How to Cite:
Hamzy, I. A. ., Alqhoson, A. I., Aljarbou, A. M., & Alhajri, M. A. (2017). Advancements in intelligent drug delivery systems and their clinical applications. *International Journal of Health Sciences*, *1*(S1), 1–27. https://doi.org/10.53730/ijhs.v1nS1.15092

Advancements in intelligent drug delivery systems and their clinical applications

Ibrahim Abdullah Hamzy
KSA, National Guard Health Affairs

Abdulelah Ibrahim Alqhoson
KSA, National Guard Health Affairs

Anas Mohammed Aljarbou
KSA, National Guard Health Affairs

Mohammed Abdulrahman Alhajri
KSA, National Guard Health Affairs

***Abstract*---Background:** Intelligent Drug Delivery Systems (DDSs) have revolutionized the way medications are administered, aiming to enhance therapeutic efficacy while minimizing side effects. Conventional DDSs often lead to systemic drug distribution and uncontrolled release, causing undesirable side effects and suboptimal therapeutic outcomes. To address these limitations, advanced controlled DDSs, particularly those leveraging nanotechnology, have been developed to target specific sites with precise regulation. **Aim:** This review aims to explore the recent advancements in intelligent drug delivery systems, focusing on their design, mechanisms, and clinical applications. It highlights the role of nanotechnology in enhancing the specificity and efficacy of drug delivery through various stimuli-responsive mechanisms. **Methods:** The review synthesizes findings from recent studies on various smart drug delivery platforms, including nanoparticle-based systems, smart polymers, liposomes, and organic-inorganic hybrids. It evaluates these systems based on their responsiveness to internal stimuli (e.g., pH, redox reactions, enzymes) and external stimuli (e.g., temperature, light, magnetic fields), and their clinical applicability. **Results:** The review identifies several innovative DDSs that employ stimuli-responsive materials to control drug release. Notable advancements include pH-responsive nanoparticles targeting tumor cells, redox-responsive systems for cancer therapy, and temperature-sensitive liposomes used in hyperthermia. Hybrid systems combining organic and inorganic materials have shown promise in improving drug release control and targeting capabilities. **Conclusion:** Intelligent drug delivery systems

International Journal of Health Sciences E-ISSN 2550-696X © 2017.
Manuscript submitted: 01 Jan 2017, Manuscript revised: 09 Jan 2017, Accepted for publication: 15 Jan 2017

represent a significant leap forward in precision medicine, offering targeted and controlled drug release mechanisms that enhance therapeutic outcomes and reduce side effects. Despite promising developments, challenges such as scalability, safety, and regulatory hurdles remain. Future research should focus on overcoming these obstacles to facilitate the broader clinical adoption of these advanced DDSs.

***Keywords*---**Drug Delivery Systems, Nanotechnology, Smart Polymers, Stimuli-Responsive Materials, Clinical Applications, Targeted Therapy.

Introduction

In order to achieve the best results from treatment and reduce any negative effects, it is essential for the active pharmaceutical ingredients to specifically gather at the affected areas for a long time with accurate management. Drug delivery refers to the methods, formulations, technologies, and systems used to safely and efficiently convey medicinal substances within the body to accomplish their desired effects [1]. Conventional drug delivery systems (DDSs) often cause widespread side effects because they distribute drugs without discrimination and release them without regulation. In order to overcome these limitations, advanced controlled drug delivery systems (DDSs) have been created to administer medicinal substances to specific sites in a controlled manner. Advanced controlled DDSs offer a notable advantage over conventional DDSs by effectively decreasing the frequency of drug administration, while yet ensuring that therapeutic drug levels are maintained in targeted organs or tissues for extended periods of time. These regulated DDSs provide significant knowledge and characteristics for limiting fluctuations in drug concentration, decreasing toxicity, and improving the effectiveness of therapy.

The unique characteristics at the nanoscale and specific biological functions of different nanomaterials provide notable benefits and novel opportunities for intelligent drug delivery systems. Nanoparticle-based drug delivery systems (DDSs) have the ability to specifically gather and attach to disease targets while maintaining controlled release characteristics. Although there have been recent developments and reviews discussing new features of nanomaterials as intelligent drug carriers [1-6], only a small number of these have been effectively implemented in clinical settings [7-9]. Important considerations to guarantee the clinical feasibility for future commercialization comprise: (i) sufficient biocompatibility and biodegradability, (ii) stability in physiological settings, and (iii) a high drug loading capacity with minimum toxicity [10]. Furthermore, apart from ensuring safety and therapeutic efficacy, it is crucial to scale up the manufacturing of these innovative nanomaterials for industrial purposes in order to make them suitable for clinical applications.

A wide range of materials, such as polymers, lipids, and inorganic compounds, have been engineered to serve as drug carriers for controlling the release of therapeutic chemicals [11-16], so producing "smart" pharmaceuticals. This paper provides an overview of advanced carriers, including smart polymer carriers,

liposomes, organic-inorganic hybrid smart nanoparticles, exosomes, and other nanomaterials, that are used for controlled drug delivery. Additionally, it investigates the clinical prospects of these regulated drug delivery nanoplatforms and the obstacles they encounter in clinical implementation.

The design rationale behind smart drug delivery nanoplatforms. Optimally, medications should be delivered to specific locations in a regulated manner to enhance the effectiveness of treatment while limiting any negative effects. Smart drug delivery systems (DDSs) are specifically engineered to selectively release medications at precise places or at highly controlled rates, hence ensuring targeted therapeutic effects. Research on stimuli-responsive biomaterials for controlled drug release has made major advancements since Tanaka's 1978 detection of phase transitions in polyacrylamide gels and the introduction of thermosensitive liposomes for drug delivery. Due to advancements in nanotechnology and nanomaterials, medications can now be combined with different nanoparticles (see to section 3.3). Nanomaterials, due to their distinct size and surface features, show great potential as intelligent drug delivery systems (DDSs).

In this review, the term "Smart DDSs" denotes systems that ensure pharmaceuticals are only released upon reaching certain target tissues/organs, or are released at a regulated pace at the intended action locations. This analysis specifically examines intelligent drug delivery systems (DDSs) that are made possible through the use of nanotechnology, rather than the drug molecules themselves. These nanoplatforms are designed to enable precise delivery of drugs to specific tissues after being administered systemically. Existing drug-loaded nanoplatforms are designed to retain pharmaceuticals in the bloodstream until they reach specific target locations. The nanocarriers concentrate at these sites using either active or passive targeting mechanisms. These sophisticated nanoplatforms are capable of responding to internal triggers, such as changes in pH, hormone levels, enzyme concentrations, small biomolecules, glucose, or redox gradients, which are associated with disease pathology. They can also react to external stimuli, such as temperature, magnetic fields, ultrasound (US), light, electric pulses, or high-energy radiation. The underlying concepts of several nanoplatforms that respond to stimuli will be briefly explored here.

Design Rationale of Smart Drug Delivery Nanoplatforms

Effective drug delivery requires that medications be released at specific target sites in a controlled manner to maximize therapeutic efficacy and minimize side effects. Smart drug delivery systems (DDSs) build on the principles of controlled release to enhance drug performance. Since Tanaka's 1978 observation of phase transitions in polyacrylamide gels [17], research into phase-transition polymeric gels has significantly advanced. Around the same time, thermosensitive liposomes were first introduced for drug delivery [18]. The field of stimuli-responsive biomaterials has since evolved, with nanotechnology and nanomaterials enabling the conjugation of drugs to various nanoparticles (see section 3.3). Leveraging the unique size and surface properties of these nanomaterials positions them as highly promising candidates for smart DDSs.

In this context, "Smart DDSs" are defined as systems that release drugs only at specific target tissues or organs, or at extremely slow rates, ensuring that drugs are released in a controlled manner at the sites of action. While drug molecules themselves can sometimes be considered "smart," this review focuses on smart DDSs achieved through nanotechnology. The sophisticated design of these nanoplatforms facilitates targeted drug release during systemic administration. Drug-loaded nanoplatforms are engineered to prevent premature drug release during blood circulation, allowing for targeted delivery where nanocarriers accumulate via active or passive targeting strategies. These advanced smart or stimuli-responsive nanoplatforms can react to both endogenous and exogenous stimuli. Endogenous triggers include pH variations, hormone levels, enzyme concentrations, small biomolecules, glucose, or redox gradients [19, 20], which are associated with disease pathology. Exogenous triggers, such as temperature, magnetic fields, ultrasound (US), light, electric pulses, or high-energy radiation, can also be employed to induce or enhance drug release at disease sites. The principles behind various stimuli-responsive nanoplatforms will be discussed further below.

Systems that respond to changes in pH:

pH is commonly used as a stimulus to initiate medication release in many applications [21-24]. Traditional pH-responsive carriers utilize the notable variations in pH levels between different organs, such as the very acidic conditions of the stomach (pH ≈ 2) compared to the more neutral pH of the intestinal tract (pH = 7). Eudragit S100-coated citrus pectin nanoparticles (E-CPNs) have been created to specifically transport 5-Fluorouracil (5-FU) to the colon [25]. These carriers are specifically engineered to detect and react to small changes in pH levels in disease locations, such as areas affected by inflammation, reduced blood supply, and tumors. They can even target specific cellular structures like endosomes and lysosomes. An exemplary instance involves pH-responsive nanocarriers designed for solid tumors [26]. The extracellular pH in normal tissues and blood is generally maintained at approximately 7.4. However, in solid tumors, the extracellular pH frequently decreases below 7.0 due to increased glycolytic activity. The acidic environment present in tumors can act as a targeted stimulus for controlled drug delivery systems (DDSs). In addition, endosomes and lysosomes have a lower pH range of 4.5 to 5.5 compared to other parts of the cell (21, 28). Therefore, fluctuations in pH play a critical role in the development of sophisticated drug delivery systems (DDSs). pH is commonly used in smart drug delivery systems (DDSs). However, incorporating other stimuli, like temperature or redox changes, might improve the accuracy and selectivity of drug release at specific locations. This has been demonstrated in studies [29-31].

