Mechanical Force-Triggered Drug Delivery

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ABSTRACT: Advanced drug delivery systems (DDS) enhance treatment efficacy of different therapeutics in a dosage, spatial, and/or temporal controlled manner. To date, numerous chemical- or physical-based stimuli-responsive formulations or devices for controlled drug release have been developed. Among them, the emerging mechanical force-based stimulus offers a convenient and robust controlled drug release platform and has attracted increasing attention. The relevant DDS can be activated to promote drug release by different types of mechanical stimuli, including compressive force, tensile force, and shear force as well as indirect formats, remotely triggered by ultrasound and magnetic field. In this review, we provide an overview of recent advances in mechanically activated DDS. The opportunities and challenges regarding clinical translations are also discussed.

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1. INTRODUCTION

Drug delivery systems (DDS) are of paramount importance to enhance the treatment efficacy of medications.^{1–4} The last two decades have witnessed great progress in sustained drug delivery.^{5–11} Nevertheless, there are many clinical situations requiring more than a zero-ordered, continuous drug release profile, but an on-demand control of therapeutics. Dosage-, spatial-, and temporal-controllable drug release, which can target diseased tissue, enhance uptake efficiency, prolong action time, and improve bioavailability of agents, has been heavily pursued in recent years.^{12–22} Such DDS can respond to either endogenous environmental conditions, including pH,^{23–28} redox,^{29–32} hypoxia,^{33–35} ATP,^{36–39} glucose,^{40–43} and enzymes,^{44–50} or exogenous signals such as temperature,^{51–53} light,^{54–57} magnetic field,^{58–61} and electric current.^{62–64}

Mechanical force, with a subclassification of compressive, tensile, and shear forces (Figure 1a),^{65,66} is ubiquitously achieved in the body or easily applied externally.⁶⁷ Force sources range from intrinsic compression/stretching via joint movements to internal shear force in vascular systems, as well as exterior acoustic and magnetic force remotely applied through the skin (Figure 1b). Easy access of mechanical stimuli facilitates treatment in a variety of conditions with convenient commands. Especially in occasions of emergence, such as heart attack and hypoglycemia, the mechanical force-mediated trigger could

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Figure 1. Different forms of mechanical force. (a) Three main types of mechanical force. (b) Mechanical force can be typically obtained in the human body or induced externally by ultrasound or magnetic field.

Figure 2. Schematic illustration of diverse mechanical force-triggered drug delivery systems. (a) Compressive or tensile force can induce drug release. (i) Physically loaded drugs can be released by deformation of carriers under compression. (ii) Tensile force can deform mechanoresponsive particles embedded in the matrices and release the encapsulated drugs. (iii) Materials can be degraded upon exposure to related enzymes under strain. (iv) Compressive force can break the chemical bond. (b) Drug release can be triggered by shear force caused by (i) dissociation of aggregates or (ii) deformation of particles. (c) Ultrasound can facilitate drug release by cavitation or radiation. (d) External magnetic field can trigger drug release by deforming ferrogels.

enable prompt delivery of therapeutics by patients in a self-administered manner. Moreover, compared to chemical or biological triggers, application of mechanical force provides a relatively predictable control in direction and an adjustable magnitude management toward precision release of therapeutics. In addition, patient-controlled drug delivery may potentially increase patient satisfaction compared with intermittent administration, since the patients themselves can conveniently regulate the release dosage and timing of the drug.

Collectively, mechanical force is a promising candidate to realize controlled drug release.^{67,68} To be specific, the compressive and tensile forces can be readily obtained by using hands or from simple daily motions, such as tension in muscles, tendons, and bone joints, as well as compression in cartilage and bones.⁶⁹ Therefore, DDS integrated with mechanoresponsive modality offers self-administration therapy without requiring additional instruments, while the shear force generated by blood flow in vascular systems⁷⁰ holds promise for noninvasive

Figure 3. Mechanically triggered drug release from thermoresponsive self-heating hydrogel. (a) Illustration of drug release from thermoresponsive nanoparticle-loaded hydrogel with dissipation as an internal heat source. Thermoresponsive nanoparticles (blue dots) and drug (red dots) are loaded inside the hydrogel (gray). (b) Temperature changes after cyclic compressive load. (Top) Temperature increases to 37 °C after 5 min loading from initial temperature (36 °C). (Bottom) Temperature increases from initial temperature (34 °C) to 34.7 °C after 5 min loading. (c) (Top) Temporal-controlled release of xylene cyanol FF triggered by dissipation properties of the hydrogel. (Bottom) Effect of nanoparticles on xylene cyanol FF release during mechanical loading. Reprinted with permission from ref 79. Copyright 2014 Elsevier.

cardiovascular drug delivery.^{71,72} The design features of formulations or devices based on the two directly interacting triggers generally involve physical deformation or mechanochemical changes of drug carriers. On the other hand, ultrasound, as a highly efficient and noninvasive trigger, has been widely explored in the drug delivery field. The longitudinal force produced by ultrasound can induce hyperthermia, cavitation, and radiation, resulting in destruction of drug carriers and drug release by either thermal or nonthermal functions.^{73–75} Additionally, magnetic force induced by a magnetic field can activate the magnetoresponsive components. Integrated with thermosensitive materials or flexible matrices, the activated magnetoresponsive particles can achieve a controlled release of cargoes by disassociation or morphology variation.⁷⁶

This review surveys the mechanical force-triggered DDS, mainly classified as direct interaction forces, including compressive, tensile, and shear forces as well as induced forces generated by other stimuli like ultrasound and magnetic field (Figure 2). We will describe representative examples of each stimulus signal, focused on the latest examples. The opportunities and challenges associated with clinical translations will also be discussed.

2. COMPRESSIVE/TENSILE FORCE-TRIGGERED DRUG DELIVERY

Compressive or tensile force-responsive DDS are mostly based on stretchable materials, such as hydrogels and elastomers.^{68,77,78}

Many formulations and devices, including nanoparticles and microgel depots, have been exploited to be hybridized into a flexible substrate to achieve on-demand release in response to mechanical stimuli. Typical mechanisms for releasing entrapped agents from systems are based on either physical deformation of carriers or chemical changes of materials, such as breakage of chemical bonds.

2.1. Deformation

Thermosensitive hydrogels have been extensively utilized for spatiotemporal-controlled drug delivery.¹⁵ However, an external heat source is usually required to activate the release. Pioletti and co-workers⁷⁹ attempted to employ the dissipative properties of hydrogel as an internal heat source (Figure 3a). The hydrogel matrix, which was formed with thermoresponsive nanoparticles, produced self-heat after a cyclic mechanical loading for 5 min, causing a temperature increase from 36 to 37 °C (Figure 3b). The temperature increase led to shrinkage of the nanoparticles, followed by contents release after 5–8 min (Figure 3c). This hybrid hydrogel with high dissipation holds promise in the delivery of growth factors by mechanical activation. Mooney and

Figure 4. Mechanoresponsive hydrogels based on block copolymer micelles (BCMs). (a) Synthesis of BCM-PAAm hydrogels. (b) Cross-sectional transmission electron microscopy (TEM) images and schematics of unstretched, stretched, and recovered BCM-PAAm gels. (c) Effects of (i) periodic stretching forces on (ii) release rate and (iii) cumulative release of pyrene from BMC-PAAm gels. Reprinted with permission from ref 82. Copyright 2012 Royal Society of Chemistry.

co-workers⁸⁰ developed a controlled delivery system based on synthetic extracellular matrices (ECMs). The natural ECMs of tissues, as depots of growth factors, are responsive to many physiological signals and can correspondingly release factors to surrounding cells. To mimic the behavior of natural ECMs, they designed a hydrogel with reversible binding to drugs. The reversible chemical binding was aimed at overcoming the limited sensing period, since physically loaded hydrogel usually cannot respond to compression after several release cycles due to rapid depletion of drugs from the hydrogel.⁸¹ In this situation, unbound vascular endothelial growth factor (VEGF) was released upon each compression. However, with re-equilibration of bound VEGF turning into unbound VEGF, the hydrogel could continuously control the release of VEGF via compressive force.

