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Smart Materials with Future Application in Drug Delivery

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Outline

Introduction

Many traditional excipients used for the delivery of active ingredients are highly inefficient. Therefore, advanced drug delivery systems have been the focus of scientific interests to overcome these limitations associated with the conventional therapeutic systems. For example, today's advancement in cell biology and biotechnology has enabled innovation of highly active molecules to reach specific intracellular receptors. They are significantly active *in vitro* in isolated cell systems but their clinical usage is limited due to poor *in vivo* uptake or short half-lives. To tackle this problem, nanosized carriers which contain 'intelligent' properties can be easily tailored by the addition of targeting moieties such as antibodies, ligands or other bioactive molecules onto their surface increasing their functionality. When nanoparticles are functionalised with biomolecules such as peptides or oligonucleotides, their assembly and dispersion can be designed, which leads different physical properties of the nanoparticles compared to the initial building blocks.
Drug delivery systems capable of releasing their payload in response to external or internal stimuli show promising potential in targeting, localisation and controllable drug release. This is particularly pertinent in chemotherapeutic applications. Anticancer therapeutics are notoriously cytotoxic, hence by targeting these drugs directly to tumour tissue before inducing triggered drug release, systemic drug circulation will be reduced and undesirable side effects will be minimised. Types of external stimuli used to manipulate these systems include temperature changes, light irradiation, magnetic flux etc., whilst internal stimuli consist of fluctuations in pH, temperature, biological ions and molecules, etc. These physical or chemical stimuli trigger changes in the delivery vehicle which can result in highly localised drug release. The most promising systems with future clinical potential are described below.

Enzyme responsive drug delivery systems

Enzymes are key factors in the field of biological nanotechnology, especially in cell regulation, with interesting bio recognition properties and outstanding catalytic capabilities. Therefore, they are suitable biomolecules for drug development and in therapeutics. In addition, detection of enzyme activity is a useful tool in diagnostics as dysregulation of enzyme expression is a characteristic feature of many diseases [1,2]. When enzyme is combined with research in nanotechnology, enzyme-responsive nano-sized particles used for controlled drug release have achieved significant development. This kind of drug delivery system has been studied as a significant way in drug delivery strategies in nanomedicine. Using enzymes as a trigger possesses many advantages as most enzymes normally catalyze chemical reactions under mild conditions such as neutral pH, low temperature, and buffered aqueous solutions, where many conventional chemical reactions fail [3,4]. Moreover, having exceptional selectivity for enzymes' substrates, allows researcher to design sophisticated, specific and biologically inspired chemical reactions [5]. In the past few years, a number of researches focussing on the design of nano-materials capable of stimuli manipulated release of their cargo at their therapeutic site via selective enzymatic cleavage such as polymer materials [6], phospholipids [7] and inorganic materials [8]. The integration of nanomaterials with enzymatic responses can endow the formulations with bio-specificity and selectivity, allowing for promising applications in diverse fields.For instance, combination of enzymes with nanobased materials has been used as enzyme responsive nanoparticles, which have high specificity for the

triggering stimulus. Moreover, synergic effect can be exploited by transformation of the carrier with enzyme to generate new therapeutic molecules.
Using enzymes with dual function, diagnosis and treatment, has led to growing interest in using enzyme responsive nanomaterials in drug delivery. These systems are composed of a chemical structure which can be recognised and transformed by the biocatalyst or product of the enzymatic reaction. For example some polymeric nanoparticles can be incorporated with biological motifs and cleave via enzymatic digestion (Fig. 10.1). Thus, nano-materials can deliver their cargo by triggered degradation of the polymeric shell, when they encounter the enzyme [5].
Polymeric nanoparticles are non-toxic, non-immunogenic materials which can show sensitivity towards enzymatic transformation. Poly ethylene glycol (PEG) is one example which can reduce the immunogenic response of conjugated biomolecules, increase blood circulations time and avoid its rapid clearance by kidneys [9]. Long circulations time of polymeric nanoparticles make them promising materials for delivering often problematic active ingredients (due to solubility) via systemic administration. By triggering payload release after enzymatic degradation, a highly controlled delivery vehicle is produced. However, utilising a robust immobilisation scheme for modifying the surface of these nanoparticles and designing ligands, which can convert the enzymatic activity into a physical change are ongoing challenges.

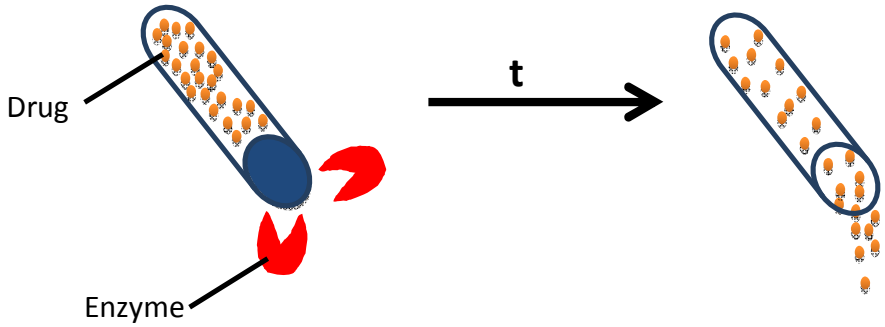

FIGURE 10.1
Schematic diagram illustrating enzyme responsive drug delivery systems