Systems that Respond to Redox Reactions:

Redox-responsive systems have received considerable interest for the treatment of diseases and are extensively utilized in intracellular drug delivery systems (DDSs) (19, 32). The redox potential fluctuates among various tissue microenvironments, providing possibilities for developing redox-responsive delivery methods. Nanoparticles that can respond to Glutathione (GSH) offer a highly effective approach for delivering drugs to specific targets. GSH is found at significantly

higher amounts in cancer cells (2 to 10 mM) compared to normal cells (2-20 μM) [34]. The significant disparity in glutathione (GSH) levels between malignant and normal cells makes redox-responsive drug delivery systems (DDSs) highly attractive for selectively targeting tumor locations. Furthermore, reactive oxygen species (ROS), which build up in specific diseased tissues, can also act as stimuli for regulated medication release. ROS levels in inflammatory tissues and colon cancer can reach levels that are 10 to 100 times greater than those found in normal tissues (19, 35). Although redox stimuli-responsive drug delivery systems (DDSs) have promising possibilities, it is difficult to get accurate control over redox mechanisms because of the intricate biological milieu and the variability of tumors.

Systems that are responsive to enzymes:

Enzyme-responsive drug delivery systems (DDSs) have been a fascinating field of study because of their ability to specifically target substrates and exhibit great selectivity even in gentle settings. [36 -39]. Enzymes like glycosidases, lipases, phospholipases, and proteases play crucial roles in several biological and metabolic processes. These enzymes can be utilized to facilitate the targeted release of drugs to specific locations affected by cancer or inflammation [38]. An important obstacle for enzyme-responsive drug delivery systems (DDSs) is the ability to precisely regulate the initial response time of the systems.

Systems that are responsive to changes in temperature:

Temperature is a superior and efficient factor for regulating drug release in comparison to other stimuli within the range of 40-42 degrees. Pathophysiological situations such as inflammation and tumors frequently display higher temperatures compared to normal tissues [43]. Functionalized nanoparticles can be strategically engineered to optimize medication release in tumor tissues by taking advantage of temperature variations. Another approach entails applying external heat to the tumor site, such as by the use of ultrasound or magnetic fields, in order to enhance the release of drugs within the tumor microenvironment [34]. Thermo-sensitive nanocarriers are usually engineered to keep their payloads intact at normal body temperatures (37°C) and release them quickly when exposed to temperatures higher than 40-45°C. The present obstacle for thermo-responsive nanoplatforms is to uphold safety while preserving sensitivity to slight temperature fluctuations.

Systems that respond to light, magnetic fields, and ultrasound:

Light-responsive systems facilitate medication release through external light activation. Photosensitive carriers can modulate drug release by manipulating the opening or closing of their nanostructures in response to light irradiation [19]. Nevertheless, the use of non-invasive techniques for deep tissues is limited due to practical constraints such as light wavelength and penetration depth. Magnetic stimuli provide a non-invasive technique to spatially and temporally manipulate carriers using external magnetic fields [47-49]. Core/shell magnetic nanoparticles (MNPs), renowned for their distinctive magnetic characteristics, possess a significant ratio of surface area to volume, which enables the conjugation of

biomolecules. This enables the implementation of accurate design and engineering to accomplish specific intelligent functionalities, such as extended circulation, precise delivery to affected regions, and controlled release of medicinal agents. When enclosed within colloidal carriers such as micelles, liposomes, or solid nanoparticles, these magnetic nanoparticles (MNPs) can exhibit sensitivity to external magnetic fields. This characteristic allows for the development of versatile formulations that can be used for both diagnostic and therapeutic purposes. Ultrasound (US) is widely used in clinical settings for both diagnosis and therapy because of its ability to penetrate tissues and its high level of safety. Ultrasonically sensitive nanocarriers enable a distinctive approach to collecting drug carriers and inducing drug release at precise locations by manipulating the frequency, duty cycles, and exposure time of ultrasound waves.

Additional Responsive Systems

In addition to the stimuli previously discussed, glucose [62-64] and electro-responsive systems [65-68[have also been utilized to control payload release within nanocarriers. The integration of hybrid stimuli can further enhance drug delivery precision. Dual stimuli-responsive DDSs are prevalent and have been explored, including combinations such as thermo- and pH-responsive systems [69, 70]; thermo- and light-responsive systems [71, 72]; redox- and pH-responsive systems [30, 31]; and ultrasonic and magnetic-responsive systems [73-77].

To achieve the smart functionality of DDSs, a variety of stimuli are employed to trigger drug release at the intended location and time within different nano-architectures. Demonstrating the viability of these strategies requires evidence of the regulation of responses to each stimulus in both in vitro and in vivo settings. This review focuses on smart nanoplatforms with significant clinical potential in stimuli-responsive DDSs. We explore smart DDSs for controlled drug release, including polymers, liposomes, organic-inorganic hybrid biomaterials, and exosomes. While smart nanoplatforms have applications across various diseases, including neoplastic, diabetes, infections, cardiovascular, and inflammatory conditions, this review specifically emphasizes carcinoma diseases and their potential for future clinical translation.

Smart Nanoscale DDS

Polymeric Nanoparticles

Polymeric nanoparticles are a major area of development in smart drug delivery systems (DDS), due to their ability to respond to external stimuli and control drug release. Smart or stimuli-responsive polymers have been explored for controlling the release of biologically active cargos for several decades. As discussed previously, stimuli such as ultrasound (US), pH, and magnetic fields can induce physical or chemical transformations in these polymers, modulating the drug release rate based on the intensity of the applied stimulus.
These smart polymer materials are generally categorized into two types: **single stimulus-responsive** and **dual-/multi-stimuli responsive** polymers.

1. **Single Stimulus Responsive Polymers:**
    - **Exogenous Stimuli:** These include temperature, magnetic fields, ionic strength, US intensity, and electric pulses. These stimuli can induce conformational changes in the polymer chains, which affect the release of the drug [1, 7, 16].
    - **Endogenous Stimuli:** Factors such as pH, enzyme concentration, hormone levels, redox gradients, and small biomolecules fall into this category. They induce changes in the polymeric materials in response to the physiological conditions at the target site [19]. Among the various stimuli, pH, redox, enzymes, light, and temperature have emerged as prominent triggers for the design of smart polymeric DDSs [20, 29, 79].
2. **pH-Responsive Polymers:**
    - These polymers often feature ionizable groups that change their conformation in response to environmental pH. This can result in controlled drug release. For instance, pH-responsive polymeric micelles, such as those using hydrazone bonds to conjugate drugs like doxorubicin (DOX), can achieve a fast release of drugs in acidic environments like tumors. Surface charge-switchable polymers enhance cellular uptake by changing surface charges from negative to positive, improving drug delivery [21, 26, 27, 80-82].

Examples include:

- **pH-Sensitive Polymeric Micelles:** The hydrazone bond conjugates doxorubicin with poly (styrene-co-maleic anhydride) derivatives, allowing controlled release in acidic tumor environments [85].
- **Surface Charge Reversal Carriers:** PIC⊕NP/Pt@PPC-DA nanoparticles enhance platinum drug accumulation in response to tumor pH changes with prolonged circulation time in the blood [87-91].

Additionally, pH-sensitive polymers are used in tumor imaging. For example, ultra pH-sensitive (UPS) fluorescent nanoprobes activate strongly in response to acidic extracellular pH, aiding in high-resolution tumor imaging [94, 95].

3. **Redox-Responsive Polymers:**
    - These systems utilize the reduction of disulfide bonds by intracellular glutathione (GSH) to release drugs. Redox-responsive polymers can degrade in the presence of GSH, leading to the rapid release of the drug. For example, thioketal nanoparticles (TKNs) degrade in response to reactive oxygen species (ROS), releasing siRNA for treating intestinal inflammation [35].

Examples include:

- **Redox-Responsive Hyperbranched Polyglycerols:** Disulfide bonds used as cross-linkers degrade under redox conditions, facilitating drug release [98].
- **Thioketal Nanoparticles (TKNs):** Designed for oral delivery of siRNA, these nanoparticles degrade in response to ROS, showing potential for treating gastrointestinal diseases [99].

4. **Light-Responsive Polymers:**
    - Light-responsive systems use photochromic moieties or photochemical reactions to trigger drug release. These systems often involve reversible transitions activated by light, such as

azobenzene or spiropyran. Photodynamic therapy (PDT) and photothermal therapy (PTT) are applications where light-responsive polymers are used for tumor destruction and imaging [100, 101].

Examples include:

- **Photosensitizers Coupled with Plasmonic Nanoparticles:** Enhance PDT and imaging capabilities [102].
- **Porphysome Nanovesicles:** Used for photothermal therapy and imaging with long-wavelength responsiveness [103].

5. **Temperature-Responsive Polymers:**
   - Polymers like poly-N-isopropylacrylamide (PNIPAAm) exhibit a phase transition at specific temperatures, commonly used to control drug release. These polymers can switch between hydrophilic and hydrophobic states based on temperature changes [106].
6. **Glucose-Responsive Polymers:**
   - These polymers are being explored for diabetes treatment, responding to glucose levels to regulate drug release. Natural polymers such as chitosan and dextrin, which can be degraded by enzymes, are examples of glucose-responsive systems [107].

Natural Polymers: Chitosan and cyclodextrins, among other natural polymers, offer controlled release and have potential applications in smart DDS and bio-imaging [108, 109]. Overall, polymeric nanoparticles represent a significant advancement in controlled drug delivery, offering potential for application in various diseases and preclinical investigations. Their versatility and responsiveness to multiple stimuli make them promising candidates for clinical use.

Liposomes

The description of swollen phospholipid systems was first reported by Alec Bangham and colleagues in 1965 [110]. Since then, a variety of enclosed phospholipid bilayer structures consisting of single bilayers have been described as "liposomes" [111]. In 1971, Gregoriadis et al. first used liposomes as drug delivery systems [112]. With the development of new preparation technology, large unilamellar liposomes (LUVs) can now be obtained by extruding multilamellar vesicles through polycarbonate filters. Particularly when the diameter of liposomes is reduced to within 100 nm or less, they have been widely used as advanced DDSs in numerous clinical trials, such as anti-cancer, anti-inflammatory, anti-fungal drugs, and gene medicines [113, 114]. Some liposome formulations have even been approved for commercial use. Doxil®, the first Food and Drug Administration (FDA)-approved nanomedicine delivery system, is based on PEGylated liposomes [115]. Besides the liposomes available on the market, a number of lipidic nanoparticles are currently in the pipeline, moving from concept to clinical application. This indicates that the use of liposomes as drug carriers may be well-developed for clinical acceptance.

