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Chapter 3

Smart Drug Delivery Strategies Based on Porous Nanostructure Materials

Qun Wang, Jianying Huang and Yuekun Lai

Additional information is available at the end of the chapter

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Abstract

The control of drug delivery can have a great effect on its efficacy. An optimum concentration range of drugs can play a significant role in the human body, and it can cause harm to humans when it exceeds the range of the drug concentration. Recently, a variety of drug deliveries and their targeted systems have been studied to minimize drug loss and maximize the amount of drug accumulated in the required area, thus increasing drug bioavailability. In addition, we should especially consider the prevention of its harmful side-effects in the human body. Innovative drug delivery systems based on biodegradable, natural or synthetic polymers, micro- or nano-particles, lipoproteins, micelles, TiO_2 nanotube arrays (TNTs), nanoporous anodic aluminum oxide (AAO), and so on were developed, which combined magnetic targeting and stimulus-responsive in drug delivery systems. The composition of delivery carriers and the stimulus-responsive elements proved stimulus-responsive drug release as a smart drug delivery system.

Keywords: Drug delivery system, carriers, stimulus-responsive, TiO_2

1. Introduction

In recent years, nanomaterials and nanotechnology have been applied in the medical field such as in disease diagnosis and therapy. Research about drug delivery and targeting systems based on nanomaterials is carried out in nanomedicine to establish systems of drug delivery [1]. Based on the systems, it is easy to find disease tissues and implement the therapy in the required location.

Drug carriers included micro- or nano-particles made of biodegradable, natural or synthetic polymers, microcapsules, lipoproteins, micelles, TNTs, nanoporous aluminum oxide, and so on. Due to its controlled size, morphology and release, and excellent biocompatibility,

biodegradable organic/inorganic micro/nano-particles have been studied extensively [2–5]. In fact, stimuli-responsive systems could facilitate drug release to reach a target environment. Stimuli-responsive elements have a functionality that sustains an energetic change in response to pH, temperature, magnetism, sound, and light [6–18].

Preparing particles from stimulus-responsive polymers can respond to certain pH value and temperature and so on to controllably release. The pH-responsive polymer was studied as a delivery system for therapeutic drugs [19–20] and was verified to prolong drug release circulation in vivo. Due to their special magnetic and optical properties, magnetic nanoparticles have played a great potential in drug release [21] and it has been used in disease diagnosis and therapy. Therefore, targeting drug delivery systems was built with the help of magnetic targeting. In addition, micellar solutions, vesicle and liquid crystal dispersions show great potentials as well as nanoparticle dispersions [22–23]. The drug delivery systems based on colloidal drug carriers can realize the target by obtaining systems of drug loading and release, low toxicity, and so on.

Recent progress in controlling drug release from nanotube and nanopore materials include TNT arrays, anodic aluminum oxide nanoporous, and so on [24–26]. TNT arrays have been applied in drug releases of therapies based on drug delivery because of its excellent properties, and it has been confirmed that TNT arrays change localized drug delivery therapies thoroughly. Furthermore, the method of preparing TNT arrays breaks a new nano-engineering path to propose the limitations of drug administration systems. Nanoporous materials with ordered pore structures were studied to avoid limitations of conventional drug therapies, especially for implantable drug delivery systems. In addition, porous AAOs are able to imitate dimensions of the natural bone and AAO films can be seen as promising coatings for the medical industry. Therefore, AAO has been used for new nano-platform for drug releases.

2. Energetic transitions of materials for drug delivery

As is known to us, it is necessary that the chemical functionalities exhibit stimuli-responsive behavior. In some cases, the triggering stimuli are in the proximity of the internal physiological environment of the drug delivery system [27]. It is also imagined that multiple stimuli-responsive systems operating in tandem assemble into a drug delivery system [28]. For example, a temperature change in a thermo-responsive system may be induced by a magnetic system.

2.1. pH-sensitive drug delivery

Polymer materials own structures with ionizable functionalities that become ionized at a specific pH where they acquire a positive or negative charge [29]. The transition of the functional group from one of water insolubility to one of water solubility under the effect of the ionization is called polyelectrolytes because of the presence of electrostatic charges in the water-soluble polymer structure.

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There is a significant difference in the behavior of polymeric-charged functionalities and their uncharged counterparts in terms of their intermolecular effects on the surrounding environment and intramolecular effects within their own polymer molecules. The two types of interaction can be segregated into a polyelectrolyte and a solvent [29], and those between a polyelectrolyte and a surface [30]. In terms of the interaction between a polyelectrolyte and a solvent, there is a transition of the Gibbs free energy of mixing shifts from negative (−ΔG) in solubility to positive (+ΔG), where it is insoluble because the transition from an intermolecular hydrogen-bonded species to an intramolecular hydrogen-bonded species causes poor entropy of mixing [31]. The function is easily seen in the change in the secondary structure of polypeptides or proteins where there is a transition from an α-helical to a random coil secondary structure as a result of deprotonation or protonation, as is shown in Fig. 1 [32].

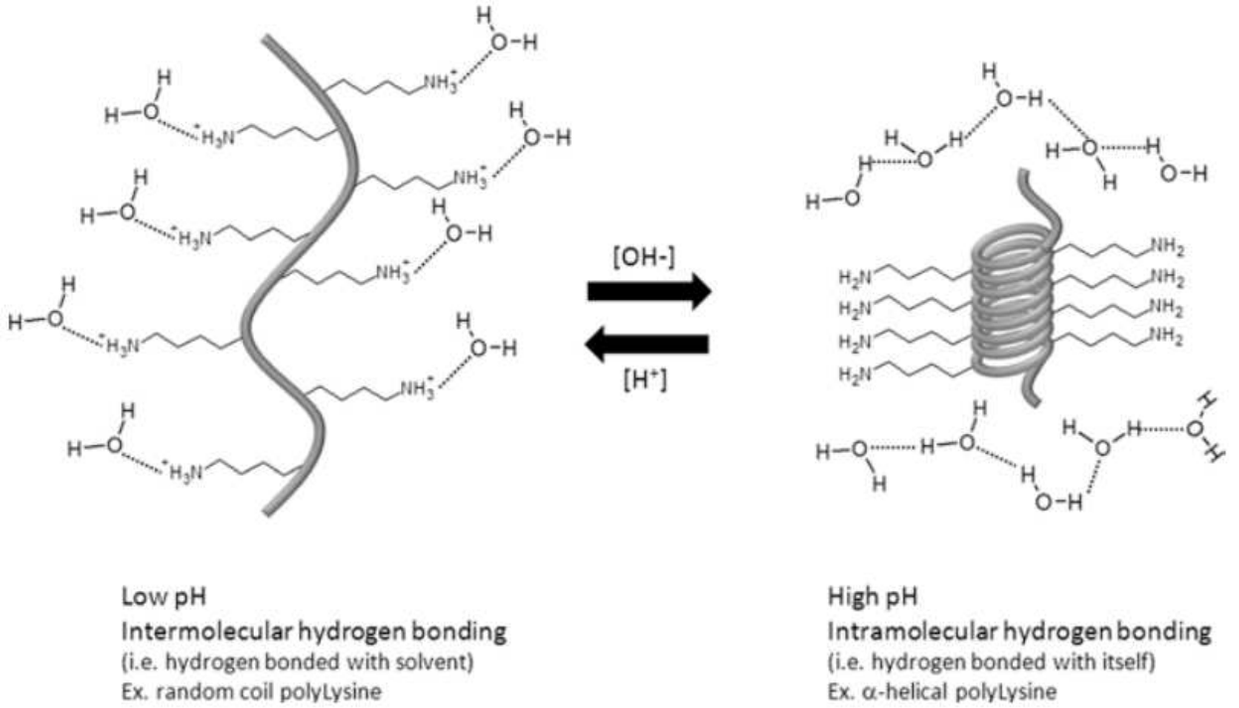

Figure 1. Diagram of the intramolecular versus intermolecular hydrogen bonding through the protonation–deprotonation of the pendant groups on the polymer chain [32].

In addition, several characteristic interactions between the polyelectrolyte and the surface can be seen. If a surface owns an oppositely charged energy, the polyelectrolyte is proposed to interact in a number of different ways. If there is a long-range of electrostatic interaction, it is possible that the rearrangement of the polyelectrolyte chain expresses charged functionalities at the surface [33]. This rearrangement would change based on the pH, the charge density, the composition and distribution of charges along the polymer chain and the ionic strength of the solvent and so on. For the purposes of our discussion in this section, we focus on the pH and ionic strength.

We know that the introduction of salt will screen the electrostatic forces between the polyelectrolyte and the surface, as well as reduce both the intermolecular and intramolecular electrostatic repulsions. There is also a non-electrostatic affinity under certain conditions in the case of interactions between polyelectrolytes and charged surfaces [34]. Any increase in the ionic strength under the presence of salts would decrease the electrostatic affinity of the polyelectrolyte to the charged surface when the adsorption of polyelectrolyte on a charged surface is driven by only electrostatic forces, and the adsorption increases to an upper limit when the non-electrostatic affinity is high enough.