Image guided drug delivery systems

Image guided drug delivery is an emerging platform for guidance and validation of targeted therapies such as cancer. In cancer treatment, late diagnosis and treatment, reduces the probability of favourable prognosis. Often, a delay between diagnosis and treatment exacerbates this. A new platform is emerging which offers simultaneous diagnosis and therapy, known as theranostics. The term “theranostics” used for first time in the literature in 2002 [10]. This dual therapy could potentially lead to reduced treatments times and better patient prognosis with localised clinical effect [11]. Although there are many obstacles before full implementation of image guided drug delivery systems, the major challenges have been identified and approaches to eliminate these barriers are ongoing. The molecular imaging probes such as magnetic resonance imaging (MRI), positron emission tomography (PET), highly sensitive ultrasound, luminescence/fluorescent and Raman can be incorporated with drugs or their carriers. Progressing knowledge and their potential for biomedical applications make image guided drug delivery systems as one of major strategy in biomedicine. These complex systems include:

Iron -platinum drug delivery systems

Platinum based drugs are amongst the most efficient chemotropic agents clinically used. This is due to the platinum's inherent property to inhibit DNA replication. Cisplatin is the most effective platinum-based chemotherapeutic drug for treatment of solid tumours, such as lung, ovary, bladder, head and neck and testicular cancers[12]. Cisplatin can be activated after administration and binds to DNA, disrupting replication and transcription, which leads cell apoptosis. The most challenging aspects of Cisplatin are: 1) small fraction of drug converted to the active form, 2) resistance due to the reduced drug uptake and efflux and 3) significant dose related side effects such as neurotoxicity, nephrotoxicity, nausea and vomiting. Nanoparticles with modified surface might overcome some of these problems by passive (enhanced permeability and retention effect (EPR)) or active targeting. Platinum nanoparticles are known sensitisers for cancer radiation chemotherapy [13, 14] and oxidative stress treatment [15, 16]. Carbon is commonly used to support platinum based materials; however, carbon corrosion might lead aggregation of platinum nanoparticles, resulting decreasing catalytic activity of them [17].To eliminate this problem metal oxide such as SiO_2, TiO_2, ZrO_2 and magnetic Fe_2O_3 have been replaced with carbon. Among this group iron oxide nanoparticles have been the focus of scientific interest due to their rapid and ease of separation, imaging ability, biocompatibility, high efficacy and cost effectiveness (Fig. 10.2).

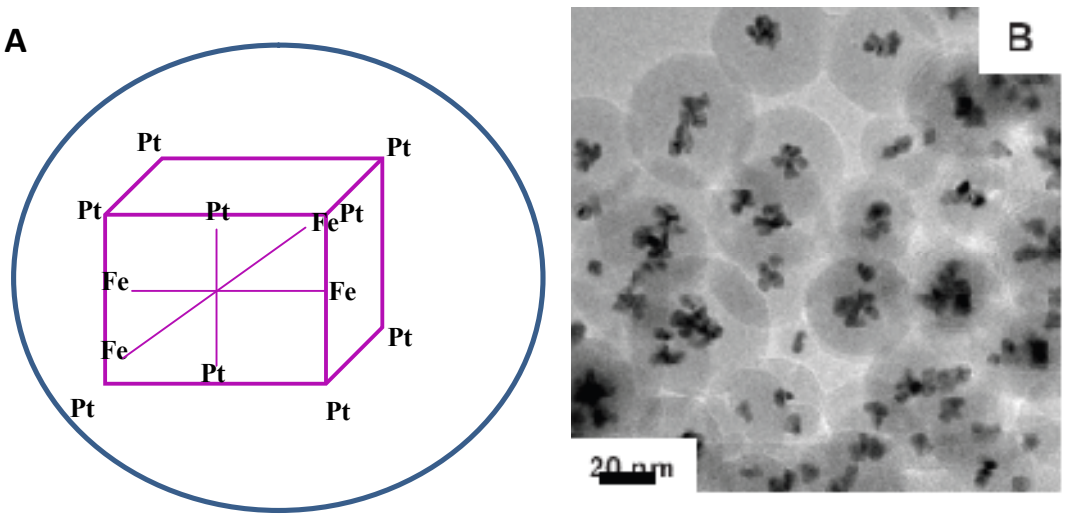

FIGURE 10.2
A)Schematic structure of an ordered iron-platinum (FePt) nanoparticle and B)TEM image of FePt nanoparticles under high magnifications [18]

Recently tumour targeting via magnetic field to probe the movement and localisation of drugs to solid tumours has generated much interest. By using magnetic nanoparticles both EPR effect and guided delivery can be exploited in one platform. Superparamagnetic iron oxide nanoparticles (SPIONs) are small synthetic α-Fe_2O_3 (hematite), γ-Fe_2O_3 (maghemite) or Fe_3O_4 (magnetite) particles with a core diameter between 10-20 nm. Among this group only maghemite and magnetite can be used for biomedical applications. Moreover, mixed oxides of iron with transition

metal ions such as manganese, cobalt, copper and nickel have superparamagnetic characteristics and also included in the SPIONs category. SPIONs are biocompatible, biodegradable and facilely tunable with rapid removal through extravasation and renal clearance. They have been shown to have high suspensibility, well reactive surface, consistent particle size distribution, and the possibility of further modifications [19]. Superparamagnetic iron oxide nanoparticles possess strong magnetism and they have used as an MRI induced cytotoxicity through near infrared derived hyperthermia [20].