Chemically cross-linked hydrogels integrated with mechano-sensitive block copolymer micelles (BCMs) were reported to have the capability to modulate drug release by mechanical force. Jia and co-workers⁸² applied drug-loaded BCMs with reactive handles as the microscopic cross-linkers instead of traditional molecular cross-linkers for poly(acrylamide) (PAAm)-based networks (Figure 4a). The restricted BCMs provided the mechanoresponsive elements for BCM-PAAm gels, and the force-induced deformation of BCMs led to drug release upon strain application. At a strain of 200%, the BCMs presented a more elongated appearance with an average dimension ratio of 1.53 ± 0.23 (Figure 4b). Furthermore, the BCMs returned to their original morphology after removal of the external force due to reversible structural deformation. Strain-dependent shape alternation could effectively control the drug release rate from the BCM-cross-linked gel (Figure 4c). The same group also prepared hyaluronic acid (HA) gels covalently embedded with

dexamethasone (DEX)-loaded BCMs to control inflammation within mechanically stressed tissues.⁸³ The HA gels markedly reduced the initial burst release and allowed sustained release in a stress-dependent manner, which offers an alternative strategy to take advantage of mechanical stress to promote tissue repair during the wound-healing process.

Jeong and co-workers⁸⁴ developed a strain-controlled system that released molecules from an array of stretchable microcapsules based on a poly(dimethylsiloxane) (PDMS) elastomer substrate using a hydrogel pattern fabrication technique (Figure 5a). The mechanical strain applied on the substrate led to deformation of the polystyrene (PS) microcapsules (Figure 5b), followed by pumped-out preload molecules. A strain of 2.5% on the substrate reduced the microcapsule volume by 17%, while a higher strain of 7.5% decreased the volume by 98%. The dosage of released molecules was highly dependent on the degree of strain (Figure 5c). The deformed PS capsules could return to their initial shape and volume upon release from stretching, which favored repeatable drug diffusion from the patch (Figure 5d).

In another example, Di et al.⁸⁵ recently exploited a multipurpose wearable elastomer that could mechanically promote release of therapeutics to achieve “elastic drug delivery” (Figure 6). The stretchable elastomer was integrated with microgel depots that contained drug-loaded nanoparticles. The drugs could be temporarily stored in the microdepots. When stretching was applied, the drug could continuously diffuse out due to deformation of the microgels, which was attributed to the enlarged surface area for diffusion and Poisson’s ratio-induced compression toward the microdepots. Therefore, an on-demand drug delivery can be realized by convenient daily body motion.

Figure 5. (a) Schematic of preparation of arrayed microcapsules. (b) Changes in the dimensions of microcapsules observed by AFM images and cross-section analysis: (i) before and (ii) after stretching. (c) Release behavior of (1) FITC-labeled dextran and (2) rhodamine B under different strains. (d) Amount of rhodamine B released upon stretching after consecutive stretching and release events. Repinted with permission from ref 84. Copyright 2011 Wiley-VCH.

On the other hand, pulsating release can be achieved through intentional administration, which allows patients to control the release timing and dose of drug on their own. Furthermore, when combined with microneedle arrays, this device could be utilized to regulate blood glucose levels (BGLs) by on-demand transcutaneous insulin delivery for type 1 diabetic mice. After several cycles of stretching and releasing, the BGLs of mice quickly reduced to a normoglycemic level within half an hour. Meanwhile, pulsating regulation of BGLs was observed when strain was applied at 4 h intervals. With this technology, diabetic patients can easily maintain BGLs via simple joint movement instead of traditional, painful insulin injection. Kim et al.⁸⁶ also designed a stretchable reservoir-based patch-type system for smart control of drug delivery. The liquid drop-based reservoir loaded in a PDMS elastomer underwent a decrease in volume and subsequently released the drug when the substrate was deformed by external strains. Furthermore, the empty rubber reservoir was readily refilled with a microsyringe to achieve long-term release.

Besides volume change, crack propagation generated by an applied strain can also be utilized to trigger drug release. On the basis of this concept, Grinstaff and co-workers⁸⁷ reported a superhydrophobic polymer composite for a stretch-triggered DDS (Figure 7). In their device, the drug-loaded hydrophilic mesh core was encased by two superhydrophobic coatings with different mechanical properties. This mismatch led to mechanical failure of the coatings under applied tension, and the resulting crack propagation allowed the cargo to diffuse from the mesh core. The localized ex vivo study of this stretch-responsive device

incorporated with a metal esophageal stent indicated that the model drug could be released to the esophageal epithelial mucosa layer from the expanded system.

Lavalle and co-workers⁸⁸ also developed a multilayer film with a mechanotransductive surface for reversible biocatalysis activation. The multilayer film, made by a layer-by-layer (LbL) method, consisted of a poly(L-lysine)/hyaluronic acid (PLL/HA) film as a reservoir, which was loaded with alkaline phosphatase (ALP) enzymes and capped with a poly-(diallyldimethylammonium)/poly(styrenesulfonate) (PDADMA/PSS) film as a barrier (Figure 8a). ALP, a hydrolase enzyme, can dephosphorylate fluorescein diphosphate (FDP). Upon stretching, the loaded ALP was exposed through the barrier; then the biocatalysis was switched on and the progress was shown in confocal fluorescent images (Figure 8b). Besides triggering of biocatalysis via stretching, biocatalytic activity can also be controlled by the thickness of the barrier film. With relatively thicker barrier layers, fewer enzymes could be brought to the substrates, resulting in a lower jump of fluorescence (Figure 8c). Reversible stretch-triggered biocatalytic activation was achieved in this LbL system. The same group further applied similar biodegradable polyelectrolyte multilayers as a mechanoresponsive drug delivery platform.^{89–91} Paclitaxel was embedded in the PLL/HA reservoir, capped with a poly(allylamine hydrochloride)/poly(styrenesulfonate) (PAH/PSS) film as the barrier. When immersed in trypsin solution, PLL inside the reservoir was cleaved by trypsin once the PAH/PSS barrier was opened by mechanical stretch. Therefore, the entrapped

Figure 6. Stretch-responsive wearable elastomer films for controlled drug delivery. (a) Schematic of tensile strain-activated drug release. (b) Photography and SEM image of prepared microneedle (MN) patch, and its application on streptozotocin (STZ)-induced type 1 diabetes mice. (c) Elastomer film for anti-cancer, anti-inflammatory, and diabetes therapy. (Top) Normalized HeLa tumor spheroid sizes and morphologies (insets) before treatment, without treatment, and treated with media from DOX-formulated devices after 10 cycles of stretching or without stretching after 3 days. Scale bars: 100 μm . (Middle) Antibacterial assay using solutions containing released ciprofloxacin after 100, 400, and 1000 cycles of finger flexions. Passive released ciprofloxacin was included as a control. (Bottom) BGL change of diabetic mice after (1) wearing devices with 10 cycles of 50% stretching with an interval of 4 h by hand (red line), (2) wearing devices without stretching (passive) (black line), (3) being subcutaneously injected with insulin solution with the same dose as applied into the microdepots used in (1) and (2) (blue line), and (4) being subcutaneously injected with phosphate-buffered saline (PBS) solution only (green line) ($n = 4$). Reprinted with permission from ref 85. Copyright 2015 American Chemical Society.

paclitaxel was released from films as a result of biodegradation of PLL/HA film in a stretch-controlled manner.

