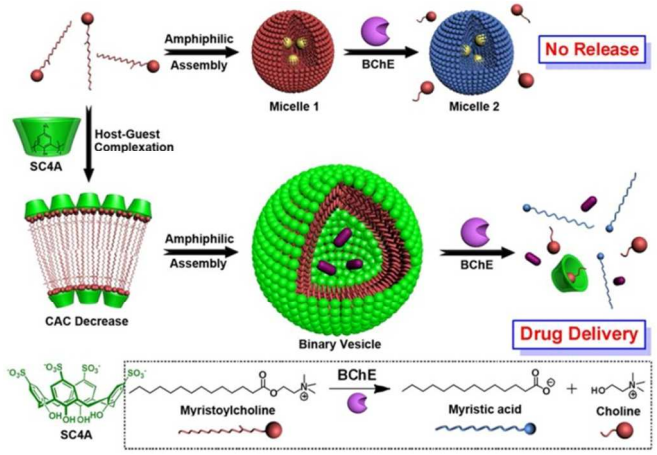

Fig. 11 Schematic illustration of amphiphilic assemblies of myristoylcholine in the absence and presence of SC4A. (Adapted from ref. 245, Copyright 2012, American Chemical Society. Reproduced with permission.)

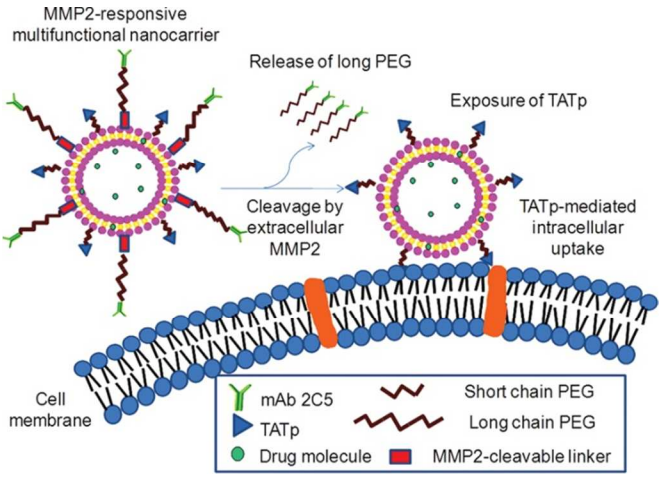

Fig. 12 Multifunctional liposomal nanocarrier responsive to matrix metalloproteinases (MMP2) for drug delivery via TAT- mediated internalization. mAB2C5; nucleosome-specific monoclonal antibody. (Adapted from ref. 247, Copyright 2012, American Chemical Society. Reproduced with permission.)

environment, surface bioactive ligands became exposed, and this enhanced the intracellular penetration compared with nanocarriers without cleavable linkers. Using this approach, systemic administration of siRNA-loaded nanoparticles resulted in an almost 70% gene silencing activity in tumor bearing mice.[249] Similarly protease-sensitive polymer coating or lipopeptides were designed to achieve triggered release from porous silica nanoparticles or liposomes.[250,251]

Similarly lysosomal enzyme cathepsine B, overexpressed in several malignant tumors, enabled cargo release by means of fast enzymatic degradation of polymersomes.[252] Transgene expressions with high cell specificity has been achieved through polymer based drug delivery systems bearing a cationic peptide as substrate of intracellular protease (or kinase) that are exclusively expressed in cell infected with human immune deficiency virus or inflamed cells.[253,254]

These examples highlight the potential of enzyme triggered drug delivery. However work is still needed to obtain precise information of the target enzyme level at the desired site to fine control cell uptake and to demonstrate that *in vivo* drug release correlated to enzyme activity.

3.5 Redox responsive systems.

Sensitivity to oxidant and reducing agents has received increased attention as a mode to realize feed-back controlled release (*e.g.* prompted by radicals produced during inflammatory processes) or a specific site-specific delivery (*e.g.* intracellular release in tumor tissues). For example, hyaluronic acid networks chemically cross-linked with EGDE have been shown to degrade *in vitro* by hydroxyl radicals produced by the reaction of H_2O_2 and $FeSO_4$, and *in vivo* in response to inflammation.[255] Networks of carboxymethyl chitosan and poly(γ-glutamic acid) cross-linked with genipin have shown to undergo conformational variations and improved drug release in the presence of gluconic acid, a product of glucose oxidation.[256]