Inspired by the promising clinical applications, the development of smart liposomes has become a hot topic in nanomedicine. These liposomes can be easily stimulated by several triggers, such as temperature, pH gradients, enzyme

changes, ultrasound (US), and light [116, 117]. These novel, smarter liposome delivery systems may exhibit even better potential in future clinical applications. Although various stimuli can be used to control drug release from liposomes, temperature stimuli might be particularly important due to considerations of safety and practicality [126, 127]. As a smart drug carrier system, ThermoDox, a temperature-sensitive doxorubicin (DOX) liposome developed by Celsion, may be the closest formulation to clinical use so far. Taking advantage of the dipalmitoylphosphatidylcholine (DPPC) lipid crystallization melting temperature at 41.5°C, doxorubicin can be released from ThermoDox at this temperature [126]. Radiofrequency ablation (RFA) has also been used to activate DOX release from ThermoDox. In a Phase I clinical trial, the liver cancer-targeted ThermoDox DDS showed an improved safety profile compared to free doxorubicin. Although the results of Phase III clinical trials with ThermoDox were not entirely satisfactory—the treatment did not extend life span by the target threshold of 33% [19]—the strategy of temperature-sensitive liposomes offers a promising clinical future for smart DDSs.

To improve the control of drug release in response to mild heating, thermosensitive polymers have been used to modify liposomes, producing temperature-sensitive polymeric liposomes. A typical example of ultra-temperature-sensitive liposomes based on a thermosensitive block copolymer has been developed by Kono's group. The synthesized poly [2-(2-ethoxy) ethoxyethyl vinyl ether (EOEOVE)], is a promising biomaterial for constructing temperature-sensitive liposomes. The poly (EOEOVE)-modified liposomes showed even higher sensitivity to temperature than poly (N-isopropylacrylamide), which could further enhance the tumor selectivity and therapeutic effectiveness of payloads.

The fabrication of liposome complexes has further advanced the development of smart liposomes. For example, after being loaded with magnetic nanoparticles (MNPs) and exposed to a magnetic field, magnetic liposomes are endowed with multifunctional properties, such as the vessel effect, surface effect, biocompatibility, targeting effect, and easy recovery. Plank and coworkers designed folate receptor-targeted magnetic liposomes. Under exposure to an external magnetic field, magnetic hyperthermia triggered drug release and localized the drug at high concentrations in tumor tissues, resulting in a significant improvement in anticancer efficacy [128].

Other recent advances in smart liposomes include the use of low pH environments for pH-triggered approaches [129-132], the use of enzymes as a trigger in enzyme-sensitive liposomes [133, 134], and US-responsive liposomes [135-137]. Additionally, light as a stimulus has been widely investigated in photosensitive liposomes [138-140]. Moreover, liposomes can serve as a platform for co-delivery of magnetic resonance imaging (MRI) agents and therapeutic drugs [141-143]. As an important smart drug carrier, stimuli-sensitive liposomes represent a pathway toward the design of nanocarriers with significantly improved efficacy. Although successful in vivo applications of these systems remain a challenge, it is believed that more clinical products based on smart liposomal platforms will emerge in the near future.

Organic-Inorganic Hybrid Smart Nanoparticles

Organic-inorganic hybrid smart biomaterials refer to materials that combine the characteristics of organic and inorganic materials and can respond to stimuli after hybridization. The hybrid materials can be constructed by connecting organic or polymer molecules with nano-metal particles or nano-oxides like silica and titanium dioxide [144, 145]. Mesoporous silica materials as smart DDSs have attracted extensive attention in the past decade [145-148]. In addition, gold nanoparticles (AuNPs) have been widely explored for photothermal therapy (PTT) in the biomedical field [149-154]. Their specific surface chemistry, with facile functional modification, provides hybridization with more possibilities [145]. Besides, upconversion nanoparticles [155, 156], magnetic-sensitive nanocrystals in liposomes [157, 158], US-responsive liposomes with perfluorocarbon bubbles [159], and photoacoustic nanoparticles [160] can also be used as hybrid smart nano-DDSs for controlled drug release.

Although mesoporous silica nanoparticles (MSNPs) possess a large loading capacity, the loaded drugs are often released immediately after administration. Similar to conventional therapy methods, this can lead to lower therapeutic efficacy and severe side effects due to off-target effects. To minimize the premature release of the payloads before reaching the target site, different organic molecules or polymers have been used as smart gatekeepers on the pore outlets to prevent drugs from leaking out of the carriers until the carrier is exposed to internal or external stimuli [161]. The outer layer can be operated by stimuli such as pH, temperature, photo irradiation, redox potential, electromagnetic fields, and biomolecules [162], which can adjust the drug release speed from the pores of MSNPs. The strategy of modifying MSNPs with organic molecules to make them smart is analogous to the approach used for smart polymers. The first enzyme-sensitive cap on MSNPs was described in 2008 [163]. The MSNPs were functionalized by cyclodextrin (CD) torus with a PEG thread, connected by an enzyme-cleavable site. The drug was released when the enzyme-responsive bond was cleaved in the presence of esterase. Mondragón et al. [164] prepared two novel MSNP hybrid systems with a poly-L-lysine outer surface using two different anchoring strategies. One strategy utilized the formation of urea bonds, while the other focused on attachment by amide bonds. Almost no cargo was released into water for both nanoparticles. After introducing proteases into the release medium, a notable payload was released because the poly-L-lysine cap on the surface smartly responded to the enzyme in a controlled manner. Other organic constituents have also been used to modify inorganic compounds to fabricate smart hybrid materials, such as polypeptides, polyesters, and polysaccharides [165, 166]. These can act as capping agents when grafted to the entrance of the pores of MSNPs, and cargo will be released in the presence of protease, esterase, galactosidase, and other such enzymes [161]. Although MSNPs serve as organic-inorganic hybrid smart DDSs and show superior biocompatibility compared to other inorganic nanoparticles, the pharmacokinetics and pharmacodynamics of MSNPs should be further evaluated.

Gold Nanoparticles (AuNPs)

- **Types and Development**: AuNPs such as nanoshells, nanocages, and nanorods are advanced as photothermal therapy (PTT) agents [154, 167-169].
- **Biodegradability Issue**: AuNPs, being inorganic, are not biodegradable and accumulate in the body. Surface modifications with organic functional groups can address this [170].
- **Liposome Complexes**: Kojima and colleagues found that liposomes enhance the stability of AuNPs in isotonic conditions [170].
- **Dendrimers and AuNPs**: PEG-attached poly(amidoamine) (PAMAM) dendrimers loaded with AuNPs show strong cytotoxicity against human cervical cancer (HeLa) cells under light [171].
- **Drug Delivery Systems**: Wang's group developed a system with doxorubicin (DOX) modified onto AuNPs (DOX-Hyd@AuNPs) using an acid-labile linkage, which helps overcome multidrug resistance (MDR) and achieves controlled drug release [153].

Magnetic Nanoparticles (MNPs)

- **Applications and Control**: MNPs can be manipulated with an external alternating magnetic field (AMF) for drug and gene delivery, diagnostics, and therapeutics [75, 172].
- **Magnetic Microbubbles**: Superparamagnetic iron oxide (SPIO) Fe_3O_4 nanoparticles in microbubbles are used for dual imaging and controlled delivery via ultrasound [75, 172].
- **Smart Microcontainers**: Polymeric microspheres with SPIO Fe_3O_4 nanoparticles can switch between "open" and "closed" states under magnetic fields, facilitating gas generation and targeted therapy [73, 173].
- **Theranostics**: SPIOs serve as contrast agents for MRI and carriers for anticancer drugs, combining imaging with hyperthermia for tumor therapy [50]. Xie et al. developed magnetic nanocrystals (MNCs) with excellent imaging and therapeutic capabilities [55].

Exosomes

- **Characteristics and Applications**: Exosomes are nano-sized vesicles used for drug delivery due to their specific tissue targeting, biocompatibility, and drug-loading capacity [174-178].
- **Therapeutic Applications**: Exosome-based systems like catalase-loaded exosomes (exoCAT) are used to treat neurodegenerative disorders [179]. Exosomes from mouse dendritic cells loaded with DOX and iRGD peptides efficiently target tumors with minimal toxicity [180].
- **Challenges**: Issues include maintaining biological properties during loading, achieving large-scale production, and developing effective evaluation and testing methods for clinical applications [181].

General Challenges for Smart Nanoplatforms in Clinical Applications

- **Design Simplicity**: Smart DDSs often have complex structures, making them difficult to scale up. Simplicity in design is crucial for successful clinical translation [8, 182, 183].

- **Stimuli Control**: Control of endogenous triggers (e.g., pH, enzyme levels) is challenging due to variability among patients. Exogenous stimuli-responsive systems are easier to control but require improvements in tissue damage and penetration [19].
- **Safety and Toxicity**: Safety issues including biocompatibility, toxicity, and reproducibility need thorough investigation. The pharmacokinetics and pharmacodynamics of nanoscale DDSs must be well studied [184, 190].
- **Industrial Scale-Up**: Challenges include ensuring reproducibility, scalability, and control over physicochemical properties. Standardization and regulatory frameworks are needed for widespread clinical application [191, 192].
- **Regulatory Frameworks**: Existing regulations are insufficient for nano-pharmaceuticals. Comprehensive frameworks are needed to guide the development, characterization, and approval of nanomedicines [192].

Limitations Between Animal Evaluation and Clinical Effect

- **Model Relevance**: Current animal models may not accurately reflect human disease complexity. Diverse and relevant models are needed for better predictive value [8, 193].
- **Evaluation Standards**: Different animal species should be used to assess various diseases, and drug dosage and administration must be aligned with human trials [194, 195].
- **Advanced DDS Evaluation**: Effective evaluation strategies for toxicology, pharmacokinetics, and pharmacodynamics in animal models are necessary for translating findings to clinical settings.

Conclusion

The advent of intelligent drug delivery systems (DDSs) has marked a transformative shift in therapeutic strategies, offering targeted and controlled drug release mechanisms that significantly enhance treatment efficacy while mitigating side effects. Conventional DDSs, characterized by their lack of specificity and uncontrolled release profiles, often lead to systemic drug distribution that can result in adverse effects and reduced therapeutic effectiveness. In contrast, advanced controlled DDSs, particularly those incorporating nanotechnology, provide a more refined approach to drug administration. Nanoparticle-based systems have emerged as a prominent solution, utilizing their unique properties to deliver drugs precisely to targeted sites. These systems leverage stimuli-responsive mechanisms to release drugs only in the presence of specific internal or external triggers, such as pH changes, redox conditions, or temperature variations. For example, pH-responsive nanoparticles can selectively target acidic environments typical of tumor tissues, while redox-responsive systems exploit the higher levels of glutathione in cancer cells to release drugs selectively. The review also highlights significant advancements in other DDS technologies, including smart polymers, liposomes, and organic-inorganic hybrid materials. Smart polymers, such as those responsive to temperature or light, provide controlled release capabilities that can be finely tuned to match the therapeutic needs. Liposomes, particularly those modified with stimuli-responsive features, offer enhanced drug delivery options

with improved safety profiles. Organic-inorganic hybrid nanoparticles combine the benefits of both organic and inorganic materials, providing versatile platforms for controlled drug release. Despite these advancements, several challenges remain, including ensuring biocompatibility, scalability, and regulatory approval. The complexity of stimuli-responsive mechanisms and the need for precise control over drug release further complicate the translation of these technologies from the laboratory to clinical practice. In conclusion, while intelligent DDSs represent a significant step forward in drug delivery technology, continued research and development are crucial to overcoming existing challenges and achieving widespread clinical implementation. The potential benefits of these advanced systems in improving patient outcomes and reducing treatment-related adverse effects underscore the importance of ongoing innovation in this field.