2.2. Mechanochemical Change

Mechanical force-induced chemical changes, including isomerization, ring opening, chain scission, and other intermolecular interactions can be useful in many biomedical applications, such as self-healing, actuators and sensors, as well as DDS.^{67,68,78,92,93}

Larsen and Boydston⁹⁴ developed a mechanochemical-sensitive elastomeric matrix embedded with mechanophores that had the capacity to load and release a furan derivative in response to physical stress (Figure 9). The mechanophore with an oxanorbornadiene group could be activated upon mechanical stress. During this process, the applied stress directed the bond-bending motion to further break bonds orthogonal from the polymer backbone through retro [4 + 2] cycloaddition. Consequently, with the flex-activated mechanophore inside the cross-linked polyurethane network, the elastomer performed in a force-activated manner. It could release small molecules over multiple load cycles, which showed the potential of sequential release in an on-demand feature. In another work, Izawa et al.⁹⁵ reported a β -cyclodextrin (CyD) cross-linked alginate gel for

patient-controlled drug delivery via mechanical regulation of host–guest interactions. In this study, the CyD moiety was chosen as the mechanophore, which underwent deformation upon compression and released the entrapped ondansetron (ODN) due to the variation in inclusion capability of CyD.

The previously explored examples indicate the potential of compressive or tensile force-responsive materials for controlled drug release by simple bodily motion during daily life. The tensile and compressive forces can be conveniently obtained without additional external instruments. However, more robust dosage control is required for further clinical applications.

3. SHEAR FORCE-INDUCED DRUG DELIVERY

Hemodynamic shear force, known as a crucial parameter of vascular pathophysiology, is a frictional drag force imposed by blood flow.⁹⁶ Obstruction of normal blood flow results in a dramatic increase in shear stress (1–2 orders in magnitude), which poses a threat to millions of people around the world for stroke and atherosclerosis.⁹⁷ Specifically, shear stress in normal vessels generally remains below $\sim 70 \text{ dyn/cm}^2$, while a 95%

Figure 7. Stretch-triggered drug delivery based on superhydrophobic polymer composites. (a) Schematic of preparation and mechanism of tension-responsive system. The electrospayed barrier coating (yellow) prevents unwanted drug release from the core (green). (b) SEM image of device cross-section and advancing water contact angles for electrospayed hydrophobic (top, PCL) and superhydrophobic (bottom, PCL:PGC-C₁₈ 1:1) coatings. (c) Contrast-enhanced microcomputed tomography (mCT) images observed before and after tensile strain application and sequential images during stretching along the x -axis. (d) Release profiles of model hydrophilic dye from the tension-responsive system via crack propagation. Reprinted with permission from ref 87. Copyright 2016 Wiley–VCH.

constricted stenotic or thrombosed artery possesses stress above 1000 dyn/cm².^{98–100}

Although there are a multitude of stimuli-responsive DDS, covering redox, temperature, and external signals,^{101,102} as well as many formulations such as liposomes and micelles,^{103–106} it still remains challenging to construct on-demand drug delivery for cardiovascular diseases.^{107,108} Given the distinguishable shear force in vascular fluid, shear-sensitive DDS may be an emerging outlet for noninvasive therapy of vascular-related diseases.^{109–111} In this section, shear force-promoted DDS will be reviewed that are based on either disaggregation or deformation of drug carriers.

3.1. Disaggregation

Platelets, components in blood with a long circulation time, aggregate and coagulate to cease bleeding during blood vessel injuries.¹¹² Once shear force increases, platelets sense this change and respond by activating and adhering to the vascular wall at these narrowed sites.⁹⁹ Inspired by the physiological response of platelets, Ingber and co-workers⁷² designed microscale aggregates of nanoparticles to mimic platelets, which could remain intact in normal physiological flow. However, they broke up into individual nanocomponents once activated by high shear force and then adhered and accumulated at stenotic regions. The disaggregated nanoparticles were exposed to much lower drag force compared to the microscale aggregates, allowing for localization and accumulation on endothelial cells (Figure 10). On the other hand, an increase in total exposed surface area of the particles further facilitated release of the payload that was immobilized on the nanoparticle surface. In vivo experiments implied that the microaggregates coated with tissue plasminogen activator (tPA) rapidly dissolved the clot in 5 min in a mesenteric injury model (Figure 10c) and remarkably enhanced the survival rate up to 80% in another fatal mouse pulmonary embolism model.

Most recently, Chen et al.¹¹³ took advantage of shear force as a weapon for antithrombus therapy (Figure 11a). Heparin, an anticoagulant drug, was formed into nanoparticles via hybridization with polypeptide PLL. These positively charged heparin nanoparticles (cNPs) were then absorbed to negatively charged red blood cells (RBCs) via electrostatic attraction for long-term circulation. The large size of RBCs prevented the cNPs from extravascular diffusion and benefited the drug's intravascular release. On thrombus sites, the shear stress significantly increased due to narrowing of the blood vessels, which led to site-specific release of cNPs from RBCs. Scanning electron microscopic (SEM) images indicated that, with higher shear stress (10 Pa vs 1 Pa), more desorption of cNPs from RBCs was observed after 24 and 48 h (Figure 11b). With the help of RBCs as the drug delivery vehicle, the drug could be delivered to target destinations with a prolonged circulation time.

3.2. Deformation

Another strategy is to utilize shear force-induced deformation of carriers to release therapeutics. Budtova and co-workers¹¹⁴ first presented a shear-induced controlled release from hydrogels and microcapsules. They observed the solvent release from either hydrogels or microcapsules upon exposure to silicon oil flow, and over 30% deformation was generated by the flow shear stress. Their results showed that there was a threshold for shear stress to produce deformation. Once above the critical point, the particles would break up and release the cargo inside, which indicates that shear force-induced release is feasible.¹¹⁵ Furthermore, they designed a microgel that could release contained fullerene by the function of shear and swelling.¹¹⁶ Holme et al.⁷¹ demonstrated that lenticular-shaped vesicles could sense elevated shear stress (Figure 12a). The lenticular liposome was prepared from the artificial phospholipid Pad-PC-Pad through an extrusion method (Figure 12b). The two amide bonds of lipid can increase the stability of the polar region on the membrane via hydrogen

Figure 8. Stretch-activated biodegradation of LbL reservoir films. (a) Mechanism of stretch-activated biocatalysis: (i) Catalysis is off when the film is unstretched. (ii) After stretching, enzymes are exposed and the biocatalysis turns on. (iii) Released phosphate ions inhibit enzymes in a feedback manner. (iv) After rinsing, the enzymes are reactivated for further catalysis. (b) Confocal microscope section (x,z) images of silicone sheets with multilayer films loaded with ALP enzymes. (c) Biocatalytic activity of reservoir/barrier films triggered by stretching for three different barrier thicknesses (m = number of bilayers). α = 0% (unstretched state) and α = 110% (stretched state). Reprinted with permission from ref 88. Copyright 2009 Nature Publishing Group.

bonds. The Pad-PC-Pad substitution at 1- and 3-positions of the original glycerol backbone was attributed to directional hydrogen-bond formation in the polar region (Figure 12d). The lenticular shape of the Pad-PC-Pad liposomes led to preferential breaking points along the equator upon application of shear force and subsequent transient leakage of trapped cargos. With a 100% Pad-PC-Pad component, the vesicles were more stable and showed specific release in the high-shear-stress constricted-artery model (Figure 12c). The results from an in vitro cardiovascular model showed that almost 30% more dye was released from lenticular vesicles when flowing through a constricted tube compared with a patent tube. Further in vivo studies need to be conducted. If successful, this observation might be applied in vascular-targeted treatment. Mitragotri and co-workers^{117,118} also designed biomimetic platelets for targeted drug delivery to vascular injuries. Platelet-like nanoparticles (PLN) were synthesized by the LbL approach (Figure 13a). Specifically, complementary layers of poly(allylamine hydrochloride) (PAH) and bovine serum albumin (BSA) were coated on a template

particle, which is a PS nanoparticle.¹¹⁸ After removal of the template core, the PAH/BSA multilayer shell collapsed into a flexible particle and could change its shape in response to shear force (Figure 13b). It was found that small particles were more likely to adhere and aggregate under high-velocity flow in a microfluid model, which was due to the weaker shear detachment force experienced by relatively small particles. PLNs with 200 nm diameter covered more surface area of the fluid channel than either spherical or disc-like particles of the same size, which mainly contributed to their flexible shape under shear. Moreover, with targeted peptide modification on their surfaces, the PLNs exhibited significantly higher adhesion to injury sites under shear stress in an in vitro wound model (Figure 13c). And these functional peptides, which were collagen- and von Willebrand factor-binding peptides (CBP and VBP) and fibrinogen-mimetic peptide (FMP), could simultaneously bind to activated natural platelets and injured endothelial sites to amplify platelet aggregation for hemostasis. They showed that the peptide-