One perceptible method for the intracellular controlled release of drugs is the use of polysaccharides with disulfide bonds that can be cleaved to thiol groups by glutathione in the

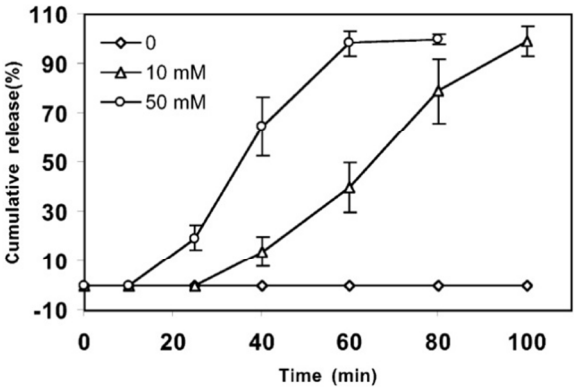

Fig. 13 Cumulative release of blue dextran from disulfide crosslinked hyaluronan hydrogels in Dulbeco's phosphate buffered saline (pH 7.4) with different concentrations of dithiotreitol. (Adapted from ref. 259, Copyright 2002, American Chemical Society. Reproduced with permission.)

cells.[39] The intra cellular concentration of this reducing agent is higher (210 mM) than the extracellular one (2 μm). Also, the glutathione concentration in tumor tissues is, higher than in the healthy tissue. Taking benefit of these physiological variances, it has been stated the synthesis of 6-mercaptopurine-modified carboxymethyl chitosan, using a disulfide linker, with self-assembly properties. This system showed pH- and glutathione-dependent release of 6-mercaptopurine.[257]

Another stimulating method involved the usage of thiolated heparin-pluronic for the synthesis of nanogels crosslinked by disulphide bonds. In the absence of glutathione, the nanogels released 30–50% of the loading of RNase A, while in medium with glutathione complete release was achieved.[258] Thiol-modified hyaluronic acid was synthesized coupling dithio bis(propanoic dihydrazide) and dithio bis(butyric dihydrazide) to hyaluronic acid via carbodiimide chemistry.[259] The disulfide crosslinked hydrogels can be formed under physiological conditions, by oxidation of thiols to disulfides. Hydrogels crosslinked through oxidation with H_2O_2 only released the cargo in the presence of the reductive agent dithiotreitol; the higher the concentration of dithiotreitol, the faster the release was, as shown in Fig. 13.

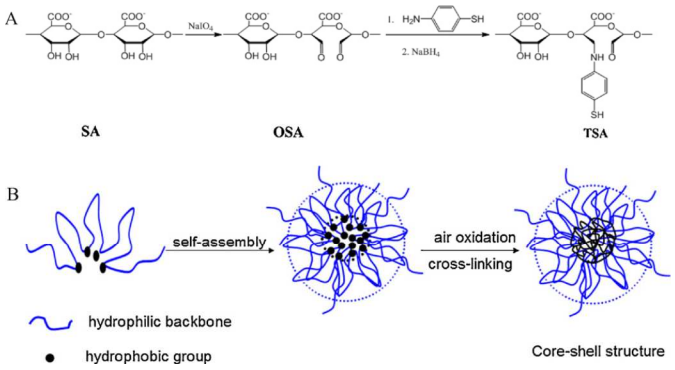

Fig. 14 Steps of the preparation of pH-sensitive and reduction-responsive nanospheres for site-specific drug delivery to inflamed colonic tissues. Sodium alginate (SA) was first oxidized with sodium periodate, and then modified by immobilization of a hydrophobic thiol-bearing ligand, namely 4-aminothiophenol, in the backbone of SA. This modified derivative form core crosslinked nanospheres by self-assembly in deionized water and subsequent air oxidation of thiol groups to disulfide bonds. (Adapted from ref. 260, Copyright 2012, Elsevier Ltd. Reproduced with permission.)