References

1. Hrubý M, Filippov SK, Štěpánek P. Smart polymers in drug delivery systems on crossroads: Which way deserves following? *European Polymer Journal.* 2015;65:82–97. [Google Scholar]
2. Kopeček J, Yang J. Hydrogels as smart biomaterials. *Polymer International.* 2007;56:1078–98. [Google Scholar]
3. Lee BK, Yun YH, Park K. Smart nanoparticles for drug delivery: Boundaries and opportunities. *Chemical Engineering Science.* 2015;125:158–64. [PMC free article] [PubMed] [Google Scholar]
4. Bamrungsap S, Zhao Z, Chen T, Wang L, Li C, Fu T. et al. Nanotechnology in therapeutics: a focus on nanoparticles as a drug delivery system. *Nanomedicine.* 2012;7:1253–71. [PubMed] [Google Scholar]
5. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Advanced Drug Delivery Reviews.* 2013;65:36–48. [PubMed] [Google Scholar]
6. Couvreur P. Nanoparticles in drug delivery: past, present and future. *Advanced Drug Delivery Reviews.* 2013;65:21–3. [PubMed] [Google Scholar]
7. Alvarez-Lorenzo C, Concheiro A. Smart drug delivery systems: from fundamentals to the clinic. *Chemical Communications.* 2014;50:7743–65. [PubMed] [Google Scholar]
8. Crommelin DJ, Florence AT. Towards more effective advanced drug delivery systems. *International Journal of Pharmaceutics.* 2013;454:496–511. [PubMed] [Google Scholar]
9. Holzapfel BM, Reichert JC, Schantz J-T, Gbureck U, Rackwitz L, Nöth U. et al. How smart do biomaterials need to be? A translational science and clinical point of view. *Advanced Drug Delivery Reviews.* 2013;65:581–603. [PubMed] [Google Scholar]
10. Grund S, Bauer M, Fischer D. Polymers in drug delivery—state of the art and future trends. *Advanced Engineering Materials.* 2011;13:B61–B87. [Google Scholar]
11. Annabi N, Tamayol A, Uquillas JA, Akbari M, Bertassoni LE, Cha C. et al. 25th anniversary article: rational design and applications of hydrogels in regenerative medicine. *Advanced Materials.* 2014;26:85–124. [PMC free article] [PubMed] [Google Scholar]

12. Chang H-I, Yeh M-K. Clinical development of liposome-based drugs: formulation, characterization, and therapeutic efficacy. *International Journal of Nanomedicine.* 2012;7:49–60. [PMC free article] [PubMed] [Google Scholar]
13. Kumari A, Yadav SK, Yadav SC. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and Surfaces B: Biointerfaces.* 2010;75:1–18. [PubMed] [Google Scholar]
14. Rossi F, Ferrari R, Castiglione F, Mele A, Perale G, Moscatelli D. Polymer hydrogel functionalized with biodegradable nanoparticles as composite system for controlled drug delivery. *Nanotechnology.* 2014;26:015602. [PubMed] [Google Scholar]
15. Shimoni O, Postma A, Yan Y, Scott AM, Heath JK, Nice EC. et al. Macromolecule functionalization of disulfide-bonded polymer hydrogel capsules and cancer cell targeting. *ACS Nano.* 2012;6:1463–72. [PubMed] [Google Scholar]
16. Stumpel JE, Gil ER, Spoelstra AB, Bastiaansen CW, Broer DJ, Schenning AP. Stimuli-Responsive Materials Based on Interpenetrating Polymer Liquid Crystal Hydrogels. *Advanced Functional Materials.* 2015;25:3314–20. [Google Scholar]
17. Tanaka T. Collapse of gels and the critical endpoint. *Physical Review Letters.* 1978;40:820. [Google Scholar]
18. Yatvin MB, Weinstein JN, Dennis WH, Blumenthal R. Design of liposomes for enhanced local release of drugs by hyperthermia. *Science.* 1978;202:1290–3. [PubMed] [Google Scholar]
19. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. *Nature Materials.* 2013;12:991–1003. [PubMed] [Google Scholar]
20. Kelley EG, Albert JN, Sullivan MO, Epps III TH. Stimuli-responsive copolymer solution and surface assemblies for biomedical applications. *Chemical Society Reviews.* 2013;42:7057–71. [PMC free article] [PubMed] [Google Scholar]
21. Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A. et al. pH-Sensitive nano-systems for drug delivery in cancer therapy. *Biotechnology Advances.* 2014;32:693–710. [PubMed] [Google Scholar]
22. Ganesh VA, Baji A, Ramakrishna S. Smart functional polymers-a new route towards creating a sustainable environment. *RSC Advances.* 2014;4:53352–64. [Google Scholar]
23. Gao W, Chan JM, Farokhzad OC. pH-responsive nanoparticles for drug delivery. *Molecular Pharmaceutics.* 2010;7:1913–20. [PMC free article] [PubMed] [Google Scholar]
24. Yu P, Yu H, Guo C, Cui Z, Chen X, Yin Q. et al. Reversal of doxorubicin resistance in breast cancer by mitochondria-targeted pH-responsive micelles. *Acta Biomaterialia.* 2015;14:115–24. [PubMed] [Google Scholar]
25. Subudhi MB, Jain A, Jain A, Hurkat P, Shilpi S, Gulbake A. et al. Eudragit S100 coated citrus pectin nanoparticles for colon targeting of 5-Fluorouracil. *Materials.* 2015;8:832–49. [PMC free article] [PubMed] [Google Scholar]
26. Stubbs M, McSheehy PM, Griffiths JR, Bashford CL. Causes and consequences of tumour acidity and implications for treatment. *Molecular Medicine Today.* 2000;6:15–9. [PubMed] [Google Scholar]
27. Neri D, Supuran CT. Interfering with pH regulation in tumours as a therapeutic strategy. *Nature Reviews Drug Discovery.* 2011;10:767–77. [PubMed] [Google Scholar]

28. Lee ES, Oh KT, Kim D, Youn YS, Bae YH. Tumor pH-responsive flower-like micelles of poly (L-lactic acid)-b-poly (ethylene glycol)-b-poly (L-histidine) *Journal of Controlled Release.* 2007;123:19–26. [PMC free article] [PubMed] [Google Scholar]
29. Cheng R, Meng F, Deng C, Klok H-A, Zhong Z. Dual and multi-stimuli responsive polymeric nanoparticles for programmed site-specific drug delivery. *Biomaterials.* 2013;34:3647–57. [PubMed] [Google Scholar]
30. Pan Y-J, Chen Y-Y, Wang D-R, Wei C, Guo J, Lu D-R. et al. Redox/pH dual stimuli-responsive biodegradable nanohydrogels with varying responses to dithiothreitol and glutathione for controlled drug release. *Biomaterials.* 2012;33:6570–9. [PubMed] [Google Scholar]
31. Chen W, Zhong P, Meng F, Cheng R, Deng C, Feijen J. et al. Redox and pH-responsive degradable micelles for dually activated intracellular anticancer drug release. *Journal of Controlled Release.* 2013;169:171–9. [PubMed] [Google Scholar]
32. Huo M, Yuan J, Tao L, Wei Y. Redox-responsive polymers for drug delivery: from molecular design to applications. *Polymer Chemistry.* 2014;5:1519–28. [Google Scholar]
33. Wang J, Sun X, Mao W, Sun W, Tang J, Sui M. et al. Tumor Redox Heterogeneity-Responsive Prodrug Nanocapsules for Cancer Chemotherapy. *Advanced Materials.* 2013;25:3670–6. [PubMed] [Google Scholar]
34. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. *Nature Reviews Drug Discovery.* 2014;13:813–27. [PMC free article] [PubMed] [Google Scholar]
35. Wilson DS, Dalmasso G, Wang L, Sitaraman SV, Merlin D, Murthy N. Orally delivered thioketal nanoparticles loaded with TNF-α-siRNA target inflammation and inhibit gene expression in the intestines. *Nature Materials.* 2010;9:923–8. [PMC free article] [PubMed] [Google Scholar]
36. Nguyen MM, Carlini AS, Chien MP, Sonnenberg S, Luo C, Braden RL. et al. Enzyme-Responsive Nanoparticles for Targeted Accumulation and Prolonged Retention in Heart Tissue after Myocardial Infarction. *Advanced Materials.* 2015;27:5547–52. [PMC free article] [PubMed] [Google Scholar]
37. Callmann CE, Barback CV, Thompson MP, Hall DJ, Mattrey RF, Gianneschi NC. Therapeutic Enzyme-Responsive Nanoparticles for Targeted Delivery and Accumulation in Tumors. *Advanced Materials.* 2015;27:4611–5. [PMC free article] [PubMed] [Google Scholar]
38. De La Rica R, Aili D, Stevens MM. Enzyme-responsive nanoparticles for drug release and diagnostics. *Advanced Drug Delivery Reviews.* 2012;64:967–78. [PubMed] [Google Scholar]
39. [39] Lock LL, Tang Z, Keith D, Reyes C, Cui H. Enzyme-Specific Doxorubicin Drug Beacon as Drug-Resistant Theranostic Molecular Probes. *ACS Macro Letters.* 2015;4:552–5. [PubMed] [Google Scholar]
40. Shi Y, van den Dungen ET, Klumperman B, van Nostrum CF, Hennink WE. Reversible Addition-Fragmentation Chain Transfer Synthesis of a Micelle-Forming, Structure Reversible Thermosensitive Diblock Copolymer Based on the N-(2-Hydroxy propyl) Methacrylamide Backbone. *ACS Macro Letters.* 2013;2:403–8. [PubMed] [Google Scholar]
41. Shi Y, van Steenbergen MJ, Teunissen EA, Novo Ls, Gradmann S, Baldus M. et al. Π-Π stacking increases the stability and loading capacity of