The responsiveness of a molecule to pH presents an interesting target for stimulated drug delivery. As we know, when an encapsulated drug species is internalized by a cell, it will enter the lysosome at some point within the process. The lysosome cell has a pH of 4.5–5.0 [35], which is exclusively different from other intracellular vesicle species. Therefore, a collapse or dissociation of the self-assembled species is triggered by pH and will result in the release of the encapsulant.

We know the role of the hydrophobic domain in the self-assembly of micellar systems is to minimize the interfacial free energy between incompatible phases. The hydrophobicity could be adjusted by increasing the molecular weight into the entanglement regime, which more effectively stabilizes both the hydrophobic domain and the self-assembled species. If we begin to change the composition of the hydrophobic domain, it will destabilize the condensed, self-assembled structure [36].

The pH-responsive vesicle or micellar systems would not be orally relevant if the stimuli range is ~5 since the premature release of drug cargo would occur in the acidic environment of the stomach (pH 1–3) [37]. The hydrogel particles are designed such that the cross-linked domains are a combination of covalent bonds and the collapse of multiple hydrophobic domains. In these cases, a change in the pH of the environment surrounding leads to a nonpolar, collapsed hydrophobic species to turn into a charged species. The change to charged groups also leads to the electrostatic repulsion of polyelectrolyte chains within close proximity to one another, which further drives the expansion of the gel network pore structure [38]. The design is typically used in drug applications where the drug needs to be delivered within the immediate proximity of a desired cell and does not require the system to facilitate the cellular internalization response. In either of these cases, systems can be designed with negative charges as well, which shifts the operable pH range to more basic stimuli. One can envision tuning their respective systems by compositionally shifting their ratios of cationic to anionic stimuli-responsive groups to allow for a specific release window (Fig. 2) [38].

2.2. Temperature-sensitive drug delivery

The combination of a polymer with a solvent in a binary mixture involves a series of phases of varying degrees of stability primarily in relation to its composition and temperature. Within some compositional range, a material can reach a minimum energy equilibrium state known as the binodal curve that describes a critical limit at which two phases can be either stable on one side or unstable on the other side, representing the limits of solvent interaction between two phases [39]. Plus, a curve known as the spinodal curve describes the limit of absolute

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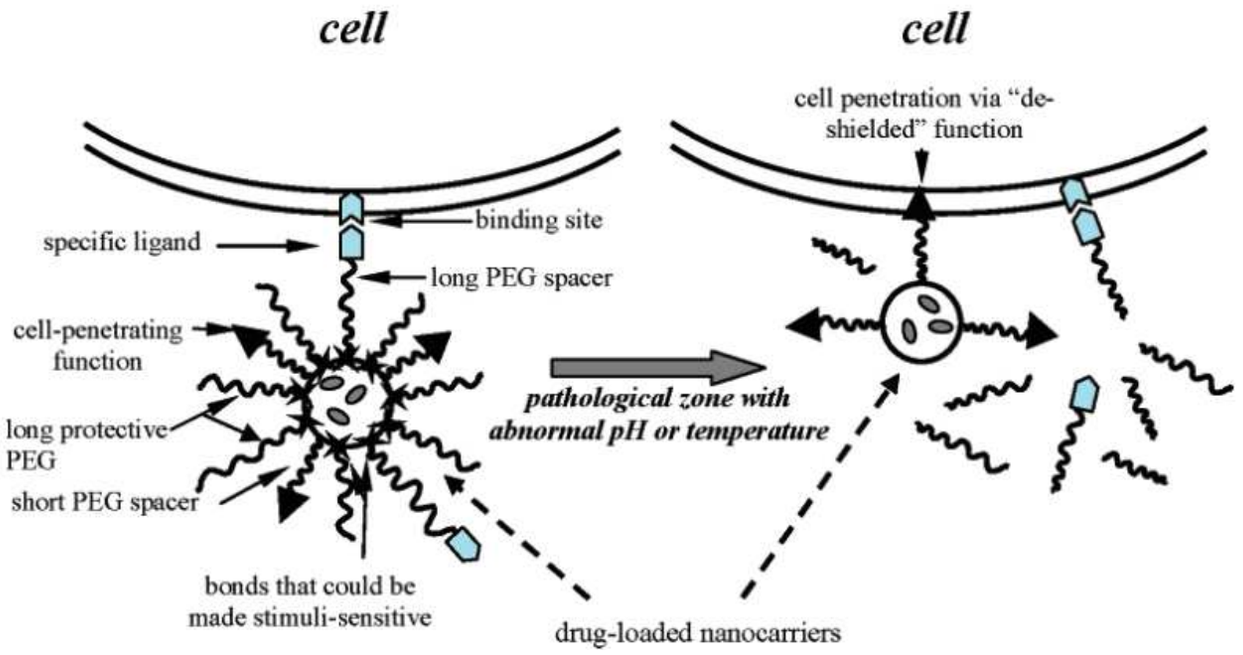

Figure 2. Interaction of the multifunctional pH-responsive pharmaceutical nano-carrier with the target cell. Local stimuli-dependent removal of protecting PEG chains or mAb-PEG moieties allows for the direct interaction of the CPP moiety with the cell membrane [38].

instability between phases. A complete decomposition of the system is produced when it is changed to composition within the spinodal curve [40].

The point at which the spinodal and binodal curves meet is known as the lower critical solution temperature (LCST) [41]. The LCST represents a point below which the material becomes miscible, where the Gibbs free energy of mixing is negative ($-\Delta G$) and above which it is completely immiscible, and where the Gibbs free energy of mixing is positive ($+\Delta G$) due to poor entropy of mixing [42]. The degree of polymerization and the polydispersity of the polymer chains can be a strong influence on the energetics of mixing and therefore can shift the values for the LCST. Typically, polymer chains with higher degrees of polymerization lead to higher values for the LCST. Polymers that exhibit an LCST behavior can have their solubility tuned based on temperature change.

We have known that the self-assembly of vesicle and micellar species is controlled by several factors, such as chemical composition, shape, charge, and so on, and species with specific size, shape, stability, and delivery efficiency are assembled under the effect of these factors [43]. For a vesicle species comprised of amphiphilic copolymers, there is much focus about their design. The chemical functionality tells us the rigidity of the system and the way hydrophobic or hydrophilic are, as well as whether a charged species is present [44].

The bond rotation of rigid species require a higher number of polymer repeats, and there are limitations in the modes of bending, so higher molecular weights is required in order to reach the entanglement regime for the more rigid systems. The closer the molecular weight is to the entanglement molecular weight, the more stable the assembled species [45]. The chemical

composition will tell us the ratio of the hydrophilic and hydrophobic components, as well as the degree of polymerization of the collapsed hydrophobic domain.

Yatvin and Weinstein pioneered the concept of temperature-triggered local drug delivery using temperature-sensitive liposomes (TSLs) [46–47]. Here, a chemotherapeutic drug is encapsulated in a heat-sensitive nanovesicle that prevents extravasation of the drug into healthy tissues at physiological temperature. The experiment about temperature-induced drug delivery was performed in small rodents with a subcutaneous tumor on the hind limb where hyperthermia was realized through putting the leg into a water bath [48]. Both tumor tissue and the whole hind limb were found with temperature-induced drug delivery phenomenon. The control of the temperature remained demanding when temperatures were monitored with thermocouples inserted into the tumor. The concept of temperature-triggered drug delivery has been extended to magnetic resonance (MR) image-guided drug delivery by the co-encapsulation of a paramagnetic magnetic resonance imaging (MRI) contrast agent in the lumen of TSLs (Fig. 3) [49].

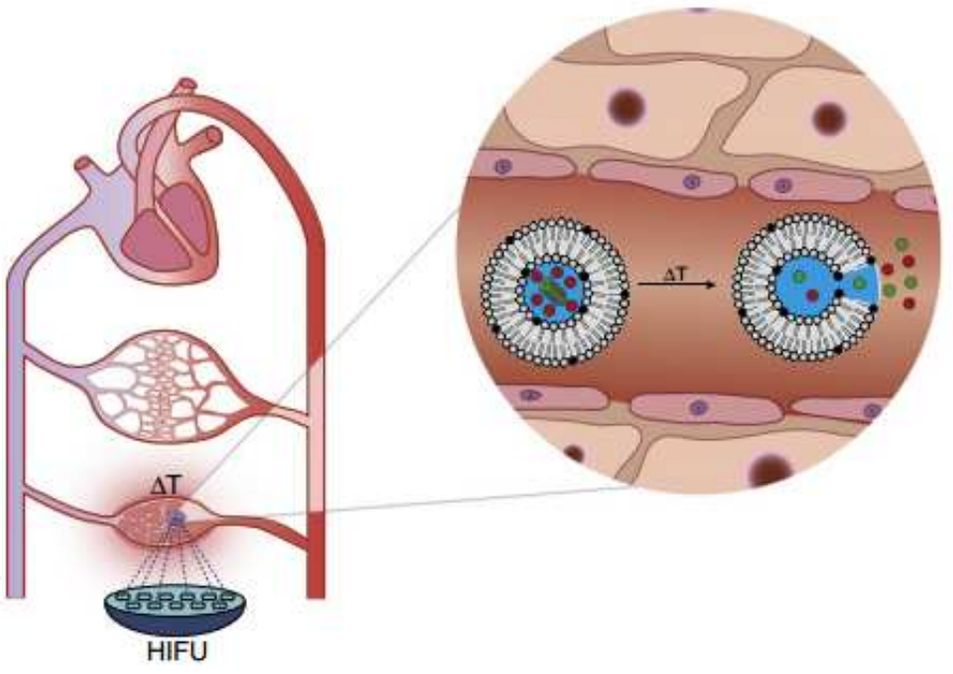

Figure 3. MR image-guided drug delivery illustration of the release of temperature-triggered drug using temperature-sensitive liposomes and HIFU. The co-release of MRI contrast agents from the liposome loaded with temperature-sensitive drug allows to non-invasively visualize and quantify the drug release process [49].