Integrated platinum nanoparticle decorated iron oxide nanoparticle could potentially offer simultaneous imaging and therapy which interact with DNA as an anticancer drug whilst retaining the imaging capability of iron oxide. Interestingly, these nanoparticles have been reported to exhibit imaging contrast at least 6.5 times stronger compared to current clinical MRI agents [18]. FePt nanoparticles have also shown to be effective as nanoprobes for remotely sensing temperature of aqueous environments. Application of such functions can be applied in fields such as magnetic optical imaging [21], tumour inhibition [22] and hyperthermia treatments [18]. However, multiple platinum nanoparticles attachment had proved difficulties so far and strong interaction between metal nanoparticles limited further attachment. Furthermore, the size controlling during synthesis was challenging. For instance, 23 platinum-based drugs have entered clinical trials in last 30 years but only three (cisplatin, oxaliplatin and carboplatin) of these approved internationally [23].

Iron oxide-silica drug delivery systems

Recently, multifunctional drug delivery platforms, especially mesoporous nanoshell particles, have received a lot of interests due to the versatile loading capacity of these nanostructures [24,25]. Moreover, mesoporoussilica nano-structures are known to be nontoxic [26]. Silica nanoparticles with uniform shape and size, and well-defined mesoporous structure were synthesised [27], which are capable to carry dyes or drugs [28]. Magnetic iron oxide nanoparticles are useful as drug carriers due to their high surface area, tuneable diameter and narrow size distribution. The inherent magnetism of these particles resulted in their use clinically as magnetic resonance imaging (MRI) contrast agents which can reduce signal intensity (increased contrast) in the T_2-weighted images. For clinical application, it is essential to coat iron oxide nanoparticles with a biocompatible and stable coating to reduce the toxicological issues which occur upon free radical production after iron oxide degradation [29,30]. Silica coating of these particles results in increased solution stability and renders them acceptable for biomedical application (Fig. 10.3). Moreover, these small nanomaterials can penetrate the cell membrane via endocytosis which could accumulate in cancerous tissues via EPR effect.The silica shell allows for extensive further functionalization due to the presence of silanol groups. For example modified mesoporous silica oxide nanoparticles have an excellent cancer cell targeting ability after functionalization with folic acid [31]. There are two different methods for applying silica coatings onto iron oxide nanoparticles. The first strategy based on hydrolysis and poly condensation of tetraethoxysilane under alkaline conditions in ethanol. The second method relies on microemulsion synthesis and particles which are made by this approach have smooth surfaces with suitable monodispersity [32].

Iron oxide-silica core-shell nanoparticles possess dual function for imaging and delivery. Additionally, their drug delivery capabilities can also be tailored for thermally-responsive release upon application of an external alternating magnetic field [33]. Here the presence of the alternating magnetic field induces heat formation via relaxation loss of the magnetic nanoparticles. This

phenomenon can be exploited for both inducing cellular hyperthermia [34] and triggering drug release [35].

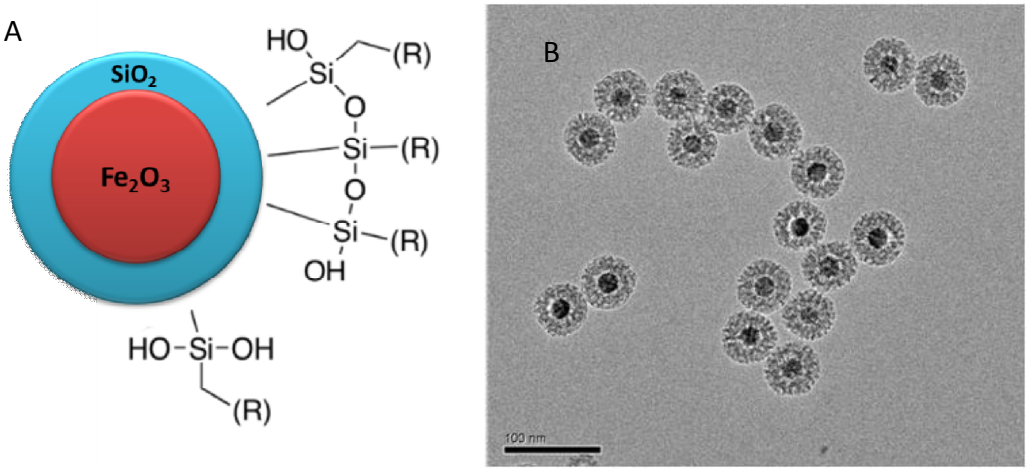

FIGURE 10.3
A) Schematic diagram of silica-iron oxide nanoparticles and B) TEM images of core–shell iron oxide silica nanoparticles [36]