thermosensitive polymeric micelles for chemotherapeutic drugs. *Biomacromolecules.* 2013;14:1826–37. [PubMed] [Google Scholar]
42. Shi Y, Cardoso RM, Van Nostrum CF, Hennink WE. Anthracene functionalized thermosensitive and UV-crosslinkable polymeric micelles. *Polymer Chemistry.* 2015;6:2048–53. [Google Scholar]
43. Danhier F, Feron O, Préat V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. *Journal of Controlled Release.* 2010;148:135–46. [PubMed] [Google Scholar]
44. Adelsberger J, Kulkarni A, Jain A, Wang W, Bivigou-Koumba AM, Busch P. et al. Thermoresponsive PS-b-PNIPAM-b-PS micelles: aggregation behavior, segmental dynamics, and thermal response. *Macromolecules.* 2010;43:2490–501. [Google Scholar]
45. Zhao Y, Fan X, Liu D, Wang Z. PEGylated thermo-sensitive poly (amidoamine) dendritic drug delivery systems. *International Journal of Pharmaceutics.* 2011;409:229–36. [PubMed] [Google Scholar]
46. Lal S, Clare SE, Halas NJ. Nanoshell-enabled photothermal cancer therapy: impending clinical impact. *Accounts of Chemical Research.* 2008;41:1842–51. [PubMed] [Google Scholar]
47. Sun J, Zhang Y, Chen Z, Zhou J, Gu N. Fibrous Aggregation of Magnetite Nanoparticles Induced by a Time-Varied Magnetic Field. *Angewandte Chemie International Edition.* 2007;46:4767–70. [PubMed] [Google Scholar]
48. Liu J, Zhang Y, Wang C, Xu R, Chen Z, Gu N. Magnetically sensitive alginate-templated polyelectrolyte multilayer microcapsules for controlled release of doxorubicin. *The Journal of Physical Chemistry C.* 2010;114:7673–9. [Google Scholar]
49. Chen Z, Yin J-J, Zhou Y-T, Zhang Y, Song L, Song M. et al. Dual enzyme-like activities of iron oxide nanoparticles and their implication for diminishing cytotoxicity. *Acs Nano.* 2012;6:4001–12. [PubMed] [Google Scholar]
50. Fang K, Song L, Gu Z, Yang F, Zhang Y, Gu N. Magnetic field activated drug release system based on magnetic PLGA microspheres for chemo-thermal therapy. *Colloids and Surfaces B: Biointerfaces.* 2015;136:712–20. [PubMed] [Google Scholar]
51. Yang F, Zhang X, Song L, Cui H, Myers JN, Bai T. et al. Controlled Drug Release and Hydrolysis Mechanism of Polymer-Magnetic Nanoparticle Composite. *ACS Applied Materials & Interfaces.* 2015;7:9410–9. [PubMed] [Google Scholar]
52. Hu K, Sun J, Guo Z, Wang P, Chen Q, Ma M. et al. A novel magnetic hydrogel with aligned magnetic colloidal assemblies showing controllable enhancement of magnetothermal effect in the presence of alternating magnetic field. *Advanced Materials.* 2015;27:2507–14. [PubMed] [Google Scholar]
53. Wang F, Kim D-K, Yoshitake T, Johansson S, Bjelke B, Muhammed M. et al. Diffusion and clearance of superparamagnetic iron oxide nanoparticles infused into the rat striatum studied by MRI and histochemical techniques. *Nanotechnology.* 2010;22:015103. [PubMed] [Google Scholar]
54. Yue-Jian C, Juan T, Fei X, Jia-Bi Z, Ning G, Yi-Hua Z. et al. Synthesis, self-assembly, and characterization of PEG-coated iron oxide nanoparticles as potential MRI contrast agent. *Drug Development and Industrial Pharmacy.* 2010;36:1235–44. [PubMed] [Google Scholar]

55. Xie J, Zhang Y, Yan C, Song L, Wen S, Zang F. et al. High-performance PEGylated Mn-Zn ferrite nanocrystals as a passive-targeted agent for magnetically induced cancer theranostics. *Biomaterials.* 2014;35:9126–36. [PubMed] [Google Scholar]
56. Xiong F, Chen Y, Chen J, Yang B, Zhang Y, Gao H. et al. Rubik-like magnetic nanoassemblies as an efficient drug multifunctional carrier for cancer theranostics. *Journal of Controlled Release.* 2013;172:993–1001. [PubMed] [Google Scholar]
57. Song L, Zang F, Song M, Chen G, Zhang Y. Effective PEGylation of Fe3O4 nanomicelles for in vivo MR imaging. *Journal of Nanoscience and Nanotechnology.* 2015;15:4111–8. [PubMed] [Google Scholar]
58. Liu D, Wu W, Chen X, Wen S, Zhang X, Ding Q. et al. Conjugation of paclitaxel to iron oxide nanoparticles for tumor imaging and therapy. *Nanoscale.* 2012;4:2306–10. [PubMed] [Google Scholar]
59. Yang H-W, Hua M-Y, Liu H-L, Huang C-Y, Tsai R-Y, Lu Y-J. et al. Self-protecting core-shell magnetic nanoparticles for targeted, traceable, long half-life delivery of BCNU to gliomas. *Biomaterials.* 2011;32:6523–32. [PubMed] [Google Scholar]
60. Hayashi K, Nakamura M, Sakamoto W, Yogo T, Miki H, Ozaki S. et al. Superparamagnetic nanoparticle clusters for cancer theranostics combining magnetic resonance imaging and hyperthermia treatment. *Theranostics.* 2013;3:366–76. [PMC free article] [PubMed] [Google Scholar]
61. Paris JL, Cabañas MV, Manzano M, Vallet-Regí M. Polymer-Grafted Mesoporous Silica Nanoparticles as Ultrasound-Responsive Drug Carriers. *ACS Nano.* 2015;9:11023–33. [PubMed] [Google Scholar]
62. Guo Q, Zhang T, An J, Wu Z, Zhao Y, Dai X. et al. Block versus Random Amphiphilic Glycopolymer Nanopaticles as Glucose-Responsive Vehicles. *Biomacromolecules.* 2015;16:3345–56. [PubMed] [Google Scholar]
63. Wu Q, Wang L, Yu H, Wang J, Chen Z. Organization of glucose-responsive systems and their properties. *Chemical Reviews.* 2011;111:7855–75. [PubMed] [Google Scholar]
64. Gu Z, Aimetti AA, Wang Q, Dang TT, Zhang Y, Veiseh O. et al. Injectable nano-network for glucose-mediated insulin delivery. *ACS Nano.* 2013;7:4194–201. [PMC free article] [PubMed] [Google Scholar]
65. Murdan S. Electro-responsive drug delivery from hydrogels. *Journal of Controlled Release.* 2003;92:1–17. [PubMed] [Google Scholar]
66. Yun J, Im JS, Lee Y-S, Kim H-I. Electro-responsive transdermal drug delivery behavior of PVA/PAA/MWCNT nanofibers. *European Polymer Journal.* 2011;47:1893–902. [Google Scholar]
67. Ying X, Wang Y, Liang J, Yue J, Xu C, Lu L. et al. Angiopep-Conjugated Electro-Responsive Hydrogel Nanoparticles: Therapeutic Potential for Epilepsy. *Angewandte Chemie International Edition.* 2014;53:12436–40. [PubMed] [Google Scholar]
68. Curcio M, Spizzirri UG, Cirillo G, Vittorio O, Picci N, Nicoletta FP. et al. On demand delivery of ionic drugs from electro-responsive CNT hybrid films. *RSC Advances.* 2015;5:44902–11. [Google Scholar]
69. Schmaljohann D. Thermo-and pH-responsive polymers in drug delivery. *Advanced Drug Delivery Reviews.* 2006;58:1655–70. [PubMed] [Google Scholar]

70. Zhang L, Guo R, Yang M, Jiang X, Liu B. Thermo and pH Dual-Responsive Nanoparticles for Anti-Cancer Drug Delivery. *Advanced Materials.* 2007;19:2988–92. [Google Scholar]
71. Zhang Z, Wang J, Chen C. Near-Infrared Light-Mediated Nanoplatforms for Cancer Thermo-Chemotherapy and Optical Imaging. *Advanced Materials.* 2013;25:3869–80. [PubMed] [Google Scholar]
72. Jochum FD, Theato P. Thermo-and light responsive micellation of azobenzene containing block copolymers. *Chemical Communications.* 2010;46:6717–9. [PubMed] [Google Scholar]
73. Yang F, Chen P, He W, Gu N, Zhang X, Fang K. et al. Bubble microreactors triggered by an alternating magnetic field as diagnostic and therapeutic delivery devices. *Small.* 2010;6:1300–5. [PubMed] [Google Scholar]
74. Yang F, Hu S, Zhang Y, Cai X, Huang Y, Wang F. et al. A Hydrogen Peroxide-Responsive O2 Nanogenerator for Ultrasound and Magnetic-Resonance Dual Modality Imaging. *Advanced Materials.* 2012;24:5205–11. [PubMed] [Google Scholar]
75. Yang F, Zhang M, He W, Chen P, Cai X, Yang L. et al. Controlled release of Fe3O4 nanoparticles in encapsulated microbubbles to tumor cells via sonoporation and associated cellular bioeffects. *Small.* 2011;7:902–10. [PubMed] [Google Scholar]
76. Yang F, Li M, Cui H, Wang T, Chen Z, Song L. et al. Altering the response of intracellular reactive oxygen to magnetic nanoparticles using ultrasound and microbubbles. *Science China Materials.* 2015;58:467–80. [Google Scholar]
77. Cai X, Yang F, Gu N. Applications of magnetic microbubbles for theranostics. *Theranostics.* 2012;2:103–12. [PMC free article] [PubMed] [Google Scholar]
78. Delcea M, Möhwald H, Skirtach AG. Stimuli-responsive LbL capsules and nanoshells for drug delivery. *Advanced Drug Delivery Reviews.* 2011;63:730–47. [PubMed] [Google Scholar]
79. Stuart MAC, Huck WT, Genzer J, Müller M, Ober C, Stamm M. et al. Emerging applications of stimuli-responsive polymer materials. *Nature Materials.* 2010;9:101–13. [PubMed] [Google Scholar]
80. Gao GH, Li Y, Lee DS. Environmental pH-sensitive polymeric micelles for cancer diagnosis and targeted therapy. *Journal of Controlled Release.* 2013;169:180–4. [PubMed] [Google Scholar]
81. Du J-Z, Mao C-Q, Yuan Y-Y, Yang X-Z, Wang J. Tumor extracellular acidity-activated nanoparticles as drug delivery systems for enhanced cancer therapy. *Biotechnology Advances.* 2014;32:789–803. [PubMed] [Google Scholar]
82. Meng F, Zhong Y, Cheng R, Deng C, Zhong Z. pH-sensitive polymeric nanoparticles for tumor-targeting doxorubicin delivery: concept and recent advances. *Nanomedicine.* 2014;9:487–99. [PubMed] [Google Scholar]
83. Liu R, Li D, He B, Xu X, Sheng M, Lai Y. et al. Anti-tumor drug delivery of pH-sensitive poly (ethylene glycol)-poly (L-histidine-)-poly (L-lactide) nanoparticles. *Journal of Controlled Release.* 2011;152:49–56. [PubMed] [Google Scholar]
84. Li H, Li M, Chen C, Fan A, Kong D, Wang Z. et al. On-demand combinational delivery of curcumin and doxorubicin via a pH-labile micellar nanocarrier. *International Journal of Pharmaceutics.* 2015;495:572–8. [PubMed] [Google Scholar]