Figure 9. (a) Schematics of flex activation in an oxanorbornadiene-based mechanophore. The oxanorbornadiene group is released upon mechanical stress as a result of breaking bonds orthogonal from the polymer backbone through retro[4 + 2] cycloaddition. (b) Synthesis of polyurethane networks. Reprinted with permission from ref 94. Copyright 2014 American Chemical Society.

modified PLNs could reduce the tail bleeding time of mice by ~65% in a tail amputation test (Figure 13d).

Besides the shear-induced deformation of drug carriers, shear force can also be employed to temporarily disrupt cell membranes for intracellular drug delivery.¹¹⁹ The Langer and Jensen laboratories¹¹⁹ designed a microfluidic device that can deliver a range of materials, including macromolecules, into cells (Figure 14a). A relatively narrow channel (30–80% smaller than cell diameter) was fabricated in the device to produce compression and shear force. When cells, such as embryonic stem cells and immune cells, passed through the constricted channel, transient holes on the cell membrane were generated, which further enabled the diffusion of surrounding cargos across the membrane. Moreover, it demonstrated 10-fold enhanced delivery efficiency of transcription factors compared to cell-penetrating peptides (Figure 14b). Besides application in cell reprogramming, this technique also enabled direct delivery of quantum dots, carbon nanotubes, and proteins to cell cytosol for probe-based sensing (Figure 14c). The diffusion delivery mechanism was proved and characterized by monitoring the delivery kinetics, which indicated 70–90% cargo delivery within the first minute (Figure 14d). The membrane disruption-based mechanism offers flexibility in delivery, since it does not rely on exogenous materials or endocytotic pathways. Furthermore, unlike current existing methods, the microfluidic device showed no damage to either payloads or cells, and hence improved biological activities. Such capabilities of the technique expand its prospects in therapeutic applications, and a company (SQZ Biotech) was established on the basis of this concept, aiming to improve the CellSqueeze platform for efficient cell therapy.

Thereafter, relevant research on interactions between microfluid and platelet mimetics or vesicles was conducted to promote shear-responsive DDS.^{120–124} PEG [poly(ethylene glycol)] coating, multilamellar shell, and surface charge all affect the stability and uptake efficacy of carriers. The influence of platelet endothelial cell adhesion molecules (PECAMs) on shear stress differently regulated endothelial uptake of nanocarriers was also evaluated.^{125,126} These targeting agents, including PECAMs and glycoproteins, were adhered to nanocarriers for targeted endothelial drug delivery.^{127,128}

The research discussed above strengthens the feasibility of shear force-induced drug delivery for cardiovascular disease treatment. Shear force-sensitive drug carriers are able to achieve spatial- and temporal-controlled release in a noninvasive manner. However, their clinical application is still limited due to several challenges such as short circulation time and safety issues.

4. ULTRASOUND-ACTIVATED DRUG DELIVERY

Ultrasound is a sound wave with frequencies above 20 kHz.¹²⁹ It can generate longitudinal force/pressure that induces mechanical force or/and local heating in a noninvasive manner.¹³⁰ Ultrasound has been widely used for therapeutic purposes since the beginning of the 20th century, including tissue ablation, kidney stone shattering, imaging, liposuction, and transdermal drug delivery.^{131–135}

Ultrasonic waves can map the location and promote drug release from carriers by causing localized hyperthermia, acoustic cavitation, or/and acoustic radiation forces as designed.¹³⁰ The acoustic force can change the permeability or absorption of tissues and “push” the drug into the cells or across the tissue. Furthermore, it can also change the chemical properties of

Figure 10. Shear force-triggered system for targeted delivery to obstructed blood vessels. (a) Preparation of platelets mimicking microscale aggregates. (b) Schematic of hemodynamic shear targeting to stenotic vessels by use of platelet mimetics. (c) Change of clot size after injection of tPA-coated shear-activated nanotherapeutics (SA-NTs) (left) compared to PBS treatment (right) in a partially occluded mesenteric artery. Scale bar, 100 μm. Reprinted with permission from ref 72. Copyright 2012 American Association for the Advancement of Science.

materials. In 1989, Kost et al.¹³⁶ reported that ultrasound could facilitate the degradation process of polymer materials and subsequently enhance the release of incorporated substances. Afterward, drug-loaded microbubbles were illustrated to be intentionally ruptured by ultrasound, which presented effective spatiotemporal control of drug release with a nondestructive feature.¹³⁷ To date, a wide range of drug carriers, such as liposomes, micelles, nanoparticles, and micromotors, have been explored for ultrasound-triggered drug delivery.^{75,138–140}

Ultrasound with frequency between 20 and 100 kHz is defined as low-frequency ultrasound (LFUS), which is usually used to induce sonophoresis and affect drug carriers such as liposomes.^{132,141,142} LFUS was also applied to temporarily enhance permeability of skin for transdermal drug delivery.^{143,144} Mitragotri et al.^{145,146} and others¹⁴⁷ reported that large molecular proteins, such as insulin (~6 kDa) and erythropoietin (~48 kDa), as well as other drugs can be transported across the skin due to the disorganization of tissue induced by LFUS. Recently, it was reported that LFUS could locally promote drug delivery in gastrointestinal systems.¹⁴⁸ In both mouse and pig models, it showed treatment efficacy without significant safety issues.

High-frequency ultrasound (HFUS), which has a frequency greater than 1 MHz, is used to trigger oscillations in microbubbles.¹⁴⁹ Additionally, it has been shown that the

acoustic pressure associated with cavitation derived from ultrasound waves can induce carrier destruction, drug release, and temporary increase in membrane permeability, thus facilitating the cellular uptake of therapeutic agents.^{150–152}

The following sections will mainly focus on nonthermally activated drug delivery. Since microbubbles have been widely discussed in a number of reviews,^{74,153–155} here we briefly introduce the most recent progress.

4.1. Microbubbles

Microbubbles, which are gas-filled spheres dispersed in aqueous medium with an average size between 1 and 8 μm, have been widely employed in ultrasound imaging as ultrasound contrast agents.^{74,156} The bubbles experience oscillations under a HFUS field when driven by a frequency near resonance and even can end up with a rupture.^{137,157} By decreasing the threshold for cavitation, the collapse of drug-encapsulating microbubbles can also be used in ultrasound-activated drug delivery (Figure 15).¹⁵⁸ Furthermore, Dayton and co-workers¹⁵⁹ discovered that microbubbles serve as cavitation nuclei and can enhance ultrasound energy deposition in cells and tissues, thus facilitating intracellular drug transport by disruption of their membranes.^{160,161}

Recently, numerous studies have been reported on the application of microbubbles for drug or gene delivery, particularly in brain tumor in situ/targeted treatment and

Figure 11. Shear force-triggered system for antithrombus therapy. (a) Schematic of preparation of cNPs adsorbed to red blood cells (RBC-cNPs) and mechanism of shear-induced release of cNPs. (b) SEM images showing shear force-triggered desorption of heparin/polypeptide hybrid nanoparticles cross-linked with disulfide bonds (cNPs) from red blood cells (RBCs) as a function of time. (A) RBC-adsorbed cNPs (RBC-cNPs) under static conditions. (B, C) RBC-cNPs under 10 Pa shear-stress treatment for (B) 24 and (C) 48 h. (D, E) RBC-cNPs under 1 Pa shear-stress treatment for (D) 24 and (E) 48 h. Scale bar = 4 μm. Reprinted with permission from ref 113. Copyright 2016 Wiley–VCH.