Iron oxide-gold drug delivery systems

Degradation of iron oxide into ions in physiological environments has been reported to increase free radical production in cells causing damage which may cause cell death [30]. This resulted in the withdrawal of clinically used Feridex® from use in humans in the United Kingdom. Feridex® was an iron oxide nanoparticle coated with a flexible dextran polymer. It is proposed that the flexible nature of the coating did not shield the iron oxide core sufficiently from degradation, hence leading to toxicological implication. This setback has been overcome by coating the iron oxide nanoparticles with a rigid gold shell. The rigidity of the gold coating eliminates the potential for oxidative degradation of the iron oxide core into toxic free radicals.
Gold is renowned for its biocompatibility, chemical stability and ease of functionality. Colloidal gold possess unique surface plasmon resonance (SPR) properties (Fig. 10.4) [37-39]. When nanoparticles are irradiated with light at their SPR wavelength, absorption and scattering of the photons occurs which rapidly results in conversion of the light energy into thermal output [30]. This unique property can be exploited for further applications such as photo thermal ablation and thermo-responsive drug delivery [40]. Clinically, the optimal wavelength for laser irradiation of gold nanoparticles is within the 'biological near infrared region (NIR)' [40]. Light of wavelength inside the NIR window are capable of deep tissue penetration due to the high transmisivity of water and haemoglobin within these wavelengths [41].

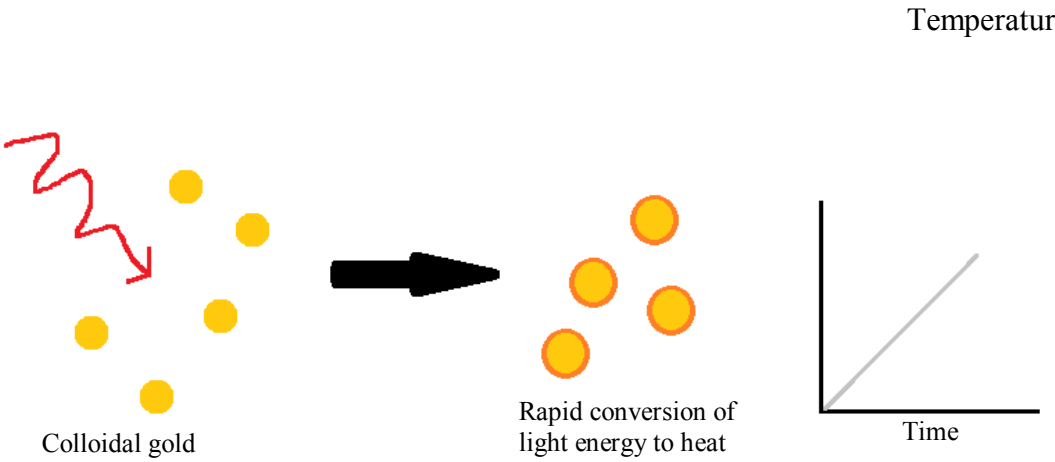

FIGURE 10.4
Schematic representation of nanoparticle heating after laser irradiation at unique surface plasmon resonance (SPR) wavelength

Iron oxide-gold as hybrid nanoparticles have recently been the focus of investigations and are becoming increasingly applicable in biomedicine. Matrix-dispersed iron oxide-gold nanoparticles can be fabricated by a variety of different states and increase the size of naked iron oxide nanoparticles (Fig. 10.5). The mosaic assembly are usually synthesised in the hollow silica spheres with iron oxide NPs and the shell-core structure can be produced through individual iron oxides that are attached with their inner layer. Shell-core-shell structure can be formed via layer-by-layer strategy, which might overcome some limitations of iron oxide NPs such as degradation (producing free radicals, which lead to cell damage and cell death), aggregation (making clusters, which are undesirable for biomedical applications) and precipitation (reducing colloidal stability) [42-44]. The outer shell can be a polymer, metal NPs and quantum dots, but the inner shell may be the same or different functional materials. This type of nano-composite is estimated to highly increase the range of application of iron oxide NPs. Dumbbell structure is usually fabricated by epitaxial growth of iron oxide on the inorganic compound.

By using both iron oxide and gold within one drug delivery vehicle, a multifunctional and stable system can be developed. This exploits the surface chemistry and SPR of the gold whilst retaining the magnetic character of the iron oxide, allowing for imaging [45], heating [45] and drug carrier capabilities [46, 47]. Moreover, the presence of the Au shell on magnetic core makes it possible to functionalise the NPs with thiolated molecules by exploiting the Au-S chemistry [46]. Although this is a relatively new field, studies have shown the successful conjugation of anticancer agents such as 6-thioguanine and cisplatin to these hybrid nanoparticles in order to enhance tumour targeting with external magnetic fields [46, 47].

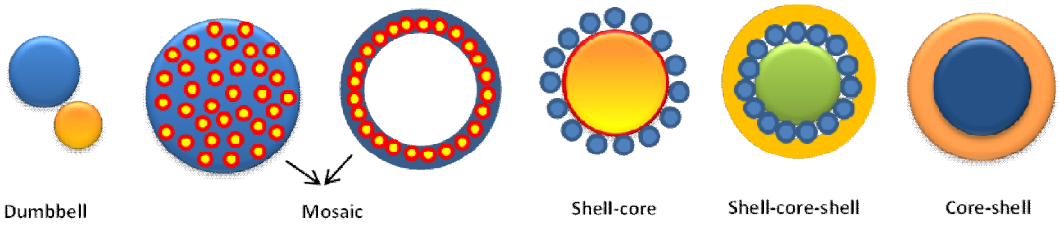

FIGURE 10.5
Schematic functionalised iron oxide nanoparticle (iron oxide assumed as the core)

Ultrasound-triggered image guided drug delivery systems

Ultrasonic (US) drug delivery coupled with image guidance can improve localised accumulation of drug compounds and hence decrease systemic circulation and undesirable side effects [48]. Ultrasound has been utilised as an enhancer for gene delivery into cells and vascular permeabiliser to increase drug extravasation. US is the first choice modality for guiding and positioning of radiofrequency needles [49] and laser fibres in tumour ablation [50]. Imaging by ultrasound allows for precise control of a drugs biodistribution (by enhancing localised drug delivery or changing the microenvironment of the tumour), the pharmacodynamics and pharmacokinetics. US can promote drug accumulation in desired areas using heat, cavitation, radio force etc.