85. Duan X, Xiao J, Yin Q, Zhang Z, Yu H, Mao S. et al. Smart pH-sensitive and temporal-controlled polymeric micelles for effective combination therapy of doxorubicin and disulfiram. *ACS Nano.* 2013;7:5858–69. [PubMed] [Google Scholar]
86. Shi Y, van Nostrum CF, Hennink WE. Interfacially Hydrazone Cross-linked Thermosensitive Polymeric Micelles for Acid-Triggered Release of Paclitaxel. *ACS Biomaterials Science & Engineering.* 2015;1:393–404. [PubMed] [Google Scholar]
87. Du JZ, Sun TM, Song WJ, Wu J, Wang J. A Tumor-Acidity-Activated Charge-Conversional Nanogel as an Intelligent Vehicle for Promoted Tumoral-Cell Uptake and Drug Delivery. *Angewandte Chemie International Edition.* 2010;122:3703–8. [PubMed] [Google Scholar]
88. Du J-Z, Du X-J, Mao C-Q, Wang J. Tailor-made dual pH-sensitive polymer-doxorubicin nanoparticles for efficient anticancer drug delivery. *Journal of the American Chemical Society.* 2011;133:17560–3. [PubMed] [Google Scholar]
89. Yuan YY, Mao CQ, Du XJ, Du JZ, Wang F, Wang J. Surface charge switchable nanoparticles based on zwitterionic polymer for enhanced drug delivery to tumor. *Advanced Materials.* 2012;24:5476–80. [PubMed] [Google Scholar]
90. Yang X-Z, Du J-Z, Dou S, Mao C-Q, Long H-Y, Wang J. Sheddable ternary nanoparticles for tumor acidity-targeted siRNA delivery. *ACS Nano.* 2011;6:771–81. [PubMed] [Google Scholar]
91. Yang XZ, Du XJ, Liu Y, Zhu YH, Liu YZ, Li YP. et al. Rational design of polyion complex nanoparticles to overcome cisplatin resistance in cancer therapy. *Advanced Materials.* 2014;26:931–6. [PubMed] [Google Scholar]
92. Mo R, Sun Q, Xue J, Li N, Li W, Zhang C. et al. Multistage pH-Responsive Liposomes for Mitochondrial-Targeted Anticancer Drug Delivery. *Advanced Materials.* 2012;24:3659–65. [PubMed] [Google Scholar]
93. Ju C, Mo R, Xue J, Zhang L, Zhao Z, Xue L. et al. Sequential intra-intercellular nanoparticle delivery system for deep tumor penetration. *Angewandte Chemie International Edition.* 2014;53:6253–8. [PubMed] [Google Scholar]
94. Zhou K, Wang Y, Huang X, Luby-Phelps K, Sumer BD, Gao J. Tunable, Ultrasensitive pH-Responsive Nanoparticles Targeting Specific Endocytic Organelles in Living Cells. *Angewandte Chemie International Edition.* 2011;50:6109–14. [PMC free article] [PubMed] [Google Scholar]
95. Wang Y, Zhou K, Huang G, Hensley C, Huang X, Ma X. et al. A nanoparticle-based strategy for the imaging of a broad range of tumours by nonlinear amplification of microenvironment signals. *Nature Materials.* 2014;13:204–12. [PMC free article] [PubMed] [Google Scholar]
96. Sun H, Guo B, Cheng R, Meng F, Liu H, Zhong Z. Biodegradable micelles with sheddable poly (ethylene glycol) shells for triggered intracellular release of doxorubicin. *Biomaterials.* 2009;30:6358–66. [PubMed] [Google Scholar]
97. Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery. *Journal of Controlled Release.* 2008;126:187–204. [PubMed] [Google Scholar]
98. Son S, Shin E, Kim B-S. Redox-Degradable Biocompatible Hyperbranched Polyglycerols: Synthesis, Copolymerization Kinetics, Degradation, and Biocompatibility. *Macromolecules.* 2015;48:600–9. [Google Scholar]

99. Kountouras J, Chatzopoulos D, Zavos C. Reactive oxygen metabolites and upper gastrointestinal diseases. *Hepato-gastroenterology.* 2000;48:743–51. [PubMed] [Google Scholar]
100. Wang W, Lin J, Cai C, Lin S. Optical properties of amphiphilic copolymer-based self-assemblies. *European Polymer Journal.* 2015;65:112–31. [Google Scholar]
101. Lovell JF, Liu TW, Chen J, Zheng G. Activatable photosensitizers for imaging and therapy. *Chemical Reviews.* 2010;110:2839–57. [PubMed] [Google Scholar]
102. Farhadi A, Roxin Á, Wilson BC, Zheng G. Nano-enabled SERS reporting photosensitizers. *Theranostics.* 2015;5:469. [PMC free article] [PubMed] [Google Scholar]
103. Lovell JF, Jin CS, Huynh E, Jin H, Kim C, Rubinstein JL. et al. Porphysome nanovesicles generated by porphyrin bilayers for use as multimodal biophotonic contrast agents. *Nature Materials.* 2011;10:324–32. [PubMed] [Google Scholar]
104. Wang F, Banerjee D, Liu Y, Chen X, Liu X. Upconversion nanoparticles in biological labeling, imaging, and therapy. *Analyst.* 2010;135:1839–54. [PubMed] [Google Scholar]
105. Liu Q, Yin B, Yang T, Yang Y, Shen Z, Yao P. et al. A general strategy for biocompatible, high-effective upconversion nanocapsules based on triplet-triplet annihilation. *Journal of the American Chemical Society.* 2013;135:5029–37. [PubMed] [Google Scholar]
106. Liu T-Y, Hu S-H, Liu D-M, Chen S-Y, Chen I-W. Biomedical nanoparticle carriers with combined thermal and magnetic responses. *Nano Today.* 2009;4:52–65. [Google Scholar]
107. Kim H, Kang YJ, Kang S, Kim KT. Monosaccharide-responsive release of insulin from polymersomes of polyboroxole block copolymers at neutral pH. *Journal of the American Chemical Society.* 2012;134:4030–3. [PubMed] [Google Scholar]
108. Bonnet V, Gervaise C, Djedaïni-Pilard F, Furlan A, Sarazin C. Cyclodextrin nanoassemblies: a promising tool for drug delivery. *Drug Discovery Today.* 2015;20:1120–6. [PubMed] [Google Scholar]
109. Ryu JH, Hong S, Lee H. Bio-inspired adhesive catechol-conjugated chitosan for biomedical applications: A mini review. *Acta Biomaterialia.* 2015;27:101–15. [PubMed] [Google Scholar]
110. Bangham A, Standish MM, Watkins J. Diffusion of univalent ions across the lamellae of swollen phospholipids. *Journal of Molecular Biology.* 1965;13:238–IN27. [PubMed] [Google Scholar]
111. Deamer DW. From “Banghasomes” to liposomes: A memoir of Alec Bangham, 1921-2010. *The FASEB Journal.* 2010;24:1308–10. [PubMed] [Google Scholar]
112. Gregoriadis G, Ryman B. Liposomes as carriers of enzymes or drugs: a new approach to the treatment of storage diseases. *Biochemical Journal.* 1971;124:58P. [PMC free article] [PubMed] [Google Scholar]
113. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Joo SW, Zarghami N, Hanifehpour Y. et al. Liposome: classification, preparation, and applications. *Nanoscale Research Letters.* 2013;8:102. [PMC free article] [PubMed] [Google Scholar]
114. Torchilin V. *Liposomes in drug delivery.* Fundamentals and Applications of Controlled Release Drug Delivery: Springer; 2012. p289-328. [Google Scholar]

115. Barenholz YC. Doxil®—the first FDA-approved nano-drug: lessons learned. *Journal of Controlled Release.* 2012;160:117–34. [PubMed] [Google Scholar]
116. Bibi S, Lattmann E, Mohammed AR, Perrie Y. Trigger release liposome systems: local and remote controlled delivery? *Journal of Microencapsulation.* 2012;29:262–76. [PubMed] [Google Scholar]
117. Sawant RR, Torchilin VP. Liposomes as 'smart'pharmaceutical nanocarriers. *Soft Matter.* 2010;6:4026–44. [Google Scholar]
118. Park JW. Liposome-based drug delivery in breast cancer treatment. *Breast Cancer Research.* 2002;4:95. [PMC free article] [PubMed] [Google Scholar]
119. Clemons KV, Stevens DA. Comparative efficacies of four amphotericin B formulations—Fungizone, Amphotec (Amphocil), AmBisome, and Abelcet against systemic murine aspergillosis. *Antimicrobial Agents and Chemotherapy.* 2004;48:1047–50. [PMC free article] [PubMed] [Google Scholar]
120. Petre CE, Dittmer DP. Liposomal daunorubicin as treatment for Kaposi's sarcoma. *International Journal of Nanomedicine.* 2007;2:277. [PMC free article] [PubMed] [Google Scholar]
121. Chamberlain MC. Neurotoxicity of intra-CSF liposomal cytarabine (DepoCyt) administered for the treatment of leptomeningeal metastases: a retrospective case series. *Journal of Neuro-oncology.* 2012;109:143–8. [PubMed] [Google Scholar]
122. Nicolini A, Giardino R, Carpi A, Ferrari P, Anselmi L, Colosimo S. et al. Metastatic breast cancer: an updating. *Biomedicine & Pharmacotherapy.* 2006;60:548–56. [PubMed] [Google Scholar]
123. Barnes LD, Giuliano EA, Ota J. Cellular localization of Visudyne® as a function of time after local injection in an in vivo model of squamous cell carcinoma: an investigation into tumor cell death. *Veterinary Ophthalmology.* 2010;13:158–65. [PubMed] [Google Scholar]
124. Zhang Q, Huang X-E, Gao L-L. A clinical study on the premedication of paclitaxel liposome in the treatment of solid tumors. *Biomedicine & Pharmacotherapy.* 2009;63:603–7. [PubMed] [Google Scholar]
125. Silverman JA, Deitcher SR. Marqibo®(vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemotherapy and Pharmacology.* 2013;71:555–64. [PMC free article] [PubMed] [Google Scholar]
126. Chen K-J, Chaung E-Y, Wey S-P, Lin K-J, Cheng F, Lin C-C. et al. Hyperthermia-mediated local drug delivery by a bubble-generating liposomal system for tumor-specific chemotherapy. *ACS Nano.* 2014;8:5105–15. [PubMed] [Google Scholar]
127. Kono K, Ozawa T, Yoshida T, Ozaki F, Ishizaka Y, Maruyama K. et al. Highly temperature-sensitive liposomes based on a thermosensitive block copolymer for tumor-specific chemotherapy. *Biomaterials.* 2010;31:7096–105. [PubMed] [Google Scholar]
128. Pradhan P, Giri J, Rieken F, Koch C, Mykhaylyk O, Döblinger M. et al. Targeted temperature sensitive magnetic liposomes for thermo-chemotherapy. *Journal of Controlled Release.* 2010;142:108–21. [PubMed] [Google Scholar]