It has been revealed that the external aqueous medium was separated from the liposomal aqueous lumen by a single continuous bilayer of phospholipids that is from the self-assembly of phospholipids into liposomes [50]. These self-assembled structures have been investigated as molecular MRI contrast agents for drug delivery systems. Temperature-sensitive liposomes release encapsulated drugs at the melting phase transition temperature (Tm) of the lipid bilayer (Fig. 3). Structural changes in the lipid membrane occur as it transfers from a gel to the liquid-

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crystalline phase at transition temperature [51]. In comparison to the liquid-crystalline phase, liposomal membranes in the gel phase are less permeable to water and drugs.

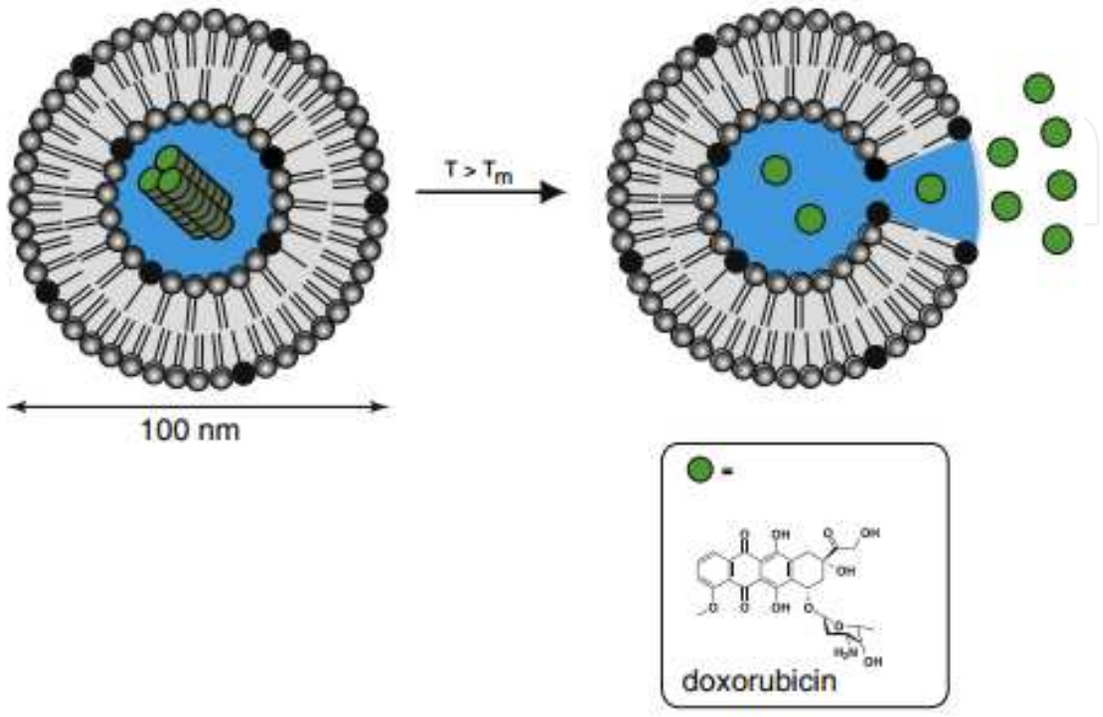

Figure 4. Schematic representation of heat-triggered dox release from TSLs [49].

There are several other thermo-responsive functionalities that can be incorporated within the polymer domain in order to stimulate porosity or swelling of a system in addition to NIPAAm, and each system has a different LCST, or in some cases a tunable LCST [52]. Appropriate selection of the thermo-responsive functionality for eliciting the desired behavior is critical. It is also important to keep in mind that the selection of the responsive functionality should reflect the rationalization that the system should be at the very least bioinert in order to be a candidate for a drug delivery system.

2.3. Magnetic-sensitive drug delivery

The stimuli-responsive behavior is dependent on the local physiological environment, such as in both cases of pH and temperature. We could direct the stimuli toward the targeted area of delivery instead of the stimuli-responsive behavior depending on a localized environment. We will adjust the chemical functionality to allow for a relevant response if there is fine control over sources that induce a direct movement including a magnetic field, light, and sound. The response is an attractive or repulsive force relative to the field direction in the case of magnetic materials. Both the material chemical functionality and the viscosity properties of the particle within a physiological system are critical in determining the extent of the response to a magnetic field (Fig. 5) [53–54]. Magnetic particles are typically divided based on size into

single-domain and multi-domain particles [55]. The single-domain particles fall in a small size regime, where decreases in size correspond to an increase in coercivity to a peak level before dropping to zero. The zero point identifies a superparamagnetic material, which is one whose magnetic moment is induced in the direction of the applied magnetic field and in the absence of a magnetic field returns to an unaligned state [56].

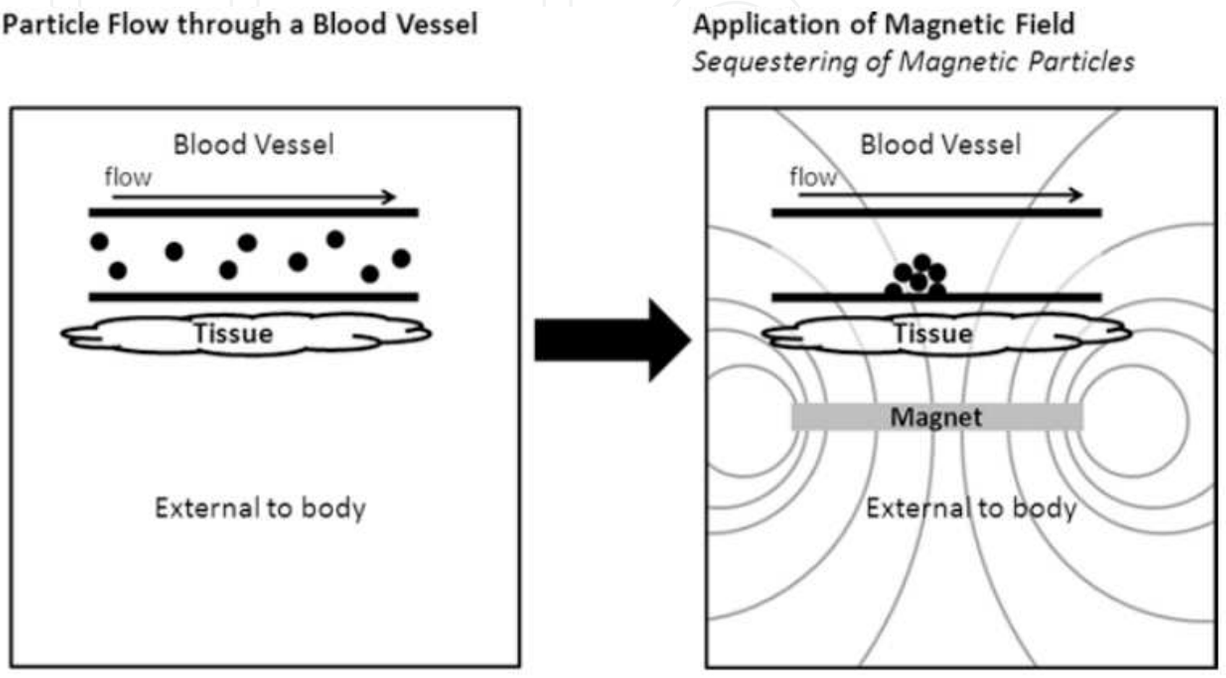

Figure 5. Diagram of the basic forces involved in the sequestration of magnetic nanoparticles in the bloodstream [53].