The energy of incoming US can be adsorbed or converted into heat, which can be exploited in photo-thermal therapy, thermo-responsive drug delivery or thermal ablation. Intensity and frequency of the propagating US wave affect the amount of generated heat. However, hyperthermia cannot influence the extravasation of particles which are smaller than pores of the tumour vessels [51]. Interestingly, extravasation of particles larger than 100 nm decreases drastically with increasing size. Using temperature-sensitive liposomes for US triggered drug delivery is an example, which cytotoxic drugs are encapsulated for increasing circulating and reducing systemic toxicity (Fig. 10.6).

Acoustic cavitation is activity and/or formation of gas-filled bubbles of natural or artificial origin in a medium exposed to US. US induced cavitation effects can increase the permeability and cellular uptake of nanoparticles with the presence of microbubbles. This method has been used for cancer drug delivery of weak-permeable hydrophobic molecules, promoting local release of chemotherapeutic agents, facilitates internalisation of plasmid DNA and SiRNA and enhances the transport across the blood brain barriers. Studies have shown membrane disruption via optically controlled microbubble cavitation [52].

The incoming energy of US is not only converted into heat, but also transformed as mechanical force (radiation force), which may develop shear forces between displaced and none displaced tissue [53]. This might cause gaps between endothelial cells and increases intracellular drug diffusion. However, in spite of huge progression, the exact mechanism in this method is not cleared and further research is needed to validate previous *in vitro* and *in vivo* studies. By using US as an initiator for triggering stimulus, drugs could be deposited in a localised area. This system is extremely promising to deliver small and macromolecular drugs in cancer treatment and gene therapy.

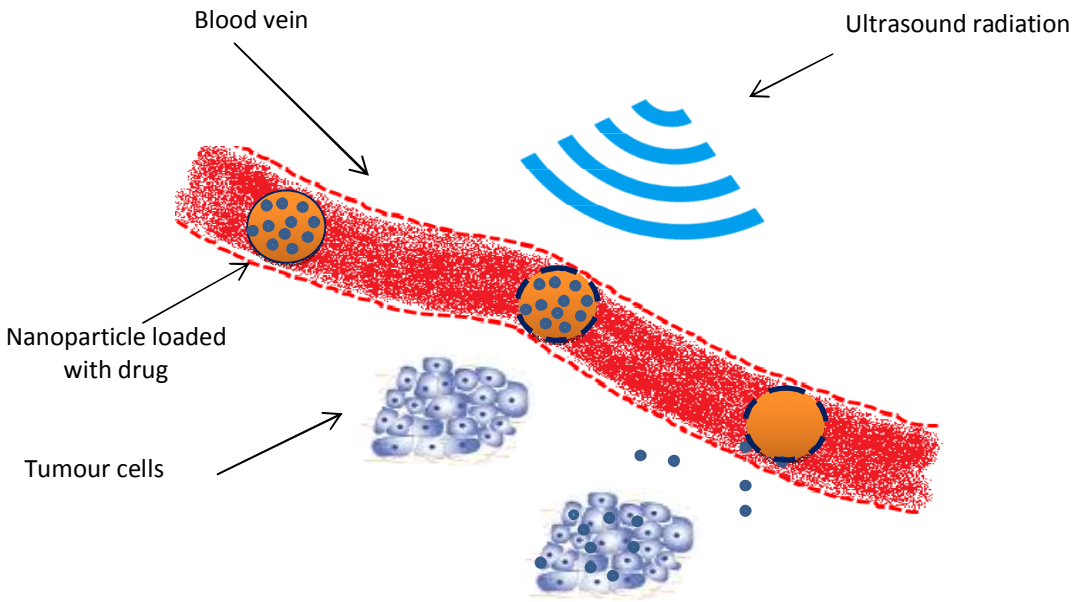

FIGURE 10.6
Schematic representation of temperature-sensitive liposomes in ultrasound-triggered drug delivery systems

Magneto-micelles drug delivery systems

Micelles are nano-sized aggregates of amphiphilic molecules, which when present in aqueous environments possess a hydrophobic core. This core can be used to solubilise poorly water soluble therapeutic agents. Among nano-carriers, polymeric micelles from amphiphilic block copolymers and graft polymers are an alternative choice for cancer therapy and imaging due to the availability of versatile polymerisation techniques to control the molecular structure. This leads to prolong circulation in the blood stream and high accumulation at the tumour site via EPR effect. Some challenges in this system are easily disassembling upon dilution and allergic reactions. To tackle this problem biocompatible, hydrophobic-hydrophilic copolymers have been developed. However, the main problem associate with conventional polymeric micelles is low stability and poor loading capacity [54]. Unfortunately no effort has been made to improve loading capacity of active substances in a single platform system. Multifunctional magnetomicelles have drug delivery, imaging and core protecting capabilities [55]. Moreover, in this system the site and rate of release can be controlled precisely. These systems consist of long chain amphiphilic polymers with metallic nanoparticles within their structure (Fig. 10.7).