129. Simões S, Moreira JN, Fonseca C, Düzgüneş N, Pedroso de Lima MC. On the formulation of pH-sensitive liposomes with long circulation times. *Advanced Drug Delivery Reviews.* 2004;56:947–65. [PubMed] [Google Scholar]
130. Obata Y, Tajima S, Takeoka S. Evaluation of pH-responsive liposomes containing amino acid-based zwitterionic lipids for improving intracellular drug delivery in vitro and in vivo. *Journal of Controlled Release.* 2010;142:267–76. [PubMed] [Google Scholar]
131. Chiang Y-T, Lo C-L. pH-responsive polymer-liposomes for intracellular drug delivery and tumor extracellular matrix switched-on targeted cancer therapy. *Biomaterials.* 2014;35:5414–24. [PubMed] [Google Scholar]
132. Cuomo F, Lopez F, Ceglie A, Maiuro L, Miguel MG, Lindman B. pH-responsive liposome-templated polyelectrolyte nanocapsules. *Soft Matter.* 2012;8:4415–20. [Google Scholar]
133. [133] Wan Y, Han J, Fan G, Zhang Z, Gong T, Sun X. Enzyme-responsive liposomes modified adenoviral vectors for enhanced tumor cell transduction and reduced immunogenicity. *Biomaterials.* 2013;34:3020–30. [PubMed] [Google Scholar]
134. Zhu G, Mock JN, Aljuffali I, Cummings BS, Arnold RD. Secretory phospholipase A2 responsive liposomes. *Journal of Pharmaceutical Sciences.* 2011;100:3146–59. [PMC free article] [PubMed] [Google Scholar]
135. Huang S-L. *Ultrasound-responsive liposomes.* Liposomes: Methods and Protocols, Volume 1: Pharmaceutical Nanocarriers; 2010. pp. 113–28. [PubMed] [Google Scholar]
136. Yudina A, De Smet M, Lepetit-Coiffe M, Langereis S, Van Ruijssevelt L, Smirnov P. et al. Ultrasound-mediated intracellular drug delivery using microbubbles and temperature-sensitive liposomes. *Journal of Controlled Release.* 2011;155:442–8. [PubMed] [Google Scholar]
137. Klibanov AL, Shevchenko TI, Raju BI, Seip R, Chin CT. Ultrasound-triggered release of materials entrapped in microbubble-liposome constructs: a tool for targeted drug delivery. *Journal of Controlled Release.* 2010;148:13–7. [PMC free article] [PubMed] [Google Scholar]
138. Paasonen L, Sipilä T, Subrizi A, Laurinmäki P, Butcher SJ, Rappolt M. et al. Gold-embedded photosensitive liposomes for drug delivery: triggering mechanism and intracellular release. *Journal of Controlled Release.* 2010;147:136–43. [PubMed] [Google Scholar]
139. Leung SJ, Romanowski M. Light-activated content release from liposomes. *Theranostics.* 2012;2:1020–36. [PMC free article] [PubMed] [Google Scholar]
140. Skupin-Mrugalska P, Piskorz J, Goslinski T, Mielcarek J, Konopka K, Düzgüneş N. Current status of liposomal porphyrinoid photosensitizers. *Drug Discovery Today.* 2013;18:776–84. [PubMed] [Google Scholar]
141. Mikhaylov G, Mikac U, Magaeva AA, Itin VI, Naiden EP, Psakhye I. et al. Ferri-liposomes as an MRI-visible drug-delivery system for targeting tumours and their microenvironment. *Nature Nanotechnology.* 2011;6:594–602. [PubMed] [Google Scholar]
142. de Smet M, Heijman E, Langereis S, Hijnen NM, Grüll H. Magnetic resonance imaging of high intensity focused ultrasound mediated drug delivery from temperature-sensitive liposomes: an in vivo proof-of-concept study. *Journal of Controlled Release.* 2011;150:102–10. [PubMed] [Google Scholar]

143. de Smet M, Langereis S, van den Bosch S, Grüll H. Temperature-sensitive liposomes for doxorubicin delivery under MRI guidance. *Journal of Controlled Release.* 2010;143:120–7. [PubMed] [Google Scholar]
144. Sanchez C, Julián B, Belleville P, Popall M. Applications of hybrid organic-inorganic nanocomposites. *Journal of Materials Chemistry.* 2005;15:3559–92. [Google Scholar]
145. Yang P, Gai S, Lin J. Functionalized mesoporous silica materials for controlled drug delivery. *Chemical Society Reviews.* 2012;41:3679–98. [PubMed] [Google Scholar]
146. Li Z, Barnes JC, Bosoy A, Stoddart JF, Zink JI. Mesoporous silica nanoparticles in biomedical applications. *Chemical Society Reviews.* 2012;41:2590–605. [PubMed] [Google Scholar]
147. Tang F, Li L, Chen D. Mesoporous silica nanoparticles: synthesis, biocompatibility and drug delivery. *Advanced Materials.* 2012;24:1504–34. [PubMed] [Google Scholar]
148. Vivero-Escoto JL, Slowing II, Trewyn BG, Lin VSY. Mesoporous silica nanoparticles for intracellular controlled drug delivery. *Small.* 2010;6:1952–67. [PubMed] [Google Scholar]
149. Kim D, Park S, Lee JH, Jeong YY, Jon S. Antibiofouling polymer-coated gold nanoparticles as a contrast agent for in vivo X-ray computed tomography imaging. *Journal of the American Chemical Society.* 2007;129:7661–5. [PubMed] [Google Scholar]
150. Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA. The golden age: gold nanoparticles for biomedicine. *Chemical Society Reviews.* 2012;41:2740–79. [PMC free article] [PubMed] [Google Scholar]
151. Mieszawska AJ, Mulder WJ, Fayad ZA, Cormode DP. Multifunctional gold nanoparticles for diagnosis and therapy of disease. *Molecular Pharmaceutics.* 2013;10:831–47. [PMC free article] [PubMed] [Google Scholar]
152. Sun T-M, Wang Y-C, Wang F, Du J-Z, Mao C-Q, Sun C-Y. et al. Cancer stem cell therapy using doxorubicin conjugated to gold nanoparticles via hydrazone bonds. *Biomaterials.* 2014;35:836–45. [PubMed] [Google Scholar]
153. Wang F, Wang Y-C, Dou S, Xiong M-H, Sun T-M, Wang J. Doxorubicin-tethered responsive gold nanoparticles facilitate intracellular drug delivery for overcoming multidrug resistance in cancer cells. *Acs Nano.* 2011;5:3679–92. [PubMed] [Google Scholar]
154. Dykman L, Khlebtsov N. Gold nanoparticles in biomedical applications: recent advances and perspectives. *Chemical Society Reviews.* 2012;41:2256–82. [PubMed] [Google Scholar]
155. Wang C, Cheng L, Liu Z. Drug delivery with upconversion nanoparticles for multi-functional targeted cancer cell imaging and therapy. *Biomaterials.* 2011;32:1110–20. [PubMed] [Google Scholar]
156. Tsang M-K, Bai G, Hao J. Stimuli responsive upconversion luminescence nanomaterials and films for various applications. *Chemical Society Reviews.* 2015;44:1585–607. [PubMed] [Google Scholar]
157. Amstad E, Kohlbrecher J, Müller E, Schweizer T, Textor M, Reimhult E. Triggered release from liposomes through magnetic actuation of iron oxide nanoparticle containing membranes. *Nano Letters.* 2011;11:1664–70. [PubMed] [Google Scholar]