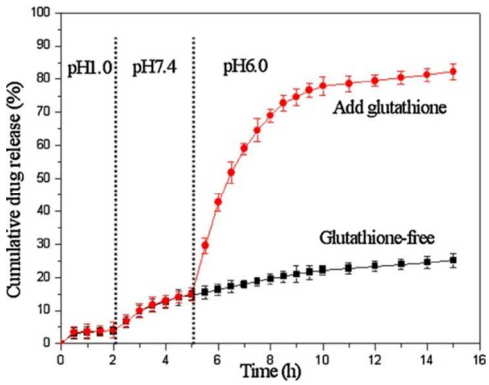

Fig. 15 Release profiles of 5-ASA from disulfide cross-linked alginate nanoparticles in control media (▪) and in simulated gastrointestinal media (•). (Adapted from ref. 260, Copyright 2012, Elsevier Ltd. Reproduced with permission.)

Excitingly, oral DDSs can also profit from redox-sensitive networks to achieve site-specific release, as the redox potential along the gastrointestinal tract differs as a function of the total metabolic and enzyme activity.[260] The redox potential changes from −67 ± 90 mV in the proximal small bowel to −196 ± 97 mV and −415 ± 72 mV in the distal small bowel and the right colon, respectively.[261]

Potential is noticeably lower than the standard reduction potential for disulfide bonds (about−250 mV). Thus, reductive cleavage of disulfide bonds is expected to happen. Keeping these particulars in mind, alginate was altered with 4-aminothiophenol to generate self-assembly cross linkable nanoparticles for treatment of inflammatory bowel disease (Fig. 14), capable to specifically release 5-aminosalicylic acid in the colon.[260]

The release of the drug from the nanoparticles was evaluated at pH values 1.0, 7.4, and 6.0 without and with 25 mM glutathione to simulate the conditions of stomach, small intestine and colon without and with reducing agents, respectively. At acidic pH, the shell shrinks and hinders drug release. While at alkaline pH, the increase in swelling degree facilitates drug diffusion from the shell, but since most is hosted in the crosslinked cores, the release was quite limited. Only when the particles are placed in a medium with glutathione, complete release can be achieved (Fig. 15).[260]

3.6 Magnetic field responsive systems

Magnetic nanoparticles have gained enormous attention due to the unique properties such as magnetic properties and generation heat under the application of an external high-frequency magnetic fields (HFMF). More important, the heat converted from magnetic energy by the hysteresis effect is useful for hyperthermia treatment. Therefore, magnetic nanoparticles attract much attention for biomedical applications, including contrast agents for MRI, magnetic hyperthermia, and magnetic guided targeting. In addition, although magnetic nanoparticles have been used for inductive heating in antitumor therapy, the efficiency has not been as good as desired. So, combination of the heat transfer and drug delivery to enhance the tumor-inhibition ability will be more interesting. Recently, various functional polymers and mesoporous silica have been used to modify the surface of magnetic nanoparticles, forming magnetic field responsive drug delivery systems. In these

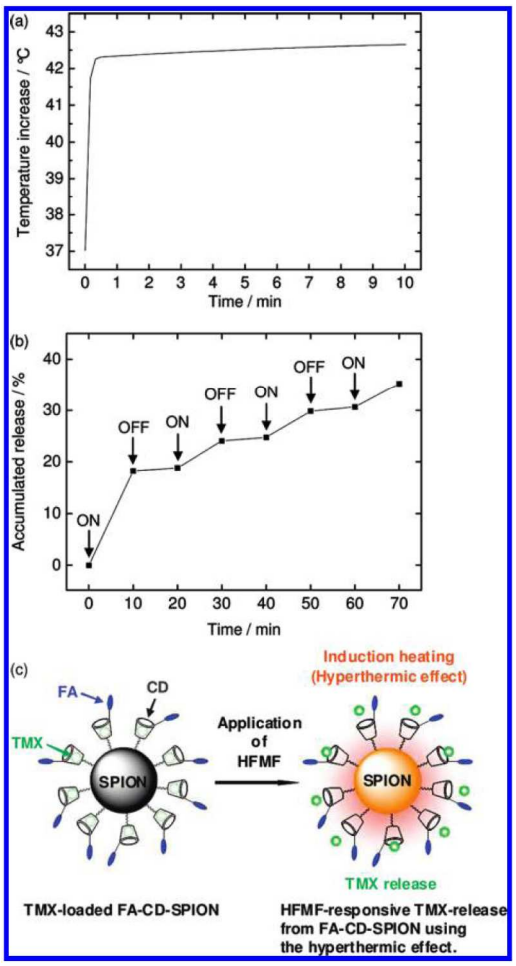

Fig. 16. (a) The temperature increase of the water dispersed with 20 mg/mL of TMX-loaded FA-CD-SPIONs under a HFMF with 230 kHz in frequency and 100 Oe in amplitude. (b) Controlled release of TMX from FA-CD-SPIONs by switching a HFMF on and off. (c) Schematic illustration of TMX release from FA-CD-SPIONs using the hyperthermic effect by applying a HFMF. (Adapted from ref. 262, Copyright 2010, American Chemical Society. Reproduced with permission.)

systems, the heat generated from HFMF has two functions: one is for hyperthermia treatment to kill cancer cells directly; another is to act as a driving force for drug-release.