As was the case of thermo-responsive and pH-responsive systems, magneto-responsive materials represent systems that interact with an applied stimulus as opposed to an encountered stimulus. Light and sound are also suitable for responsive materials as an applied stimulus [57]. The stimulus is an externally applied magnetic field that can immobilize a particle under flow in terms of magnetic materials [58]. The design of magnetic materials involves several factors including particle size, stabilizing material, atomic identity, and so on [59]. In terms of the size of the magnetic particle, paying attention to the larger the magnetic particle size, the more susceptible it will be toward manipulation by a magnetic field. The stabilizing functionality is that the particle surface is necessary to allow for the particle to effectively function as a physiological system. The atomic identity refers to the metal atoms used in the particle composition.

In the application of a magnetic field, we should pay attention to a single-domain magnetic particle strategy for the immobilization of drug species [60]. The system depends on a small particle system in order to fall within the superparamagnetic regime. For example, systems of iron oxide (Fe_3O_4) are used where drug species are conjugated to the surface. A larger silica particle system is used as matrix by these ferromagnetic particles, which is then surface-functionalized with chemically inert groups [60]. Fig. 6 displays the schematic illustration of

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the synthesis process of the drug-loading magnetic and fluorescent chitosan nanoparticles [61]. Amino groups of chitosan consisted of cationic linear polysaccharide molecules keep positively charged under weakly acidic conditions, result in the form of a long and intertwined chain with positive charges along its backbone. The aqueous negatively charged QDs, Fe_3O_4 nanoparticles, and the ionized COO^- of cefradine (pKa = 2.5 and 7.3) along the positive backbone are electrostatically attracted in weakly acidic conditions are electrostatically attracted [61].

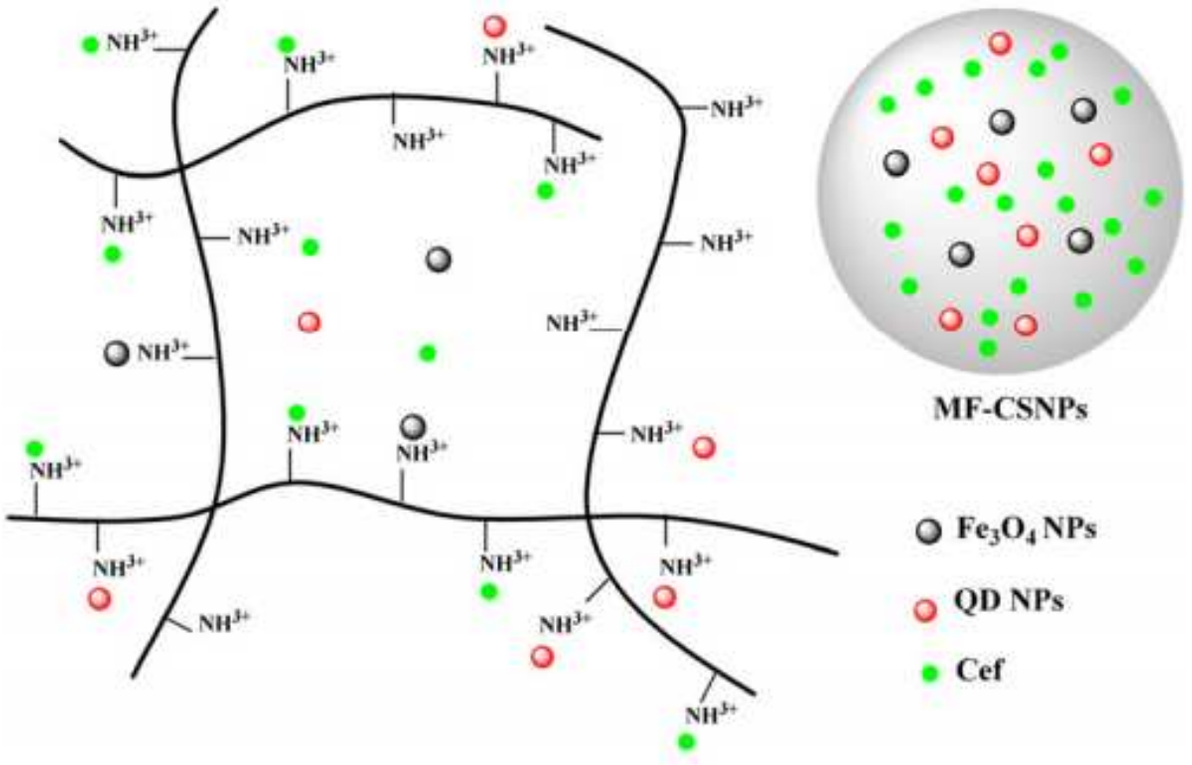

Figure 6. Schematic representation of the fabrication process of the drug-loading magnetic and fluorescent chitosan nanoparticles [61].

The introduction of surface-modifying groups for biocompatibility and the magnitude of the magnetic moment at the surface of the particle are reduced, which may limit its physiological application. Therefore, the design of these immobilized magnetic systems involves three basic factors: particle size (<10 nm), bioinert surface functionalities, and mode of drug incorporation (conjugated or dispersed within matrix) [62]. Magnetic drug delivery systems formed using this design strategy have shown promise for clinical evaluation and treatment of brain tumor patients using a tandem approach involving acoustic and magnetic targeting of tissue across the blood–brain barrier.

The domain choices allow tunable size and magnetic susceptibility for the drug delivery system. This degree of versatility allows for a multitude of surface functionalizations in order to present a drug delivery system that is physiologically bioinert.

2.4. Ultrasound-sensitive drug delivery

A self-assembled species can be induced by the use of ultrasound technology to act as a nucleation site for pore formation in a membrane barrier to enhance delivery [63]. A process of acoustic droplet vaporization pushes a superheated droplet through a phase transition to yield gas micro-bubbles, which leads to membrane pore formation by a process of sonoporation [64]. For transdermal drug delivery, the permeabilizing effects of ultrasound have been applied to a number of treatments, such as for diabetes [65]. Ultrasound has been employed for targeted disruption of drug carrier vessels such as contrast or acoustically active liposomes, releasing their therapeutic payload for uptake by the target cells (Fig. 7) [66]. In addition, sonoporation has been associated with gene therapy for the introduction of nonviral plasmid DNA into target cells.

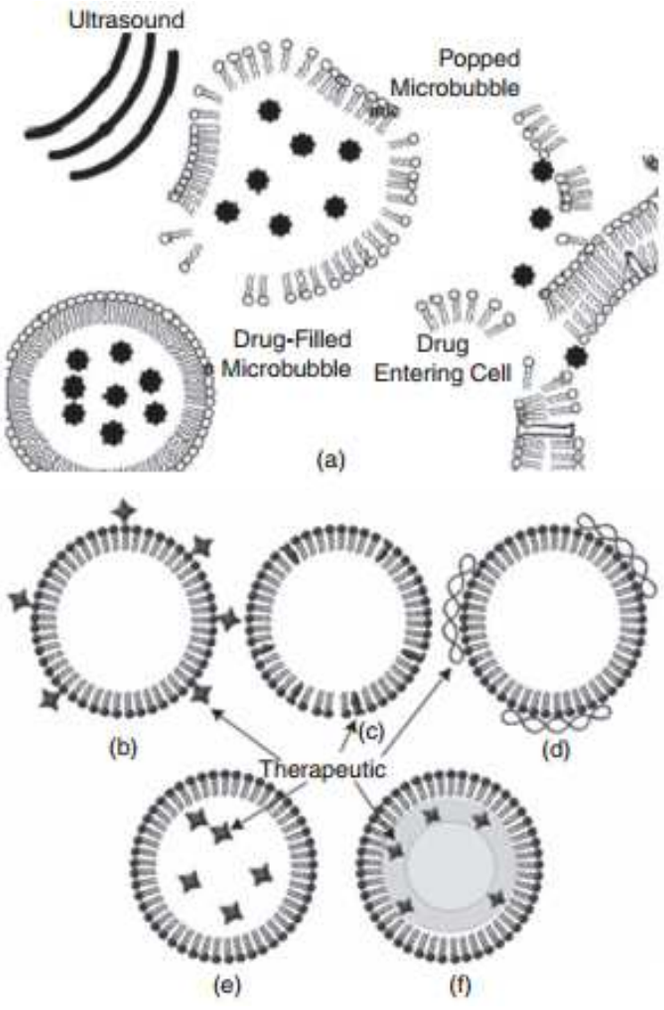

Figure 7. Various drug delivery strategies with micro-bubble carriers. (a) Schematic representation of drug delivery via targeted micro-bubble destruction with ultrasound. Models of different therapeutic agents loading styles, such as the (b) attaching to the micro-bubble membrane, (c) imbedding in the membrane, (d) bonding noncovalently to the micro-bubble surface, (e) packing in the interior of the micro-bubble, and (f) incorporating into an oily film surrounding the micro-bubble [66].

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In the case of ultrasound responsive systems, it is required for the stabilization of acoustic cavitation's gas–liquid interface and the compatibility with liquid interface to generate gas bubbles. The primary requirements of the stabilized system are extended circulation lifetime, effective size range, and efficient stimulated release of encapsulated drug via the application of ultrasound [67–68].