cardiovascular therapy.^{73,155,159,162} Effective drug delivery to brain is limited due to the blood–brain barrier (BBB) and the blood–tumor barrier (BTB).^{163–165} Focused ultrasound has shown to be capable of transiently opening the BBB in the presence of microbubbles.^{166–168} To date, a large number of therapeutic agents have overcome the barrier and have been delivered into the brain or a brain tumor.^{169,170} Yeh and co-workers¹⁷¹ designed superparamagnetic iron oxide nanoparticles conjugating with doxorubicin-loaded microbubbles (DOX-SPIO-MBs) for imaging-guided drug delivery to brain tumors (Figure 16). It was found that the superparamagnetic/acoustic properties of DOX-SPIO-MBs were suitable for imaging. Ultrasound concurrently induced BBB opening and promoted drug delivery, which enhanced the brain tumor treatment effect. They further modified targeting ligands on microbubbles to facilitate directing chemotherapeutic agents to regions of tumor vasculature.¹⁷² Kovacs et al.¹⁷³ also demonstrated that microbubbles might serve as an effective method for glioblastoma multiforme (GBM) treatment after investigating ultrasonic microbubble therapy in two GBM mouse models.

Researchers have also attempted to apply ultrasound-triggered microbubbles in ovarian cancer and prostate cancer treatment, as well as in lymph nodes and in other tumor therapy.^{174–176} Attributed to the spatial and temporal control of drug delivery that is feasible by ultrasound, microbubbles can aid in a variety of diseases therapy besides cancer. For example, drugs could be delivered to the inner ear through the round window membrane, resulting in 3.5–38 times higher delivery by ultrasound than that by spontaneous diffusion.¹⁷⁷ In addition, genetic drugs could be specifically delivered to the skeletal muscles of mice.¹⁷⁸

Besides drugs encapsulated in microbubbles, some researchers developed a new formulation with drug-loaded nanocarriers coated on microbubbles. As reported in the literature, nanoparticles have been linked to microbubbles through avidin–biotin interaction; however, the washing steps may influence the stability of the microbubbles.^{179–181} On the other hand, self-

Figure 12. Shear force-responsive lenticular vesicles for targeted drug delivery. (a) Mechanism of shear force-activated drug delivery. (b) Cryo-TEM of Pad-PC-Pad vesicles. (c) Release behavior of L-α-phosphatidylcholine (eggPC) vesicles with different Pad-PC-Pad at 37 °C before (untreated) and after one pass only through either healthy or constricted arterial models. (d) Chemical structure of phospholipid Pad-PC-Pad. Reprinted with permission from ref 71. Copyright 2012 Nature Publishing Group.

Figure 13. (a) Synthesis of platelet-like nanoparticles (PLNs). (b) SEM images of (i) sacrificial 200 nm spherical polystyrene (PS) templates, (ii) PAH/BSA-coated PS templates, and (iii) final PLNs. Scale bars = 200 nm. (c) In vitro binding of PLNs with and without functional peptides to targeting surface and nontargeting BSA surface (control) under shear stress. (d) Bleeding time was reduced after treatment of PLNs in a tail amputation model in mice. Reprinted with permission from ref 118. Copyright 2014 American Chemical Society.

assembled microbubbles loaded with liposome have recently shown their potential as a promising drug delivery carrier to cancer tissues, which could eliminate cancer cells with a very low dose of therapeutics ($0.5 \mu\text{g/mL}$ DOX) as demonstrated by De Smedt and co-workers.¹⁸² Drug-loaded liposomes, formed with functionalized (SPDP-)PEG-lipids, were conjugated to the microbubbles containing the hydrophobic perfluorobutane (C_4F_{10}) gas through thiol–maleimide linkages. Approximately 600–1300 liposomes were bound per single microbubble, and the size of the microbubbles increased from 3.6 to 4.0 μm after conjugation with liposomes (diameter around 200 nm), indicating the formation of a single liposome layer coated on the surface of the microbubbles. The same group¹⁸³ designed N-cadherin-targeted liposome-loaded microbubbles for circulating tumor cell (CTC)-specific drug delivery (Figure 17). Their results confirmed that the targeted antibodies specifically adhered to the target cells and that focused ultrasound helped transport small molecules (propidium iodide) into the cells. Sanders and co-workers¹⁸⁴ further proved that liposome-decorated microbubbles could enhance ultrasound-mediated drug delivery in vivo. They chose indocyanine green (ICG) as a model drug for intravenous injection in mice and monitored local ICG deposition post-ultrasonic therapy via fluorescence imaging.

4.2. Liposomes

The relatively large size of microbubbles results in a shorter retention time compared to nanocarriers. The inevitable retention in the lungs also restricts the use of microbubbles in

cardiovascular targets and tumor endothelia. Hence, acoustically activated liposomes, sometimes called nanobubbles, have become more prominent in ultrasonic drug delivery.^{132,185,186} This kind of ultrasound-responsive liposomes (echogenic liposomes), which are typically formed with a gas core covered with a lipid monolayer, were initially studied for ultrasound imaging as contrast agents.^{129,187,188} Lin and Thomas¹⁸⁹ found that LFUS could control the release of the payload from drug-encapsulating echogenic liposomes with nonthermal effects. Under the appropriate ultrasound frequency, echogenic liposomes rapidly grew, oscillated, collapsed, and spewed payload by cavitation. Several factors like wave frequency, membrane constituents, encapsulated gas or drug, presented media, and size and shell thickness of liposomes can affect the stability of liposomes and liposomal drug release.^{190–193}

Liposomes containing monolayer lipid-covered bubbles are known as bubble liposomes (BLs).^{194–196} Aramaki and co-workers¹⁹⁷ employed BLs along with ultrasound exposure to directly deliver plasmid DNA (pDNA) to skeletal muscles by local injection for peripheral artery disease treatment. PEG-modified BLs with perfluoropropane gas were easily fabricated through a reverse-phase evaporation method. It was found that high gene transfection efficiency was achieved in the muscle administrated with BLs and ultrasound in a hind-limb ischemia mice model, as well as an increase in capillary density and blood flow. Furthermore, in order to deliver genes to deeper tissues, novel BLs were explored for systemic injection, by use of a

Figure 14. Shear stress-responsive intracellular drug delivery. (a) Rapid deformation of a cell due to transient membrane holes, when it passes through a microfluidic constriction. (b) Western blot analysis of cellular uptake of c-Myc, Klf4, Oct4, and Sox2 by NuFF cells by cell-penetrating peptides versus a microfluidic device, which showed higher delivery efficiency by microfluidic constriction. (c) Delivery efficiency of carbon nanotubes in treated cells (left) vs endocytosis (right). Scale bars: 2 μm . (d) Live-cell delivery efficiency of different designed devices. Reprinted with permission from ref 119. Copyright 2013 U.S. National Academy of Sciences.

cationic lipid (*N*-[1-(2,3-dioleoyloxy)propyl]-*N,N,N*-trimethylammonium, DOTAP) to intensify the colocalization of pDNA and BLs via electrostatic attraction (Figure 18).¹⁹⁸ Results showed that improved design of BLs brought about higher loading efficiency of pDNA through its interaction with DOTAP and prolonged circulation time by adjusting the ratio of short- and long-length PEG (PEG₇₅₀/PEG₂₀₀₀) molecules on the surface. Additionally, Pitt and co-workers¹⁹⁹ prepared emulsion-containing liposomes (eLiposomes) for drug delivery, with a size of 200–400 nm. They demonstrated that ultrasound could cause acoustic droplet vaporization (ADV) of the contrast agent, thus breaking the liposomal membrane. After DOX loading, eLiposomes exhibited an improved therapeutic response in vitro. Some other eLiposomes were also reported in several studies.^{200,201}