Yogo and co-workers synthesized a folic acid (FA) and β-cyclodextrin (CD) functionalized superparamagnetic iron oxide nanoparticles, namely FA-CD-SPIONs.[262] UV-vis spectrophotometry shows the change in absorbance at 234 nm which increases with dispersion time, indicating that anticancer drug tamoxifen (TMX) loaded in CD on SPIONs is released by heating at 45 °C. Without alternating current (AC) magnetic field, the release rate of TMX at 45 °C is faster than that at 37 °C due to the faster rate of TMX diffusion at higher temperature. With AC magnetic field, the release properties and scheme were shown in Fig. 16. As shown, the temperature of water containing TMX-loaded FA-CD-SPIONs was increased to 42.5 °C, which is the optimum temperature for hyperthermia. More important, the hyperthermic effect can act as a driving force for the release of TMX from CD on the SPIONs , which is also a behavior that is controlled by switching the HFMF on and off (Fig. 16c). Thus, FA-CD-SPIONs can serve as a novel device for performing controlled drug delivery and hyperthermia simultaneously.

Magnetic nanoparticles also can be used as magnetic guided targeting therapy. Liu *et al.* prepared $NaYF_4$:Yb,Er@Fe_3O_4@ Au-PEG multifunctional nanocomposites (denoted as MFNPs) for MRI/up-conversion luminescence imaging-guided and magnetically targeted photothermal cancer therapy.[63] For the tumors bearing mice with MFNPs injection, under the irradiation of 808 nm NIR laser, the surface temperature of tumors can be increased to about 50 ºC under the magnetic field, while only about 38 ºC for un-injected mice, resulting an outstanding therapeutic efficacy with 100% of tumor elimination by the magnetically targeted phothothemal therapy.[56]

3.7 Ultrasound responsive systems

Ultrasound perceived as a mechanical force has certain unique advantages over other types of stimuli. For example, in comparison with light that does have the time and site selectivity, but a narrow penetration depth, ultrasound is simplistic regulation of tissue penetration depth by tuning frequency, duty cycles, and time of exposure. Ultrasound has been proved as a sensitizer to enhance chemotherapy and to overcome drug resistance. Air-encapsulated biodegradable polymersomes based on poly(ethylene glycol)-block-poly(lactic acid) (PEG-b-PLA) were prepared *via* a lyophilization/rehydration procedure in the presence of d-mannitol solution and assessed as ultrasound contrast agent.[263] It was observed that by employing a medical ultrasound frequency of 7.5 MHz, polymersome bubbles were then instantaneously envisaged as bright spots by using a medical ultrasound scanner, establishing that the polymersomes certainly enclose air and that they are acoustically active. Therefore, these air-encapsulated biodegradable polymersomes were very fascinating candidates for targeted polymersome bubbles with encapsulated anticancer drugs for tumor imaging and triggered drug release for tumor killing.

Recently, Chen and Du testified an innovative polymer vesicle that is responsive to both physical (ultrasound) and chemical (pH) stimuli and discovered their drug entrapment and release capabilities under diverse conditions.[264] Poly(ethylene oxide)-block-poly [2-(diethylamino) ethylmethacrylate-statistical-2-tetrahydrofuranyloxy) ethyl methacrylate] [PEO-b-P(DEA-stat-TMA)] block copolymer was synthesized and employed to prepare ultrasound and pH dually responsive polymer vesicles. Consequent ultrasound radiation with the power of 180 W and the frequency of 40 kHz, the vesicles become smaller detected from DLS and TEM. Further 1H NMR spectra analysis showed a physical rather than chemical process (decomposition of polymer structure) happened through this reordering process of polymer vesicles. Notwithstanding the datum that PTMA chains have been established to disorder and recrystallize upon ultrasound, the physical process of sonication effect on disruption and reassembly of polymer vesicles appears not been explained clearly. In other ways, decreasing the solution pH will lead to the complete protonation of DEA chain and finally the disassembly of vesicles. Throughout both processes, the controlled release of loaded anticancer drug can be achieved (Fig. 17). Henceforth, the ultrasound-responsive block copolymer vesicle retains encouraging perspective on designing and developing new stimuli-responsive delivery vehicles in nanomedicines.