The circulation lifetime of the gas microbubbles is associated with the amphiphilic component that stabilizes the interface. We have known that lipid bilayer systems have a significantly short thickness, which offers little stability of microbubbles in vivo in the case of gas–liquid interfaces. Amphiphilic copolymer systems offer a significant improvement to the interfacial membrane stability, while maintaining tunability to drive membrane curvature [69].

It is known that the targeted size of allowing for tumor membrane permeability and gas microbubble stabilization is less than 750 nm. The curvature can be further tuned to form nanobubbles as a preform to merge into microbubble systems at the cell membrane interface. It is an example of improving the stability of the microbubble with no discernible effect to the biological delivery. The energy of the applied ultrasound stimulus can adjust the size regimes and stabilize the desired interfacial curvature effectively (Fig. 8) [70].

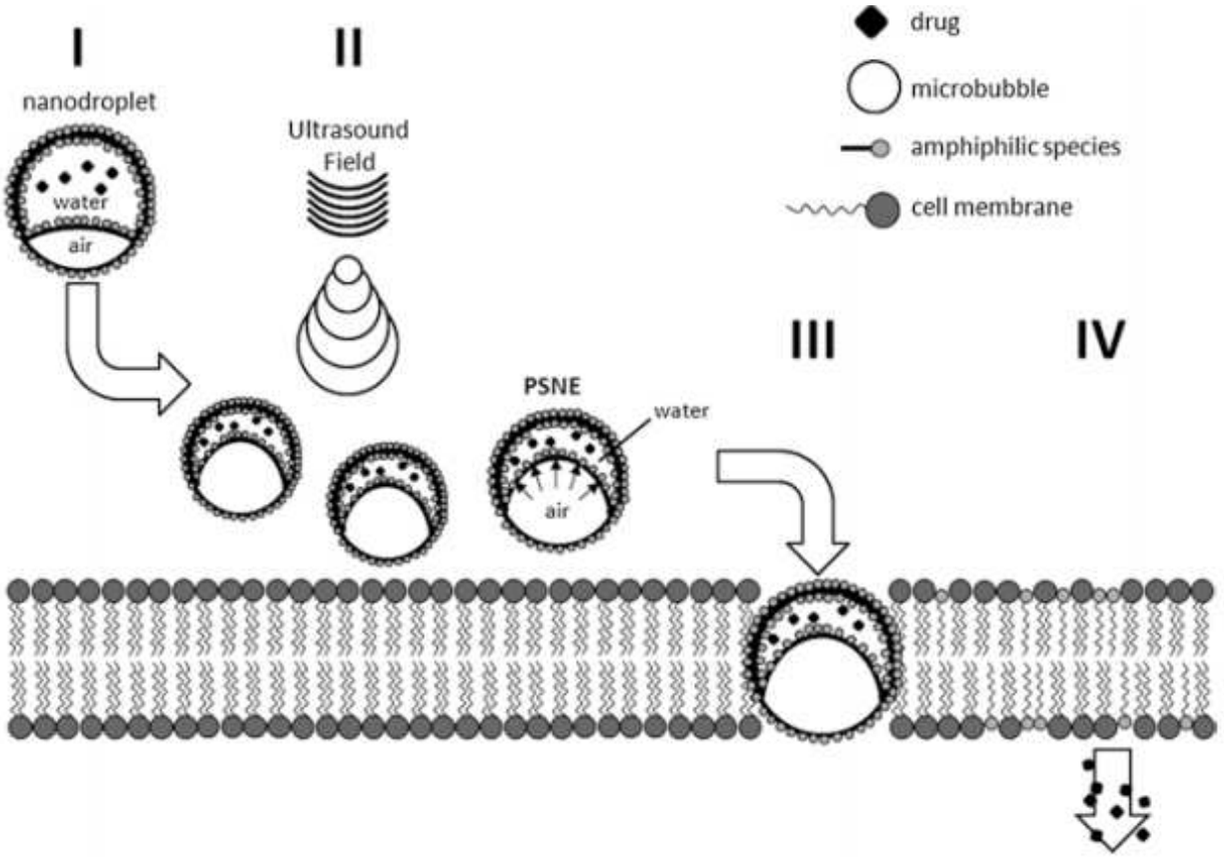

Figure 8. Diagram of the cavitation of PSNE (Phase-Shift Nanoemulsion) nanodroplets from ultrasound [70].

The effective delivery of the adhered drug is relevant to the echogenicity or the ability to bounce a signal base on oscillation, growth, and collapse of the microbubble system [71]. The echogenicity is affected by the choice of component mixtures such as water and PFP, the surfactant, and the size of the microbubble system. The trend appears to be that the maximization of the impedance between components and the stabilization of high-curvature systems can improve drug release profiles in vivo [72].

2.5. Light-sensitive drug delivery

The materials species is influenced by the presence of a specific energy wavelength of light as well as the particle species is influenced by the direction of the magnetic field in magnetic systems. The chemical structure of the drug delivery system destabilizes or changes conformation in response to the absorbed energy input when visible, ultraviolet (UV), or infrared (IR) light is directed at a desired target region. TiO_2 photocatalysts have been mostly used for the purification of air and water by UV light irradiation. However, the limited photocatalytic activity of TiO_2 within the UV range presents difficulties in biomedical and tissue engineering applications owing to the potential harmful effects of UV light. In this part, we focused on the extension of the photocatalytic activity of TiO_2 to the visible light region by doping nitrogen into the TiO_2 crystal structure, which would allow remote control of antibiotic elution by visible light irradiation [73].

A new delivery system that affords control of the time of drug elution and accurate dosing of antibiotics to the target area is required. TiO_2 nanotubes have been studied predominantly in the field of photocatalysis [74–76], solar cells [77], and biomedical engineering [78–80], because of their excellent photocatalytic activity and biocompatibility. In addition, the high surface area and unique shape of TiO_2 nanotubes make them a promising option for application in drug delivery systems. TiO_2 nanotubes arrays fabricated by electrochemical anodization can be described as a layer of tightly packed, vertically aligned and ordered nanotube structures with hexagonal arrangement, which grow perpendicularly to the Ti surface [81]. Fig. 9A and 9B show illustrations of the chemical cell and the fabrication process of TNTs by electrochemical anodization of Ti. Typical scanning electron microscopy images of prepared TNTs are shown in Fig. 9c, with the top and the cross-sectional views showing nanotubes separated into individual entities featuring closed ends at the bottom side [82].

Kyung-Suk Moon et al. [83] immobilized Gold nanorods (GNR) at the surface of TiO_2 nanotubes via a grafting technique and investigated on-off drug release triggered by near-IR laser irradiation. In addition, antimicrobial activity was monitored to assess the effectiveness of GNR-grafted TiO_2 nanotubes in allowing remotely controlled drug release by IR laser irradiation. The elution concentrations of tetracycline loaded at the surface of GNR-grafted TiO_2 nanotubes were evaluated after 30 s of IR light irradiation with a near-IR laser. The release concentrations of tetracycline from GNR-grafted TiO_2 nanotubes with IR light irradiation (674.52 ± 169.58 μ μg/mL) were significantly higher than those from other experimental conditions, such as TiO_2 nanotubes with or without IR light irradiation and GNR-grafted TiO_2 nanotubes without IR laser irradiation (Fig. 10) [83].

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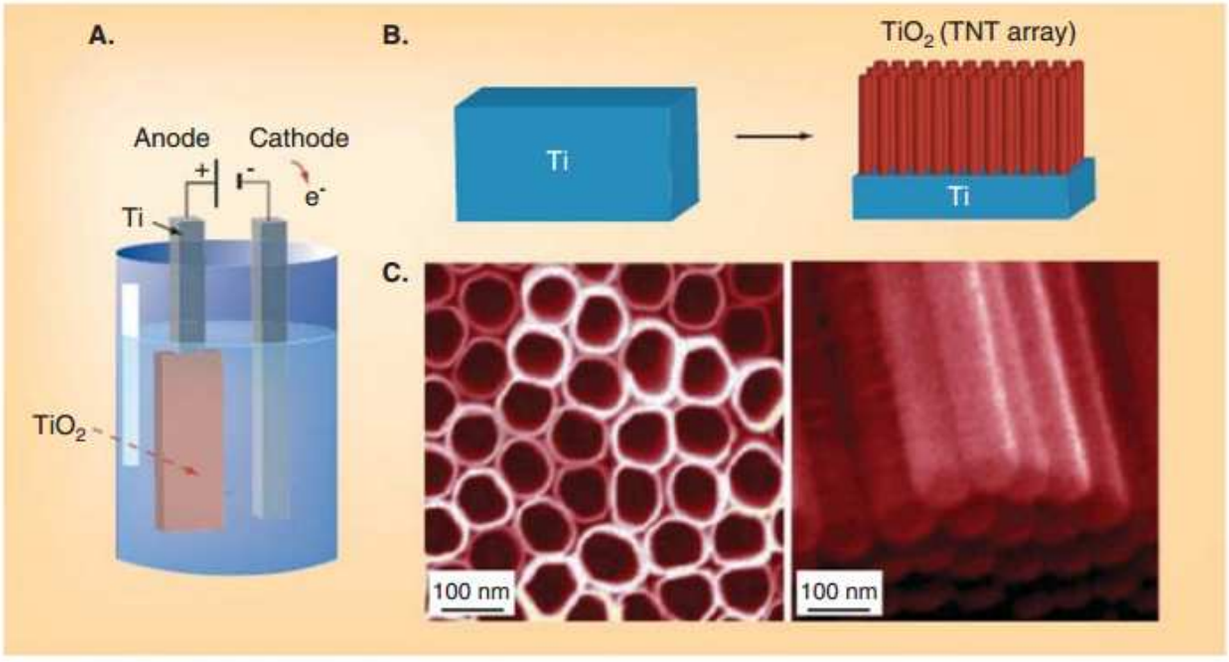

Figure 9. Schematic illustration of TNTs synthesis process and corresponding SEM images of typical morphology and structure. (a) Preparation of TNTs layer by electrochemical cell and anodization process. (b) Formation of self-organized and vertically aligned TNTs on Ti substrate. (c) SEM images of the typical morphology of TNT structures [82].