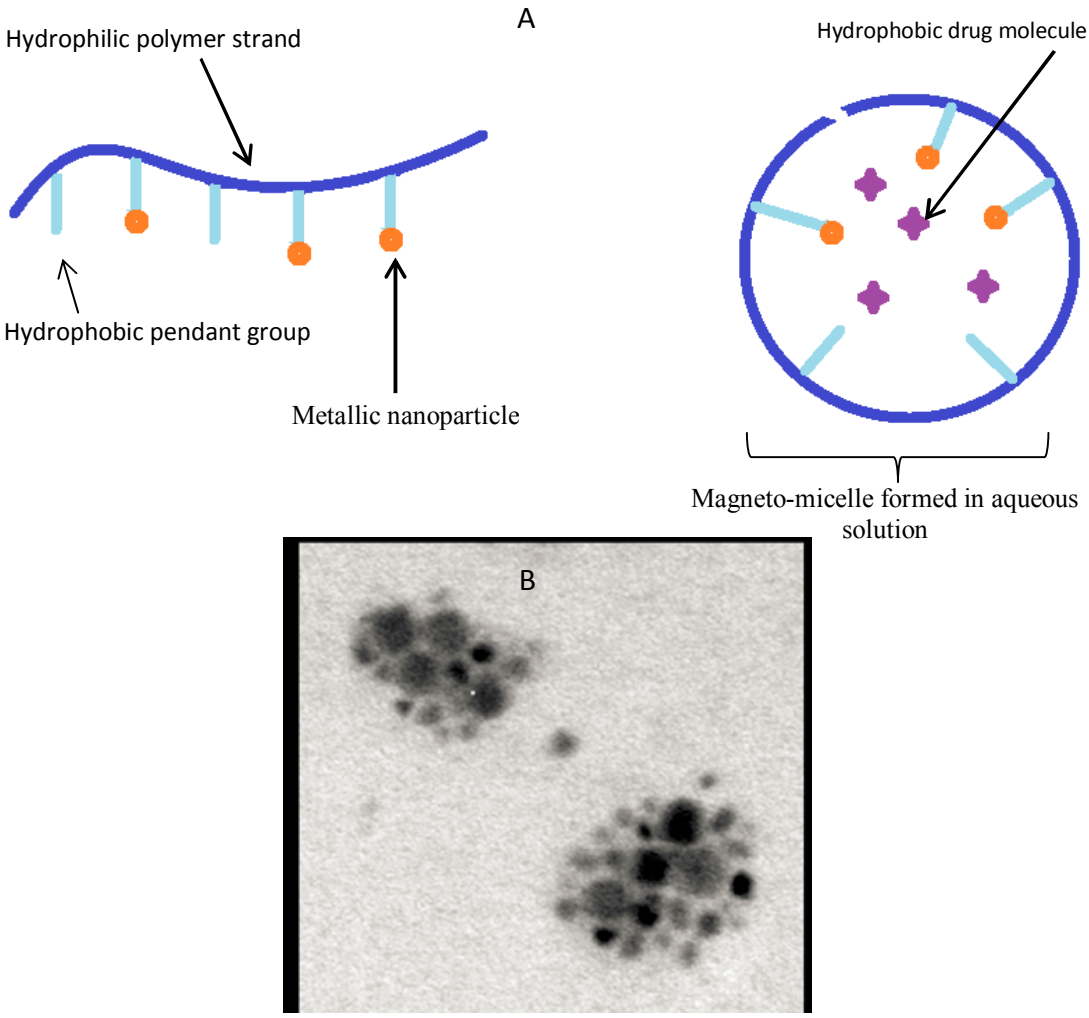

FIGURE 10.7
A) Schematic representation of magneto-micelle for drug delivery and B) TEM image of magneto-micelles [56]

The super paramagnetic iron oxide nanoparticles (SPIONs) loaded micelles are water- dispersible with high colloidal stability. In addition, clustered SPIONs in micelles increase the T2 relaxtivity, which means that final particles have higher efficacy as a contrast agent [57]. One example is coating iron oxide core with polymeric micelles assembled from a copolymer of PEG and poly-Ɛcaprolactone to increase MRI sensitivity [58].
The size of magnetomicelles is usually less than 100nm and they are extremely biocompatible with a prolonged circulation time. Investigations have been shown that drug encapsulated with polymeric micelles have greater passive accumulation in tumour, in comparison with free drugs [59]. In recent years polymeric magnetomicelles made from diacyllipid-PEG have attracted much attention in pharmaceutical sciences due to their unique characteristics. These particles are much smaller (20 nm) than other micelles and they are highly stable in low concentration [60]. Moreover, by conjugating targeting ligands, such as specific monoclonal antibodies, an active targeting agent

can be designed with increased therapeutic efficacy [61]. Barnett and co-workers have evaluated the *in vitro* pancreatic anticancer activity of magnetomicelles based on novel polyallylamine grafted with hydrophobic oxadiazole (Ox) pendant group in a 5% molar monomer as an image guided and drug delivery agent [55].