Indeed, LFUS can also induce drug release from conventional liposomes without contrast agents. By forming a gas bubble core in the hydrophobic interval between lipid bilayers, which would grow until it permeates the liposome membrane, ultrasound can finally produce transient pores for drug diffusion. Cisplatin and DOX have been widely delivered from liposomes triggered by ultrasound for cancer therapy.¹³² DOX-loaded liposomes modified with targeting ligands were applied to brain tumors with pulsed ultrasound assistance and showed improved anticancer effects.²⁰² Fossheim and co-workers²⁰³ developed sonosensitive liposomes by doping nonbilayer lipid (distearoylphosphatidylethanolamine, DSPE) on the surface of liposomes. DOX-containing liposomes composed of dioleoylphosphatidylethanolamine (DOPE) showed even higher sonosensitivity, since DOPE tended to form a more pronounced hexagonal

Figure 15. Illustration of application of drug-loaded microbubbles in drug delivery systems. Microbubbles can prevent drugs from degradation in the bloodstream and avoid uptake in unwanted areas. At the target site, the drug can be released and penetrate cell membranes by application of ultrasound. Reprinted with permission from ref 158. Copyright 2012 Elsevier.

Figure 16. Schematic of controlled release of DOX-SPIO-MBs into brain tissues triggered by ultrasound and enhanced SPIO deposition by external magnet targeting. Reprinted with permission from ref 171. Copyright 2013 Elsevier.

structure due to its unsaturated acyl chains.²⁰⁴ Thus, upon exposure to ultrasound, the phase transition of DOPE induced membrane perturbations, followed by drug release from liposomes.

4.3. Nanoparticles

Polymeric micelles typically assembled by amphiphilic block polymers have been ubiquitously used in drug delivery for decades.¹³ Micelles made from thermosensitive polymers can be disrupted by ultrasound; therefore, ultrasound-assisted micellar drug delivery has been recently studied.²⁰⁵ Furthermore, mechanical action caused by pulsed ultrasound can also trigger drug release from micelles. Many micelle-based DDS incorporated with local sonication were reported as efficient tumor-selective treatments.^{206–208} Xia and co-workers²⁰⁹ studied ultrasound-responsive behavior of PLA-*b*-PEG [poly(lactic acid)-*b*-poly(ethylene glycol)] copolymer micelles under high-intensity focused ultrasound (HIFU) (Figure 19). Results revealed that generated transient cavitation led to the degradation of PLA-*b*-PEG under HIFU at the ultrasound focal spot. They also invented a dual-responsive micelle with a

disulfide bond that could be broken under reductive conditions.²¹⁰ Thus, this micelle can be remotely controlled by HIFU and simultaneously stimulated by an intracellular bioreductive environment.

Several publications have also reported that ultrasound can promote gene delivery from nanoparticles. Gene transfection was enhanced when complexes of genes and cationic lipids or polymers were treated by ultrasound.^{211–213} Wang et al.²¹⁴ investigated various acoustic parameters to facilitate the delivery of microRNA from PLGA-PEG [poly(lactic-*co*-glycolic acid)-poly(ethylene glycol)] nanoparticles to the tumor site in cooperation with microbubbles. Evidence showed a 7.9-fold increase in delivery efficiency compared to treatment without ultrasound. Concurrent application of ultrasound and sodium lauryl sulfate could also enhance the passive transdermal delivery efficacy of nanoparticles.²¹⁵ In addition, mesoporous silica nanoparticles (MSNs), as ultrasound contrast agents, were also reported to be useful for ultrasonic drug delivery.²¹⁶ Results demonstrated that the target antibody (herceptin) functionalized MSNs could potentially be used for ultrasound activated imaging and tumor-specific treatment for breast cancer.

Figure 17. Schematic depictions of (a) a targeted liposome-loaded microbubble and (b) intercellular uptake into circulating tumor cells. Adapted with permission from ref 183. Copyright 2013 Wiley–VCH.

It has also been shown that nanodroplets (NDs) formed with lipid-stabilized low-boiling perfluorocarbon could release their cargo via interaction with ADV caused by ultrasound. Acoustic droplets were reported for ultrasound-mediated targeted drug delivery.^{217–219} Yeh and co-workers²²⁰ prepared folate-decorated NDs (FA-CPT-NDs) entrapping camptothecin (CTP) as an acoustic drug carrier for targeted tumor theranostics in a mouse xenograft model. The FA-CPT-NDs underwent a

Figure 19. Scheme of HIFU and redox dual-responsive process of PEG-S-S-PLA micelle. Upon HIFU irradiation or glutathione treatment, degradation of the PEG-S-S-PLA chain and disruption of micelles can trigger drug release. Reprinted with permission from ref 210. Copyright 2010 Royal Society of Chemistry.

transition shift from liquid to gas upon ADV, followed by release of CTP and apoptosis of the targeted cancer cells. This formulation exhibited enhanced chemical and mechanical antitumor effects. Superparamagnetic iron oxide could also be embedded into nanodroplets to assist in magnetic control of drug deposition.²²¹

Emulsion is known as a two-phase mixture with a dispersed phase surrounded by a continuous phase. Hydrocarbon or fluorocarbon liquids are two common dispersed phases that can carry hydrophobic agents.^{162,222} Perfluorocarbon nanoemulsions stabilized by copolymers could deliver lipophilic therapeutics to solid tumors.²²³ Ultrasound would trigger ADV and reversibly transport droplets to gas in PFCE (perfluoro-15-crown-5-ether) nanoemulsions. Desired therapeutic effects were observed in both breast and pancreatic cancer animal models with ultrasonic delivery of paclitaxel loaded in PFCE nanoemulsions. The biodistribution of nanoemulsions could be simultaneously monitored via ultrasonography. Stone and co-workers²²⁴ developed an ultrasound-sensitive gas-in-oil-in-water-in-oil triple emulsion through a microfluidic method. The triple emulsions were stable in the atmosphere; thus it was possible to reinforce the emulsions through polymerization by UV light outside the device and turn it into gas-in-liquid-in-solid compound particles. When ultrasound was applied, the gas core induced breakage of emulsions and released the encapsulated contents.

Figure 18. Schematic presentation of systemic gene delivery systems using bubble liposomes (BLs) entrapping ultrasound contrast gas. This combination of BLs and ultrasound exposure provides an effective way for the delivery of plasmid DNA (pDNA) into skeletal muscles. Reprinted with permission from ref 198. Copyright 2012 American Chemical Society.

4.4. Micro/nanomotors

Micro/nanomotors are a class of miniaturized synthetic machines, which are capable of converting chemical or external energy to mechanical motion.²²⁵ Over the past decade, numerous artificial micro/nanomotors based on diverse propulsion mechanisms have been developed in a wide variety of medical applications ranging from bioanalytics to drug delivery.^{226–229} However, previously reported synthetic motors were mostly propelled by chemically catalyzed gradients or by ejecting bubbles that usually contained toxic ingredients like H_2O_2 .^{230,231}

Mallouk and co-workers²³² utilized continuous or pulsed ultrasound for the propulsion of metallic micromotors. As ultrasound-powered micromotors showed considerable promise in penetrating into deep tissues, Mallouk and co-workers²³³ further employed rod-shaped nanomotors into HeLa cells. They demonstrated that the desired intercellular uptake of gold nanorods was achieved with the assistance of ultrasound and without any chemical fuel, and insignificant toxicity was detected toward cells. Intrigued by their work, Wang and co-workers²³⁴ developed ultrasound-powered microbullets that could penetrate and deform cellular tissues and deliver drugs to diseased destinations (Figure 20). These tubular microbullets loaded