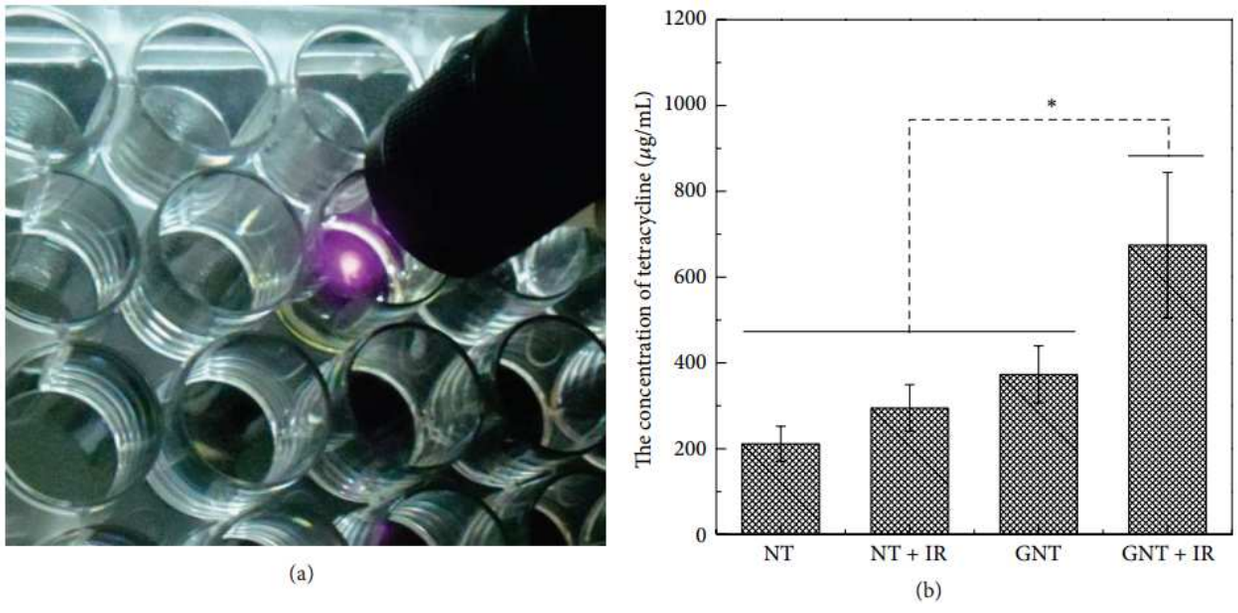

Figure 10. a) Near-IR laser and IR light irradiation and (b) the concentration of tetracycline released by IR light irradiation (NT, NT + IR, GNT, and GNT + IR in the graph designate TiO_2 nanotubes only, near-IR laser irradiated TiO_2 nanotubes, GNR-grafted TiO_2 nanotubes, and near-IR laser irradiated GNR grafted TiO_2 nanotubes, resp.) [83].

For photo-responsive materials, light can either induce the formation of an isomer or degrade a self-assembled component [84–85]. The photoisomerization strategy relies on the effective destabilization of a liquid crystal phase within the hydrophobic domain of micelle or vesicle

species that are formed from amphiphilic molecules or macromolecules. The aggregated region will be highly rigid and densely packed in the trans state if the hydrophobic domain consists of liquid crystal groups [86]. The visible light or heat is used to return the structure to its native initial state in photo-isomerization-induced systems that involve highly stable vesicle or micellar self-assembled systems that rapidly reform their densely packed domains.

2.6. Nanoporous engineered drug delivery

Recently, nanoporous anodic alumina (NAA) has become one of the most popular self-ordered periodic, porous templates. In general the highly developed, superior ordering of nanopores in NAA templates is obtained by using a two-step anodization process. NAA has been of great interest due to its outstanding material properties, including electrical insulation, optical transparency, and chemical stability, and most recently, because of its biologically inert and biologically compatibility properties [87]. The use of NAA as a drug delivery platform has been explored in several fields, such as biomedical devices for dental and bone implants, vectors, or carriers for cells transplantion. The suitability of NAA loaded with catalase, endostatin, and vitamin C as sustainable, quasi-linear drug-releasing platform for ophthalmic applications has been demonstrated by Orosz et al. [88].

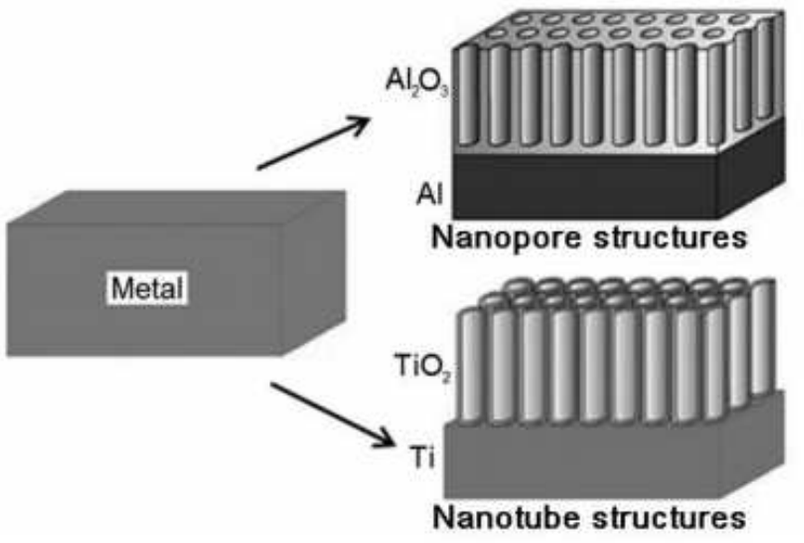

Figure 11. Schematic diagram showing the self-ordering anodization on selected metals (Al and Ti) to produce nanoporous and nanotube metal oxides (Al_2O_3 and TiO_2) with highly-ordered and self-aligning uniform structures. These two materials were explored as non-eroding drug-releasing implants for LDD applications [89].

Depending on the metal type, electrolyte, current, and voltage, two different oxide growth morphologies, such as nanoporous aluminum oxide (Al_2O_3) and nanotube titanium dioxide (TiO_2), can be obtained by a self-ordering electrochemical anodization process as shown in Fig. 11 [89]. The structural features of NAA can be controlled by the anodization parameters, so the functionalities of NAA in terms of pore geometry is an advantage for developing drug-releasing implants as the diffusion of molecules from the nanopores can be tuned by geometry

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[90]. Jeonet et al. [91] developed a sophisticated system by combining NAA chips with electrically responsive polymers, in which the pore mouths of NAA were modified with polypyrrole doped with dodecylbenzenesulfonate anion (PPy/dB) by electro-polymerization on the upper surface of NAA platforms. The large volume change of that polymeric blend was used to achieve pore mouth actuation by an external electrical stimulus (Fig. 12) [90].