UV and NIR triggered drug delivery systems

Photo therapy has been the focal point of science for the possibility of creating materials sensitive to electromagnetic radiation (UV, visible and NIR), ranging from single use (light triggers an irreversible structural change, which leads the delivery of entire dose) to multi-switchable carriers (drug is released in a pulsatile manner). Using UV and NIR irradiation as stimulus on hybrid nanoparticles, copolymers and micelles have enormously grown and hold great potential in various disease therapies. This method offering a potential for controlling release of carriers with difficult to release by other stimuli. Electromagnetic radiation range starts from gamma radiation at the high frequency and ends to radio waves at low frequency. A wide range of electromagnetic radiation (380-2500 nm) can be externally applied to the body to trigger drug release at a desirable site. Infrared radiation borders are in the end of visible light in the electromagnetic spectrum.
UV/NIR light irradiation can cause micellar disruption and disassembly (or disassociation) of light responsive copolymers by three mechanisms; 1) regulating the hydrophobicity-hydrophilicity balance, 2) the photo cleavage reaction, and 3) the cascade depolymerisation of degradation reaction in self-immolative polymers [61]. UV or blue light can apply as a stimulus for topical treatments such as skin and mucosa. UV radiation below 700 nm cannot penetrate more than 1 cm deep in the tissue due to the high level of endogenous absorber and scattering such as water, lipids and haemoglobin [62, 63]. Therefore, the majority of interest has been shifted to NIR light. NIR is the part of infrared radiation which closed to the visible red light and is absorbed relatively low by water and tissues. This externally triggered drug delivery enhances patient compliance due to easy and painless dosing and less required doses with higher bioavailability. NIR applications include measurement of oxidation of haemoglobin and triggering a drug release in the difficult to access area of the body [63, 64].
Metal nanoshells such as the gold nanoparticles or iron oxide-gold nanoparticles (discussed in Section 2.3) adsorb NIR radiation which can be applied for thermo-sensitive drug delivery systems [65] (Fig. 10.8). In this system the shell thickness affects the maximum adsorbed wavelength. Decreasing the thickness of the gold shell from 20 to 5 nm leads to SPR red shift [66]. Another strategy is incorporation of these nanoparticles into a polymeric matrix, which can reduce the aggregation of these particles and enhance the efficacy as well. Other NIR-induced drug release fabrication involves burst release of drug encapsulated in liposomes containing hollow gold nanoparticles, which shows tuneable adsorption in the NIR region. Therefore, NIR radiation can trigger drug release from liposomes attributed either transient cavitation effect or temperature increase [67]. Carbon nanotubes have also been exploited as NIR absorbing agent, whilst having drug/protein carrier capability. When these nanoparticles reach into the cells, they start to release their cargo by NIR triggering [68].

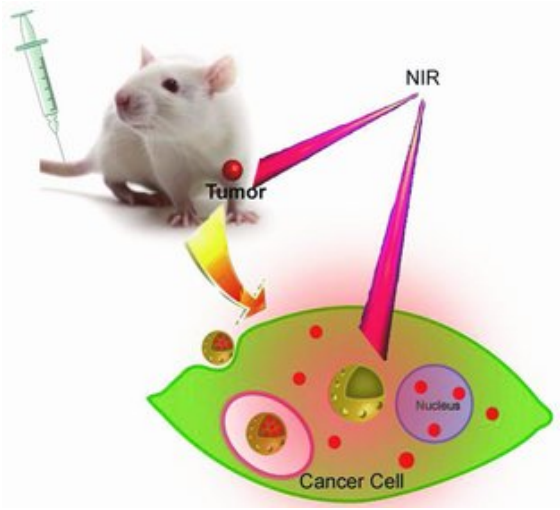

FIGURE 10.8
Laser driven anticancer drug delivery based on gold nanoparticles [65]

Dendrimers based drug delivery systems

The name dendrimer is derived from dendrom which is a Greek term and means “tree”, because of their branching structure with a number of units. They are synthetic macromolecules that characterised by three dimension shape, high branching point and nano-size range. Dendrimers with uniform shape and well-defined size have been one of the most promising polymeric DNA nano-carriers due to their ability to cross cell membranes and reduced clearance from the body. Dendrimers are synthesised from a central polyfunctional core by repetitive addition of monomers and adding monomer to each functional group develops next dendrimer generation. These particles exhibit high stability and monodispersity due to their nano-sized which make them appropriate carriers for delivering drugs with increased bioavailability and selectivity. The branched structure and globular shape result in a large number of active groups, which can be tailored. Several types of dendrimers have been made with different core materials, surface modification and branching units. Peptide dendrimers [69] and glycodendrimers [70] are two dendrimers which have generated great interest for understanding and controlling biological recognition events. Peptide dendrimers contain a peptidyl branching core and/or peripheral peptide chain [71]. They have used as surfactants, multiple antigen peptides (MAP), protein mimics, drug delivery carriers, gene delivery and esterase catalysts. Glycodendrimers that encompass sugar moieties into their structure have great specificity to lectin rich organs, which makes them suitable for drug delivery purposes [71]. There is a relationship between dendrimer size and its three dimension shape. While lower generation dendrimers have amorphous structures, higher generation tend to be spherical that suitable for loading drug molecules. Cationic terminated dendrimers have shown more toxicity than neutral or anionic group terminated dendrimers. However, by modification of cationic dendrimers with negative or neutral group such as carbohydrates, PEG and acetate the toxicity would be reduced [72]. The polyvalancy in dendrimers can play an important role in biomedical applications. Positively charged dendrimers can enhance intracellular drug delivery due to the interaction with negatively charged biological membranes. But dendrimer-membrane

interaction might cause disruption of membrane integrity, which leads leaking of important intracellular components, followed by cell death and toxicity. Drugs entrapment is achieved within the multivalent branching network or through adsorption onto the outer shell (Fig. 10.9).