Figure 20. (a) Preparation of PFC-loaded microbullets. (b) Computer-aided graphics and corresponding experimental images of PFH-loaded microbullets (i) penetrating, (ii) cleaving, and (iii) expanding a tissue following a pulsed ultrasound signal. Reprinted with permission from ref 234. Copyright 2012 Wiley–VCH.

with ultrasound contrast agent (perfluorocarbons, PFCs) inside the conical-shaped microtubes could produce sufficient force to contribute to the ADV of PFCs. Consequently, a “bulletlike” velocity of over 6 ms^{-1} , approximately 100 times faster than common micromotors, was assessed, offering PFC-loaded micromotors as a possible platform to deliver drugs through the tissue barrier. The same group developed a multifunctional nanowire motor consisting of three metallic segments (Au–Ni–

Au) that was propelled by ultrasound and guided by magnetism.²³⁵ The pH-sensitive eletropolymerized polypyrrole–poly(styrenesulfonate) (PPy–PSS) was linked to the Au–Ni–Au nanowire, serving as a drug carrier for a model drug, brilliant green (BG). Similarly, they used ultrasound to drive nanoporous Au nanowires with the drug inside toward the cancer tissue and triggered the release by near-infrared light (NIR).²³⁶ Wu et al.²³⁷ fabricated polymer-based multilayer tubular nanorockets via LbL assembly assisted with a nanoporous template, which were verified to efficiently transport drugs into cancer cells. Poly-(diallyldimethylammonium chloride)-stabilized platinum nanoparticles were incorporated into the inner layer (as framework of the nanorockets), while DOX was loaded into the outer layer (as container of the nanorockets). The self-propelling nanorockets were shown to partially penetrate into the HeLa cells and release DOX through ultrasound-mediated breaks of the outer layers. Recently, Wang and co-workers²³⁸ further developed a kind of micromotor based on natural particulates by inserting iron oxide nanoparticles inside red blood cells to prolong circulation time and improve biocompatibility.

4.5. Microcapsules

Van Hest and co-workers²³⁹ fabricated a series of hollow biodegradable polymeric microcapsules and studied the mechanical effects of PFO–PLLA [perfluorooctanol–poly(lactic acid)] capsules with varied ratios of shell thickness to diameter under different acoustic pressures. Thus, drug release from PFO–PLLA capsules could be triggered independently in a stepwise or selective fashion by control of mechanical index. In another work, Wang et al.²⁴⁰ utilized alginate microcapsules as drug carriers incorporated with pulsating ultrasound to deliver diclofenac for anti-inflammatory purposes, obtaining a 30% higher release rate in vivo. Möhwald and co-workers²⁴¹ fabricated polyelectrolyte microcapsules with ZnO nanoparticles embedded in the shell, which resulted in considerably higher ultrasound sensitivity. It was demonstrated that the shell thickness and roughness is dependent on the number of ZnO nanoparticle layers. Their different mechanical properties affected sensitivity to ultrasonic treatment. This ZnO nanocomposite showed its potential as a drug carrier with the possibility of opening with the application of ultrasound.

Moreover, lasers can also generate focused ultrasound for spatiotemporal control of drug delivery. Gu and co-workers²⁴² demonstrated a laser-generated focused ultrasound (LGFU)-triggered drug delivery device. Compared to the conventional HIFU, LGFU can focus on a tight spot with a higher resolution and reduce the heating effect on tissue. Different types of drugs, such as DOX for anticancer treatment and ciprofloxacin for antibacterial treatment, were encapsulated in PLGA nanoparticles. Then the PLGA nanoparticles were further loaded into alginate microgels. Upon applying LGFU onto microgels, a significant promoted drug release was observed at the focal point due to the cavitation effect. They demonstrated that spatiotemporally remote control of drug release could be achieved in in vitro antitumor and antibacterial studies via application of LGFU.

4.6. Injectable Depots

Recently, several injectable and ultrasound-responsive depot-based DDS have also been developed for long-term administration. For example, Gu and co-workers²⁴³ reported a smart nanonetwork that was able to regulate BGLs by ultrasound-triggered insulin release (Figure 21a). The gel-like 3D nanoscaffold was formed with alginate- and chitosan-coated PLGA

Figure 21. (a) Schematic illustration of ultrasound-mediated insulin delivery system using a nanonetwork. (b) Schematic of regulating BGLs in a noninvasive manner via ultrasonic therapy. (c) BGLs of STZ mice administrated with three cycles of ultrasound treatment. Solid columns indicate the administration window, including 5 min anesthesia and 0.5 min FUS treatment. (d) Tunable ultrasound parameters that can affect insulin release rate. Reprinted with permission from ref 243. Copyright 2014 Wiley–VCH.

nanoparticles via electrostatic attraction. Insulin was loaded in the nanoparticles, and the formed cohesive nanonetwork could be subcutaneously injected through a universal syringe due to reduced cohesive forces under high shear rate. The nanonetwork could remain stably underneath the skin with tight adhesion of oppositely charged nanoparticles. Once focused ultrasound was applied, the nanonetwork was partially dissociated, and stored insulin diffused out from the microchannels in the porous scaffold (Figure 21b). In particular, they demonstrated that the release rate could be controlled by tuning the parameters of focused ultrasound such as input voltage, pulse duration, and ultrasound administration time (Figure 21d). In vivo experiments showed that the insulin-loaded nanonetwork helped regulate BGLs of type 1 diabetic mice at normal glycemia over a week after treatment with focused ultrasound (Figure 21c).

Kohane and co-workers²⁴⁴ developed an in situ cross-linking hydrogel for repeated on-demand ultrasound-triggered drug delivery. This injectable hydrogel composed of drug-containing liposomes and gas-filled microbubbles presented a low baseline rate of drug release and prolonged the ultrasound triggerability for over 14 days. Another ultrasound-responsive hydrogel invented by Mooney and co-workers²⁴⁵ was reported as a promising DDS for sustained controlled release (Figure 22a). With the disruption induced by ultrasound and self-healing of

ionically cross-linked hydrogels, the switch of drug release correspondingly turned on and off (Figure 22b,c). Results indicated a remarkable decrease of tumor size after daily ultrasound treatment compared to the control group (Figure 22d). Similar polymers that can be ionically cross-linked are possible candidates for ultrasonic drug delivery using this approach. Grinstaff and co-workers²⁴⁶ prepared superhydrophobic meshes with poly(ϵ -caprolactone) (PCL) and poly(glycerol monostearate-co-caprolactone) (PGC-C18) for ultrasonic drug delivery. The air entrapped both at the material surface and within the structure of the 3D meshes could be removed upon treatment with HIFU, allowing cargo release from meshes.

During recent decades, numerous ultrasound-sensitive drug carriers have been developed for various medical applications. Compared to compressive/tensile and shear force-triggered drug delivery systems, the ultrasound-activated method can realize precise and repeatable dosage control. Meanwhile, the highly selective region for treatment can further avoid side effects. Despite this, the requirement for an external ultrasound source still hardly satisfies the need for a convenient and practical treatment.

Figure 22. Ultrasound-triggered drug delivery from self-healing hydrogel. (a) Scheme of ultrasound-induced disruption and self-healing of (●) ionically cross-linked hydrogel. (b) Release profiles of mitoxantrone triggered by ultrasound and diffusion. (c) Survival curves for mice implanted with tumors after receiving no treatment (black), treatment with a mitoxantrone-laden gel but no ultrasound (red), or treatment with a combination of mitoxantrone-laden gel and daily ultrasound treatment (blue). (d) Images of tumors explanted from mice. Reprinted with permission from ref 245. Copyright 2014 U.S. National Academy of Sciences.