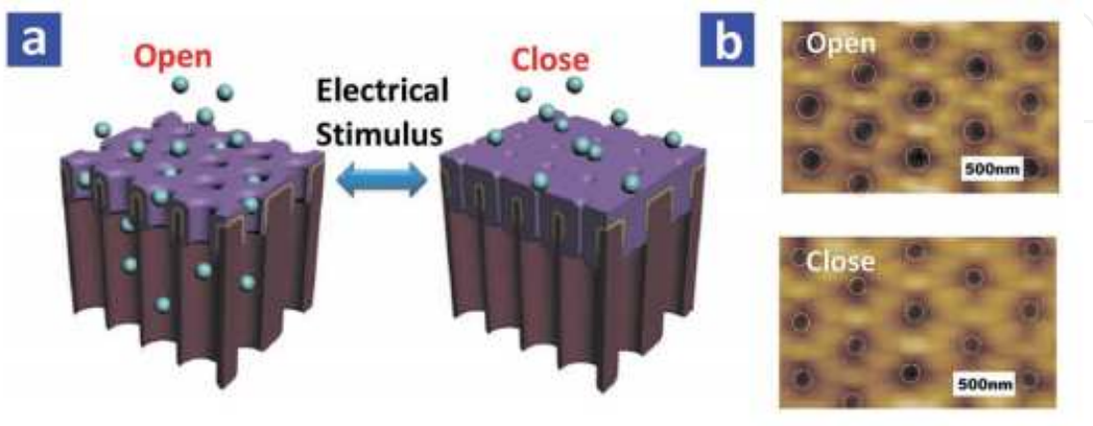

Figure 12. Electrically responsive drug-releasing NAA chip. (a) The mechanism of an electrically responsive drug-releasing chip based on NAA and PPy-DBS (reversible cycle). (b) AFM images of NAA chips before and after the application of electrical stimulus (pore mouth reduction) [90].

Titania nanotubes (TNTs) can be produced by anodizing metallic titanium (Ti) in different acid electrolytes as well as NAA; TNTs feature a nanotube structure during the anodization process (Fig. 13A and B) [92]. Different electrochemical approaches have made it possible to engineer the nanoporous structure of TNTs. TNT-based implants are recognized as one of the most promising nanomaterials to address the inherent drawbacks of conventional systemic drug administration due to their capability to localize the release of drugs over affected bones sites in a controllable manner [91].

In terms of the drug loading and release properties and capabilities of TNTs layers, the drug release from nanotubes is governed by a diffusion process when TNTs come into contact with the physiological milieu inside the host body, as schematically presented in Fig. 14 [90]. The release process is established by the mass transfer of drug molecules from the nanotubes, considering that the drug is completely soluble in the physiological solution without precipitation at particular concentrations. This diffusion-controlled process can be described by Fick's first law, which is governed by a number of factors such as the molecular size and charge of drugs, the diameter and length of nanotubes, their charge and surface chemistry, interfacial interaction between drug molecules and nanotube surface, dissolution rate of drugs, diffusion coefficient, pH, and so on [82].

In addition, the surface charges of TNTs can be rendered hydrophobic or hydrophilic to accommodate a variety of drug molecules should be mentioned. In vitro drug release with the aid of polymeric micelles as drug nano-carriers [93–94] and targeted drug release by means of

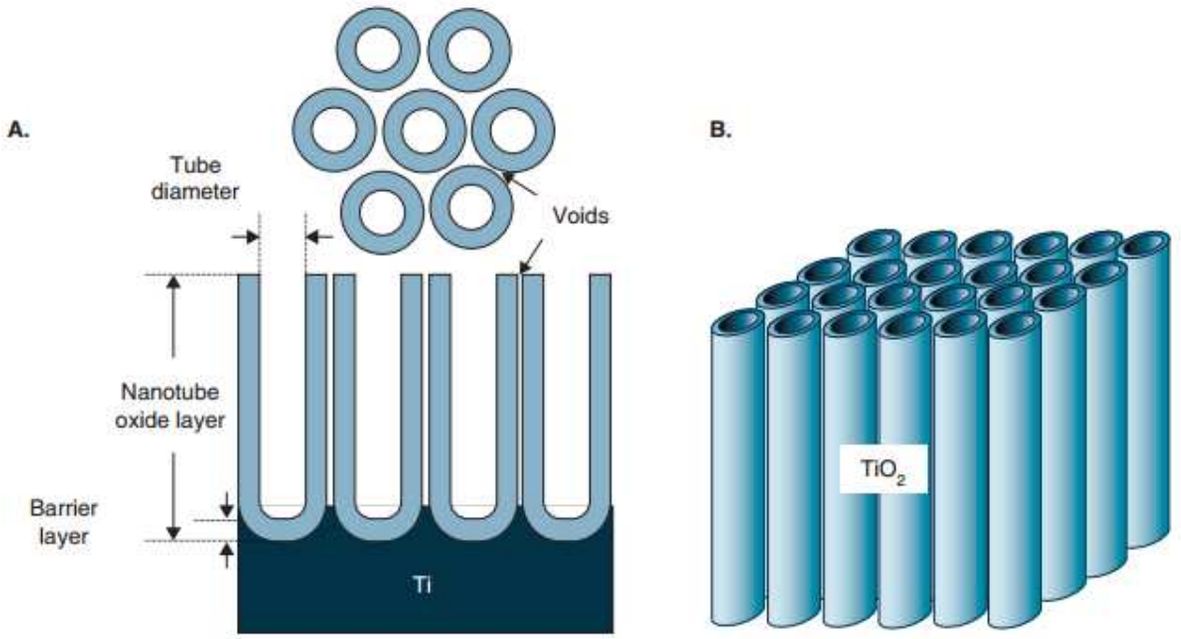

Figure 13. (a) Typical structures of nanotube titania fabricated by electrochemical anodization of titanium, (b) TiO_2 nanotube structures fabricated by electrochemical anodization in NH_4F/ethylene glycol electrolyte showing the cross-sectional image of self-supporting TiO_2 nanotube layer and the entire structure (nanotube film) not detached from Ti substrate (inset) [92].

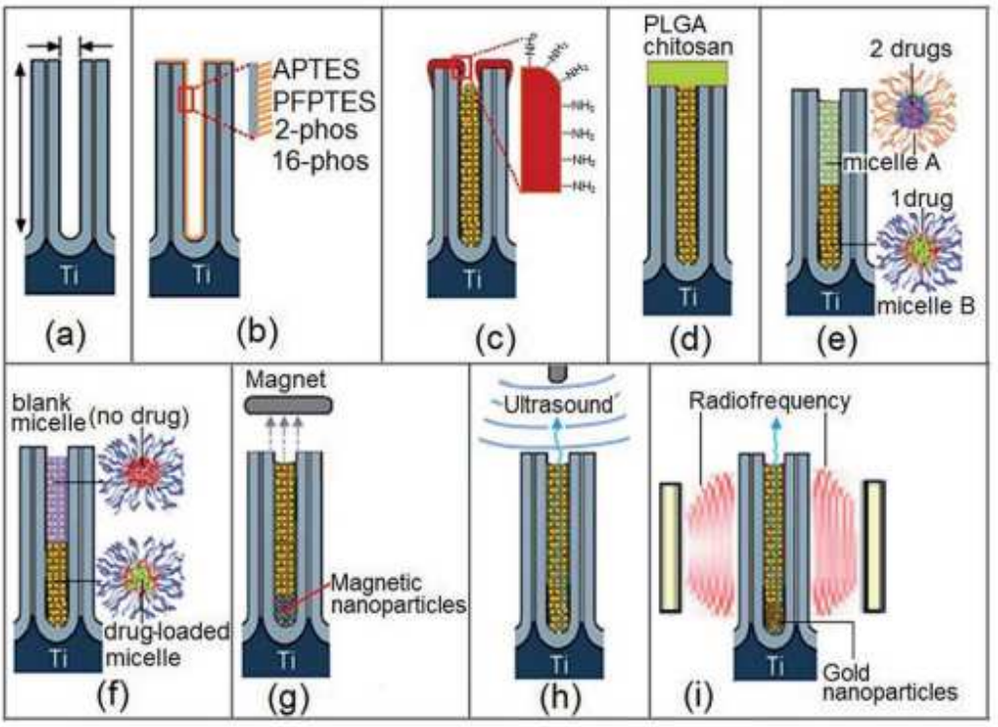

Figure 14. Schematic diagram showing different strategies developed by our group for controlling drug release from drug-releasing implants based on TNTs [90].

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gold nanoparticles stimulated by radiofrequency field [95] and magnetic nanoparticles under the influence of a magnetic nanoparticles that are under the influence of a magnetic field [96].

Properties of NAA and TNTs that can control drug release but non-degrade in vivo are not suitable for some specific applications, such as drug-releasing implants for treating eye-related diseases [90]. Other nanostructure materials including porous silicon can also be applied to develop biodegradable drug-releasing implants with improved capabilities for definite requirement of clinical applications [91].

3. Applications

3.1. Smart micelles for cancer

The ways of leveraging the enhanced permeability, ligand attachment, and specific receptor-ligand attachment could make micelles target to tumors. It is essential to increase drug bioavailability and the desired cytotoxic effect for the released drug from micelles carriers when micelles reach the tumor site. In order to realize the drug release triggered specifically at the tumor site, micelle structures should be designed as environmentally responsive systems, and such functionality is typically incorporated into micelles by introducing temperature/thermo-sensitive, pH sensitive, or ultrasound-activated polymers. As "smart micelles", it is known that micelles can dynamically change their physical properties in response to environmental triggers such as pH, temperature, and chemical species.