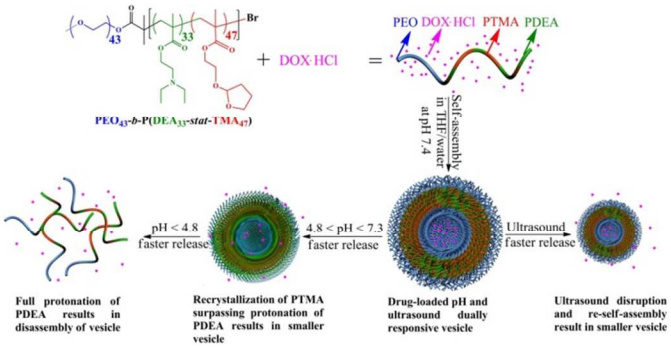

Fig. 17 Formation of ultrasound and pH dually responsive PEO 43 - b - P (DEA 33 -stat-TMA 47) vesicle and controlled drug release triggered by ultrasound radiation or decreasing pH value. (Adapted from ref. 264, Copyright 2013, Nature Publishing Group. Reproduced with permission.)

4. Outlook

The delivery of drugs to their site of action at the precise time and concentration is a key prerequisite, and presents a formidable challenge to overcome if the latent post genomic benefits to healthcare are to be realized. While this problem exists for all categories of molecules, it is principally acute for biological macromolecules. These are likely to form a significant proportion of the medicines that will be used in the future as novel approaches to tackling disease become established. This paper classifies the priority challenges and opportunities for precompetitive research in drug delivery for the next decade as follows. The prerequisite to gain better understanding of the physicochemical properties of biopharmaceuticals, macromolecules, and macromolecular delivery systems, meanwhile learn how these properties are reformed within the biological environment will determine how drug activity will be affected. One of the focal challenges for the future will be the identification of technologies that can bypass the complex biological barriers known to limit bioavailability of small and macromolecular drugs (particularly proteins, oligonucleotides, and drug-polymer conjugates). With an ultimate understanding of biological obstructions, advanced materials can be developed as carriers and devices for the delivery of pharmaceuticals. The conception of smart, stimuli sensitive systems that respond to subtle changes in the indigenous cellular environment are likely to vintage long-term solutions to many of the current drug delivery problems.

In this perspective, the design of nanocarriers sensitive to exogenous or endogenous stimuli may signify a striking substitute to targeted drug delivery. The varied range of stimuli able to trigger the drug release at the right place and time, and diversity of responsive materials that can be amassed in different architectures, permit pronounced suppleness in the design of stimuli responsive systems. However, although *in vitro* proofs of concept have been reported for a number of stimuli responsive systems, only few have been tested *in vivo* preclinical models and very few have reached clinical stages. For most of these systems, the intricacy of their architectural design and hitches in scaling up of their synthesis are likely to impede their translation from bench to bedside. Additionally their toxicity is multifunctional, reliant on composition, physiochemical properties, route of administration and dose. The benefit-to-risk ratio has therefore to be balanced according to intended medical application. Regrettably, many existing stimuli responsive systems have inadequate chances of reaching the clinic because of degradability or insufficient biocompatibility. The ability of these systems to be sensitive to discrete variation of pH, temperature, magnetic field or redox potential is not straight forward to realize and concerns related to penetration depth of the externally applied stimulus would ultimately need to be solved.

It is challenging to identify which stimuli-responsive systems have preeminent chances of reaching the clinic. The medical application of the most of the systems we have deliberated in this review link to either therapeutic niches, or to orphan diseases that are resistant to existing treatments or for which no therapeutic substitute exist. As a general rule, the simpler and easier the development of system is, the better its probabilities of reaching the clinic.

As we have revealed in this review mammoth advancement in material chemistry and drug delivery has steered to design of smart stimuli responsive concepts using well engineered nano-systems. Conceivably the emphasis should now shift towards clinically suitable systems that are more sensitive to discrete variations in specific stimuli.

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
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