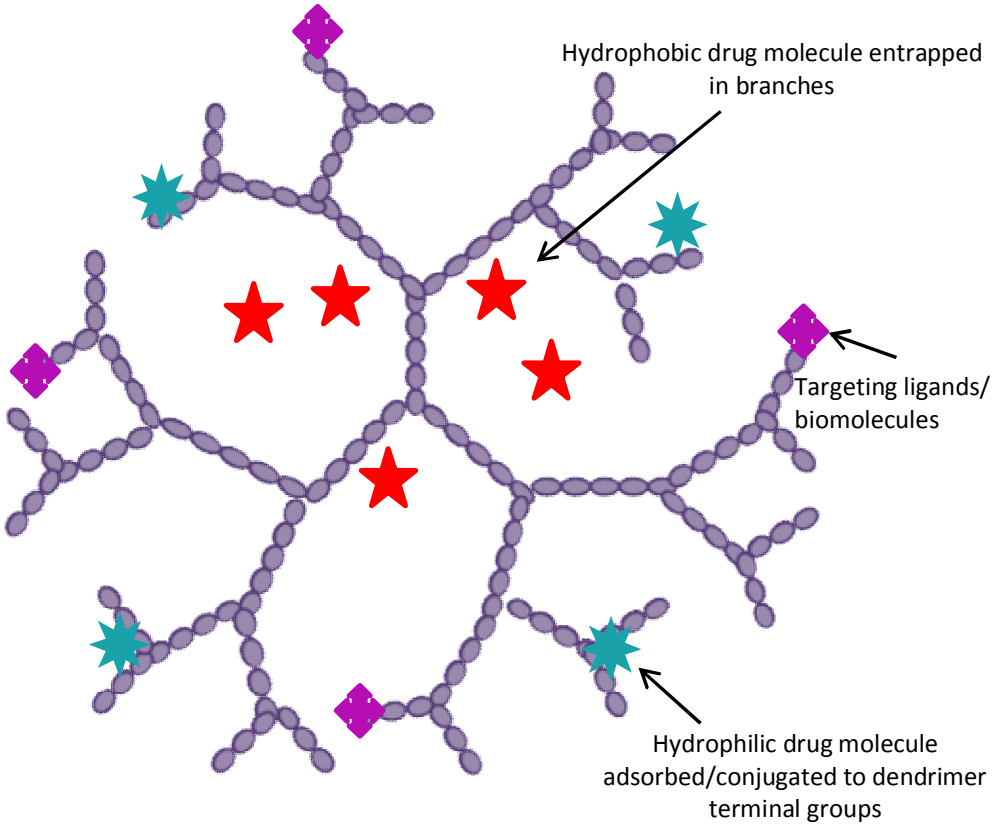

FIGURE 10.9
Schematic representation of a dendrimer macromolecule for drug delivery

When a drug is covalently attached to the outer shell of a dendrimer, it will exhibit a decreased release rate when compared to drug encapsulated by hydrophobic or electrostatic interactions [73]. Dendrimers with high drug conjugation can swiftly enter the cell and localise in the nucleus [74]. These systems are currently being studied for use as antimicrobials [75], dual chemotherapeutic carriers [76] and many more exciting applications.

Conclusion

With rapidly increasing interdisciplinary knowledge comes great potential for sophisticated multimodal systems. Application of such platforms in the biosciences holds great promise. These could ultimately revolutionise modern medicine increasing therapeutic efficacy, producing more favorable outcomes in fatal disease states and reducing patient discomfort and hospital times. As

science advances and these smart systems enter into the lengthy clinical trial process, the future of medicine looks nanosized.

Summary

- Drug delivery systems capable of releasing their payload in response to external or internal stimuli show promising potential in targeting, localisation and controllable drug release.
- Nanoparticles with modified surface can achieve both passive diffusion via the Enhanced Permeability and Retention Effect or active diffusion using specific targeting ligands.
- Work focussing on the design of nano-materials capable of stimuli manipulated release of their cargo at their therapeutic site via selective enzymatic cleavage has been reported.
- Image guided drug delivery is an emerging platform for guidance and validation of targeted therapies
- Ultrasonic (US) drug delivery coupled with image guidance can improve localised accumulation of drug compounds and hence decreases systemic circulation and undesirable side effects.
- Photo therapy has been the focal point of science for the possibility of creating materials sensitive to electromagnetic radiation (UV, visible and NIR).
- As many of these systems begin to undergo the rigour of current clinical trials, the outlook for targeted stimuli responsive delivery and enhancement in patient prognosis is promising.

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