5. MAGNETIC FORCE-TRIGGERED DRUG DELIVERY

Unlike ultrasound, the magnetic field remotely exerts force only on magnetoresponsive materials. Currently, most magnetic materials are inorganic matter, including superparamagnetic iron oxide or metals like cobalt and nickel.²⁴⁷ However, these hard materials are limited for magnetic force-triggered DDS. Usually, researchers combine magnetic nanoparticles with a

flexible polymer material to achieve magnetoresponsive properties.⁷⁶ By integration with thermoresponsive materials, the localized heating caused by magnetic particles under an alternating current magnetic field can be used to realize controlled drug release. In an alternative way, the magnetic material integrated with flexible polymers is able to deform by

Figure 23. (a) Hierarchical structure of macroporous ferrogels. Ferrogels with different pore sizes were prepared by freezing gels at different temperatures. (b) Stress vs strain curves for nanoporous and macroporous ferrogels subjected to compression tests. (c) Shape change in (top) nanoporous ferrogel and (bottom) macroporous ferrogel when subjected to a vertical magnetic field. (d) SEM images of a freeze-dried macroporous ferrogel in the undeformed and deformed states. (Scale bar 500 μm) Reprinted with permission from ref 255. Copyright 2011 U.S. National Academy of Sciences.

stretching, compressing, or bending to release the drug on demand upon exposure to a magnetic field.²⁴⁸

Ferrogel, obtained by association of a ferrofluid and a hydrogel, was first reported as a magnetic force-responsive system by Zrínyi et al. in 1996.²⁴⁸ They distributed monodomain magnetic particles with a diameter of 10 nm in a polymeric flexible network by adhesive forces. The resulting gel, namely ferrogel, had the ability to generate strain under a nonuniform magnetic field, leading to a controllable change in shape. Since then, a great deal of work on magnetic field-controlled drug delivery has been reported by taking advantage of the deformation of ferrogels under a magnetic field.^{137,249–251} For instance, a poly(vinyl alcohol) (PVA) hydrogel with Fe_3O_4 magnetic particles was capable of accumulating drug when an external magnetic field was applied.^{249,252} In contrast, the accumulated drug rapidly diffused out of the ferrogel once the magnetic field was turned off.

Due to high water content in the ferrogel, effective incorporation of hydrophobic drugs is limited.²⁵³ In order to address this issue, Muhammed and co-workers²⁵⁴ applied Pluronic copolymer [poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide)] as a gelling material to encapsulate hydrophobic drugs. Pluronic is a triblock copolymer consisting of one poly(propylene oxide) (PPO) block and two poly(ethylene oxide) (PEO) blocks. After incorporation of indomethacin, a model hydrophobic drug, PPO segments can form a hydrophobic core to entrap it. In vitro release experiments

showed that the release rate significantly increased upon applying a magnetic field. Besides small molecular drugs, Mooney and co-workers²⁵⁵ further applied the ferrogel as an active depot of various cells to achieve on-demand cell delivery. Homogeneous pores with suitable size for cell adhesion were prepared by freezing ferrogels at a specific temperature (Figure 23a). Unlike nanoporous ferrogel, the resulting macroporous gel showed reversible deformation at a compressive strain of 80% (Figure 23b). A larger deformation was also achieved in macroporous ferrogel under the same magnetic field (Figure 23c,d). Cell-binding peptides were further covalently conjugated onto the polymer to support cell adhesion and viability. The results of in vitro and in vivo tests indicated human dermal fibroblasts or mouse mesenchymal stem cells could be released under external magnetic stimulation. In particular, multiple stimulation parameters, including the strength of external magnetic field, frequency of stimulation, and number of cycles, are tunable to control the cell release in this delivery system.

In addition, an oscillating or alternating magnetic field (AMF) can cause vibration of magnetic particles. By taking advantage of this phenomenon, Hu et al.²⁵⁶ designed a drug reservoir with a magnetism-sensitive shell. A fluorescent dye was encapsulated in the silica core as a model drug, with a thin layer of poly(vinylpyrrolidone) (PVP)/ Fe_3O_4 coating on the surface (Figure 24). The core/shell nanosphere was stable in aqueous solution with no significant dye release after 24 h. Once exposed

Figure 24. Core/single-crystal-shell nanosphere. (a) Schematic of high-frequency magnetic field (HFMF)-induced cell structure variation. (b) TEM and XRD images show (I) reversible change of nanofaults under short-term field exposure and (II) permanent rupture of the thin shell under long-term exposure. Reprinted with permission from ref 256. Copyright 2008 Wiley–VCH.

to a high-frequency AMF (50 kHz) for 5 min, a large amount of preload dye diffused out to surrounding solution, as a result of enlarged nanocrevices on the shell lattice structure caused by vibration. With a shorter exposure (60 s), the physical deformation is reversible; the Fe_3O_4 shell could return to intact morphology and prevent dye diffusion for repeatable drug release, while a long-term AMF could permanently damage the magnetic shell since it received sufficient amounts of (vigorous) energy to rupture the thin shell. In vitro cell studies illustrated enhanced cell uptake efficiency in a remote-controlled manner. Besides controlled drug release, the external magnetic force can also enhance local tumor accumulation of therapeutic agents to achieve higher cancer therapy efficacy. Liu and co-workers^{257–259} demonstrated that drug-loaded iron oxide nanoparticles circulating in the blood could be guided and attracted to tumor regions by external magnetic field. Compared to passive tumor-targeting strategies like enhanced permeability and retention (EPR), this active magnetic force-guided method showed higher tumor accumulation efficiency and thus better tumor treatment efficacy.

In these reports, the application of external magnetic force provides an enhanced magnetic guided and controlled strategy for drug delivery. For future clinical application, a three-dimensional guidance and manipulation technology may further help to increase precise dosage control and enhance therapy efficiency.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

In summary, distinct mechanisms of mechanical actuation can trigger mechanical stimuli-responsive DDS for a variety of applications, ranging from enhancing intracellular transfection to assisting therapy of cancer, diabetes, and cardiovascular diseases. We anticipate this simple and effective stimulus can further offer a generic platform broadly applicable to a multitude of disease treatments. For instance, stretch-induced DDS can be utilized to deliver antibacterial agents, anticancer drugs, or growth factors, which can locally generate anti-inflammation effects, suppress tumor growth, or repair tissue in a self-administered manner; while the shear-sensitive DDS can serve as personalized medication for cardiovascular patients owing to its “intelligent” localization function. Moreover, ultrasound can readily combine imaging and drug delivery to achieve on-demand theranostics.^{260–263} Drug release could also be monitored dynamically by the imaging modality. When it comes to magnetic field-mediated activation, treatment efficacy could be further enhanced by drug accumulation in the target site, induced by the magnetic field, and promoted drug release with repeated dosing by remote control.

Regarding clinical translation, more efforts are needed to further improve most mechanical force-triggered DDS.^{264,265} First of all, it is still challenging to realize precise control of drug dosage. Due to a relatively complicated combination of passive release and dynamically triggered release, it is difficult to regulate the released dosage in a repeatable manner, which becomes even more challenging for long-term administration in a physiological environment. A delivery system with confined drug amounts or with a “rechargeable” mechanism could potentially avoid the risk of side effects due to overdose. Second, for shear-sensitive DDS, how to prolong the circulation time by modifying the surface and how to enhance specific delivery by using targeted ligands are two of the main difficulties that need to be addressed. More details related to the dynamic flow behavior of the drug carrier under shear flow should be taken into account in understanding the performance and responsiveness of DDS. Third, from the perspective of fundamental study, further detailed investigation of the mechanism inside mechanoresponsive systems would help improve treatment performance. For example, the mechanism is still ambiguous between sonoporation and cellular interactions.²⁶⁶ A more comprehensive understanding could allow optimal use of the biological implications in ultrasonic drug delivery. Last but not least, there is no consensus on parameter settings for either ultrasound- or stretch-assisted DDS. To achieve patient-centered medications,²⁶⁷ systematic tests and adjustments could be indispensable. Alternatively, wearable devices^{268–270} or implanted wireless biomedical chips^{271–273} that can dynamically monitor physiological signals could be further integrated in the mechanoresponsive DDS to enhance the performance.

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Notes

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