The micelle copolymer incorporates an ionizable component and a pH-dependent stability results from the pH sensitivity to micelles. The drug is released from the micelle when it encounters an acidic environment. The pH-sensitive micelles demonstrated the long residence time and improved half-life typical of micellar nanoparticles in animal models. Comparing to non-pH-sensitive micelles, the pH-sensitive micelles achieved a satisfying effect in tumors [97]. It reveals that the potential of pH-sensitive micelles could increase drug delivery to cancerous tumors.

An alternative way of constructing environmentally responsive micelles is to build temperature sensitivity into the micelle structure. The localized hyperthermia is used clinically to treat tumors, since the vasculature of tumor is more vulnerable to hyperthermia than normal tissue [98]. Temperature-sensitive micelles could be a part of a synergistic regimen, therefore, in which the raised temperature induces local drug release and kills tumor cells directly. It is also a common technique that makes use of a thermo-sensitive polymer with LCST behavior to design temperature-responsive micelles. A temperature increase above the LCST induces the entire system to be hydrophobic and precipitate out of the solution.

An important strategy for site-specific drug release from smart micelles is ultrasound activation. A number of mechanisms could promote the drug delivery, for example, a local temperature increase in tissues, the production of highly reactive free radical species that can accelerate polymer degradation, and the cavitation that increase the permeability of cell membranes [99]. Ultrasound was used to improve the antitumor efficacy of both free doxor-

ubicin and micelle-encapsulated doxorubicin in which micelles with ultrasound broke tumor growth an additional several days over micelles without ultrasound. Bio-distribution studies revealed that ultrasound not only increased the level of drug accumulation in the tumor, but also lowered the level of drug accumulation in the kidneys and heart [100–101]. Overall, ultrasound-sensitive micelles may have the capacity to both decrease side effects and increase chemotherapeutic effectiveness during tumor treatment.

In conclusion, micelles can be triggered by modulating temperature, pH, ultrasound, and light application. Well-designed micellar biomaterials for drug delivery could decrease mortality from cancers.

3.2. Ultrasound-sensitive drug delivery for theranostics

For smart therapies, ultrasound is a highly useful method that is already widely used clinically. In addition, ultrasound-triggered drug delivery vehicles can be combined with ultrasound contrast agents or microbubbles to create "theranostics" that incorporate both diagnostics via imaging and therapy via drug delivery [102]. Ultrasound-activated theranostics can improve the detection and treatment of cancerous tumors and cardiovascular pathologies such as atherosclerotic plaque [102].

It is demonstrated that ultrasound-triggered theranostics is a way of cancer treatment. For example, the mixtures of doxorubicin-loaded micelles with doxorubicin-loaded microbubbles were injected intravenously into mice bearing breast cancer tumors, and the agents were visualized at the tumor target site using ultrasound and were then degraded through ultrasound to release the doxorubicin at the tumor site. Ultrasound enhanced the intracellular uptake of doxorubicin by tumor cells and resulted in breast tumor regression in the mouse model. These results could have a significant impact on the treatment of other cancerous tumors via ultrasound-mediated visualization and drug delivery.

Ultrasound-triggered drug delivery vehicles can simultaneously detect areas requiring therapy and target drug delivery to these areas. The smart materials are in the early stages of development but hold potential for enabling rational treatment of diseases, improving clinical outcomes, and promoting a better quality of life for patients with complex chronic diseases.

3.3. Nanoporous implants for local drug delivery

TNTs are an alternative technology that can address some of the problems in dentistry as this is an economically affordable technology that can be easily implemented into dental implants [82]. In addition, the scope of TNT-based delivery systems can be extended to regenerative medicine and dentistry along with preventive therapy. An overview of several aspects relevant to TNT applications in dentistry, including studies of osteoblast adhesion to TNTs surfaces and its biocompatibility, release of specific drugs and silver nanoparticles and periodontium regeneration by the delivery of multiple growth factors inducing osteogenesis (Fig. 15) [82]. TNTs can also serve as a gene and DD carrier such as growth factors and stem cells, which can further enhance osseointegration and bone regeneration relevant to tooth implants [103].

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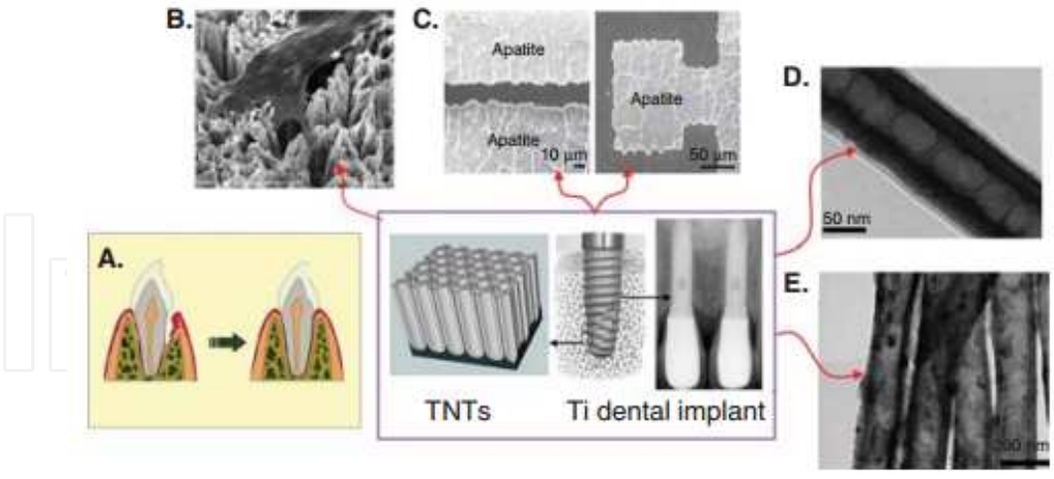

Figure 15. Schematic diagram summarizing the applications of TNTs in dentistry. (a) Periodontium problem and proposed regeneration by delivery of multiple growth factors inducing osteogenesis, (b) the adhesion of osteoblast cells to TNTs surface, (c) the growth of hydroxyapatite on TNTs, (d) the cross-sectional view of a single TNT revealing the drug sodium naproxen on the inside, and (e) anti-bacterial silver nanoparticles incorporated within TNT [82].

The encapsulation of sensitive drugs in nano-carriers such as polymer micelles were loaded in TNTs. Aw et al. put forward a prospective solution to both protect sensitive drugs and proteins from degradation and design TNT-based drug-releasing systems with an extended release capability [93]. Furthermore, based on the implementation of multi-drug payloads, polymeric micelles loaded with different drugs were loaded in the TNTs that are based on the formation of two or more immiscible layers of drug carriers that have opposite interfacial properties with hydrophobic and hydrophilic, which are used to generate a series of sequential release in a time controlled form [104].

Studies mentioned above in the discussion confirmed that NAAs and TNTs can be used for loading and releasing of wide range of therapeutics, with the ability to tune their drug releasing characteristics and provide multi-drug release of different drugs in different fashions. These approaches are aimed at achieving optimized drug dosage, release rate, and time needed for a broad range of specific therapies. The design of triggered drug-release from NAAs and TNTs using various external signaling sources (thermal, magnetic, electro-magnetic, ultrasonic, or mechanical activation) is an outstanding feature offering great perspectives and opportunities for combining NAAs and TNTs with sensing functions. NAAs and TNTs are shown to be very versatile in terms of their biomedical applications and can be applied as a new generation of smart implants and drug-delivery devices.

4. Summary

It is a highly desirable approach for effective therapeutic treatment to use smart materials to release drugs to a specific physiological environment. We have discussed the fundamental behavior and materials design associated with five stimuli-responsive systems based on pH,

temperature, magnetism, sound, and light. The stimuli-responsive systems are classified as "smart" materials, and each system includes two major strategies for the material design.

Based on our previous knowledge of degradation, release, and self-assembly, we introduce new concepts of excitation, cavitation, and magnetophoresis for strategies for materials design. A cooperative strategy of magnetophoresis, thermal phase change, and selected concept strategies of light excitation were stated in the chapter. A variety of smart material systems are currently in various stages of clinical development, such as ultrasound and magnetic hyperthermia systems, for treating cancer. It has been proven that drug-releasing systems provide better capabilities and performances than conventional therapies, offering alternative ways to deliver therapeutics effectively over different parts of the host body and reducing the side effects associated with excessive dosages of highly toxic drugs. Despite the successes described above, more exhaustive research must be carried out in order to make drug-releasing implants feasible for clinical applications.

Finally, it is worth stressing that the combination localized drug-releasing systems with other traditional treatments such as surgery, radiation, and systemic chemotherapy could provide more efficient clinical therapies for treating the most challenging and resilient diseases, such as cancer, with minimal drawbacks. What's more, it is expected that the integration of TNT implants with sensors, microchips, and development of advanced triggered drug release can come true in the future. In conclusion, it is right that smart materials were used to study the drug delivery system, and materials design involved with several stimuli-responsive systems such as pH, temperature, magnetism, light, and sound. In addition, smart material systems are currently in various stages of clinical development based on ultrasound and magnetic hyperthermia systems for treating cancer.

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