158. Sailor MJ, Park JH. Hybrid nanoparticles for detection and treatment of cancer. *Advanced Materials.* 2012;24:3779–802. [PMC free article] [PubMed] [Google Scholar]
159. Hagisawa K, Nishioka T, Suzuki R, Maruyama K, Takase B, Ishihara M. et al. Thrombus-targeted perfluorocarbon-containing liposomal bubbles for enhancement of ultrasonic thrombolysis: in vitro and in vivo study. *Journal of Thrombosis and Haemostasis.* 2013;11:1565–73. [PubMed] [Google Scholar]
160. Lu W, Huang Q, Ku G, Wen X, Zhou M, Guzatov D. et al. Photoacoustic imaging of living mouse brain vasculature using hollow gold nanospheres. *Biomaterials.* 2010;31:2617–26. [PMC free article] [PubMed] [Google Scholar]
161. Giret S, Wong Chi Man M, Carcel C. Mesoporous-Silica-Functionalized Nanoparticles for Drug Delivery. *Chemistry-A European Journal.* 2015;21:13850–65. [PubMed] [Google Scholar]
162. Baek S, Singh RK, Khanal D, Patel KD, Lee E-J, Leong KW. et al. Smart multifunctional drug delivery towards anticancer therapy harmonized in mesoporous nanoparticles. *Nanoscale.* 2015;7:14191–216. [PubMed] [Google Scholar]
163. Patel K, Angelos S, Dichtel WR, Coskun A, Yang Y-W, Zink JI. et al. Enzyme-responsive snap-top covered silica nanocontainers. *Journal of the American Chemical Society.* 2008;130:2382–3. [PubMed] [Google Scholar]
164. Mondragón L, Mas N, Ferragud V, de la Torre C, Agostini A, Martínez-Máñez R. et al. Enzyme-responsive intracellular-controlled release using silica mesoporous nanoparticles capped with ε-Poly-L-lysine. *Chemistry-A European Journal.* 2014;20:5271–81. [PubMed] [Google Scholar]
165. Coll C, Mondragón L, Martínez-Máñez R, Sancenón F, Marcos MD, Soto J. et al. Enzyme-Mediated Controlled Release Systems by Anchoring Peptide Sequences on Mesoporous Silica Supports. *Angewandte Chemie International Edition.* 2011;50:2138–40. [PubMed] [Google Scholar]
166. Bernardos A, Mondragón L, Javakhishvili I, Mas N, de la Torre C, Martínez-Máñez R. et al. Azobenzene Polyesters Used as Gate-Like Scaffolds in Nanoscopic Hybrid Systems. *Chemistry-A European Journal.* 2012;18:13068–78. [PubMed] [Google Scholar]
167. Liu H, Liu T, Wu X, Li L, Tan L, Chen D. et al. Targeting gold nanoshells on silica nanorattles: a drug cocktail to fight breast tumors via a single irradiation with near-infrared laser light. *Advanced Materials.* 2012;24:755–61. [PubMed] [Google Scholar]
168. Dong W, Li Y, Niu D, Ma Z, Gu J, Chen Y. et al. Facile synthesis of monodisperse superparamagnetic Fe3O4 core@ hybrid@ Au shell nanocomposite for bimodal imaging and photothermal therapy. *Advanced Materials.* 2011;23:5392–7. [PubMed] [Google Scholar]
169. Yeh Y-C, Creran B, Rotello VM. Gold nanoparticles: preparation, properties, and applications in bionanotechnology. *Nanoscale.* 2012;4:1871–80. [PMC free article] [PubMed] [Google Scholar]
170. Kojima C, Hirano Y, Yuba E, Harada A, Kono K. Preparation and characterization of complexes of liposomes with gold nanoparticles. *Colloids and Surfaces B: Biointerfaces.* 2008;66:246–52. [PubMed] [Google Scholar]
171. Umeda Y, Kojima C, Harada A, Horinaka H, Kono K. PEG-attached PAMAM dendrimers encapsulating gold nanoparticles: growing gold nanoparticles in the dendrimers for improvement of their photothermal

properties. *Bioconjugate Chemistry.* 2010;21:1559–64. [PubMed] [Google Scholar]
172. Yang F, Li Y, Chen Z, Zhang Y, Wu J, Gu N. Superparamagnetic iron oxide nanoparticle-embedded encapsulated microbubbles as dual contrast agents of magnetic resonance and ultrasound imaging. *Biomaterials.* 2009;30:3882–90. [PubMed] [Google Scholar]
173. Yang F, Li M, Liu Y, Wang T, Feng Z, Cui H. et al. Glucose and magnetic-responsive approach toward in situ nitric oxide bubbles controlled generation for hyperglycemia theranostics. *Journal of Controlled Release.* 2016;228:87–95. [PubMed] [Google Scholar]
174. Sun D, Zhuang X, Zhang S, Deng Z-B, Grizzle W, Miller D. et al. Exosomes are endogenous nanoparticles that can deliver biological information between cells. *Advanced Drug Delivery Reviews.* 2013;65:342–7. [PubMed] [Google Scholar]
175. Batrakova EV, Kim MS. Using exosomes, naturally-equipped nanocarriers, for drug delivery. *Journal of Controlled Release.* 2015;219:396–405. [PMC free article] [PubMed] [Google Scholar]
176. van Dommelen SM, Vader P, Lakhal S, Kooijmans S, van Solinge WW, Wood MJ. et al. Microvesicles and exosomes: opportunities for cell-derived membrane vesicles in drug delivery. *Journal of Controlled Release.* 2012;161:635–44. [PubMed] [Google Scholar]
177. Johnsen KB, Gudbergsson JM, Skov MN, Pilgaard L, Moos T, Duroux M. A comprehensive overview of exosomes as drug delivery vehicles—endogenous nanocarriers for targeted cancer therapy. *Biochimica et Biophysica Acta (BBA)-Reviews on Cancer.* 2014;1846:75–87. [PubMed] [Google Scholar]
178. Tan A, Rajadas J, Seifalian AM. Exosomes as nano-theranostic delivery platforms for gene therapy. *Advanced Drug Delivery Reviews.* 2013;65:357–67. [PubMed] [Google Scholar]
179. Haney MJ, Klyachko NL, Zhao Y, Gupta R, Plotnikova EG, He Z. et al. Exosomes as drug delivery vehicles for Parkinson's disease therapy. *Journal of Controlled Release.* 2015;207:18–30. [PMC free article] [PubMed] [Google Scholar]
180. Tian Y, Li S, Song J, Ji T, Zhu M, Anderson GJ. et al. A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. *Biomaterials.* 2014;35:2383–90. [PubMed] [Google Scholar]
181. Chen TS, Arslan F, Yin Y, Tan SS, Lai RC, Choo A. et al. Enabling a robust scalable manufacturing process for therapeutic exosomes through oncogenic immortalization of human ESC-derived MSCs. *Journal of Translational Medicine.* 2011;9:1471–82. [PMC free article] [PubMed] [Google Scholar]
182. Kopeček J. Smart and genetically engineered biomaterials and drug delivery systems. *European Journal of Pharmaceutical Sciences.* 2003;20:1–16. [PubMed] [Google Scholar]
183. Lavan DA, McGuire T, Langer R. Small-scale systems for in vivo drug delivery. *Nature Biotechnology.* 2003;21:1184–91. [PubMed] [Google Scholar]
184. Blanco E, Shen H, Ferrari M. Principles of nanoparticle design for overcoming biological barriers to drug delivery. *Nature Biotechnology.* 2015;33:941–51. [PMC free article] [PubMed] [Google Scholar]
185. Lindner LH, Hossann M, Vogeser M, Teichert N, Wachholz K, Eibl H. et al. Dual role of hexadecylphosphocholine (miltefosine) in thermosensitive

liposomes: active ingredient and mediator of drug release. *Journal of Controlled Release.* 2008;125:112–20. [PubMed] [Google Scholar]
186. Shaffer SA, Baker-Lee C, Kennedy J, Lai MS, de Vries P, Buhler K. et al. In vitro and in vivo metabolism of paclitaxel poliglumex: identification of metabolites and active proteases. *Cancer Chemotherapy and Pharmacology.* 2007;59:537–48. [PubMed] [Google Scholar]
187. Gil PR, Hühn D, Loretta L, Sasse D, Parak WJ. Nanopharmacy: Inorganic nanoscale devices as vectors and active compounds. *Pharmacological Research.* 2010;62:115–25. [PubMed] [Google Scholar]
188. Schwartz JA, Shetty AM, Price RE, Stafford RJ, Wang JC, Uthamanthil RK. et al. Feasibility study of particle-assisted laser ablation of brain tumors in orthotopic canine model. *Cancer Research.* 2009;69:1659–67. [PubMed] [Google Scholar]
189. [189] Etheridge ML, Campbell SA, Erdman AG, Haynes CL, Wolf SM, McCullough J. The big picture on nanomedicine: the state of investigational and approved nanomedicine products. *Nanomedicine: Nanotechnology, Biology and Medicine.* 2013;9:1–14. [PMC free article] [PubMed] [Google Scholar]
190. Ferrari M. Frontiers in cancer nanomedicine: directing mass transport through biological barriers. *Trends in Biotechnology.* 2010;28:181–8. [PMC free article] [PubMed] [Google Scholar]
191. Helmus MN. The need for rules and regulations. *Nature Nanotechnology.* 2007;2:333–4. [PubMed] [Google Scholar]
192. Wicki A, Witzigmann D, Balasubramanian V, Huwyler J. Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. *Journal of Controlled Release.* 2015;200:138–57. [PubMed] [Google Scholar]
193. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. *Nature.* 2012;483:531–3. [PubMed] [Google Scholar]
194. Hunter KW. Mouse models of cancer: does the strain matter? *Nature Reviews Cancer.* 2012;12:144–9. [PMC free article] [PubMed] [Google Scholar]
195. Teicher BA. Tumor models for efficacy determination. *Molecular Cancer Therapeutics.* 2006;5:2435–43. [PubMed] [Google Scholar]

التطورات في أنظمة توصيل الدواء الذكية وتطبيقاتها السريرية

الملخص:

خلفية: لقد أحدثت أنظمة توصيل الدواء الذكية (DDSs) ثورة في كيفية إدارة الأدوية، بهدف تعزيز الفعالية العلاجية مع تقليل الآثار الجانبية. غالبًا ما تؤدي أنظمة توصيل الدواء التقليدية إلى توزيع الدواء على نطاق واسع وإطلاق غير متحكم فيه، مما يتسبب في آثار جانبية غير مرغوب فيها ونتائج علاجية دون المستوى المطلوب. لمواجهة هذه التحديات، تم تطوير أنظمة توصيل الدواء المتقدمة، وخاصة تلك التي تعتمد على تكنولوجيا النانو، لاستهداف مواقع محددة مع تنظيم دقيق.

هدف: يهدف هذا الاستعراض إلى استكشاف التطورات الأخيرة في أنظمة توصيل الدواء الذكية، مع التركيز على تصميمها وآلياتها وتطبيقاتها السريرية. ويسلط الضوء على دور تكنولوجيا النانو في تعزيز خصوصية وفعالية توصيل الدواء من خلال آليات استجابة للمحفزات المختلفة.

طرق: يجمع هذا الاستعراض بين النتائج المستخلصة من الدراسات الحديثة حول مختلف منصات توصيل الدواء الذكية، بما في ذلك الأنظمة القائمة على الجسيمات النانوية، والبوليمرات الذكية، والليبوسومات، والمواد الهجينة العضوية وغير العضوية. ويقوم بتقييم هذه الأنظمة بناءً على استجابتها للمحفزات الداخلية (مثل الرقم الهيدروجيني، التفاعلات الحمراء، الإنزيمات) والمحفزات الخارجية (مثل درجة الحرارة، الضوء، المجالات المغناطيسية) وقابليتها للتطبيق السريري.

نتائج: يحدد هذا الاستعراض العديد من أنظمة توصيل الدواء المبتكرة التي تستخدم مواد تستجيب للمحفزات للتحكم في إطلاق الدواء. تشمل التطورات البارزة الجسيمات النانوية المستجيبة للرقم الهيدروجيني التي تستهدف الخلايا السرطانية، والأنظمة المستجيبة للتفاعلات الحمراء لعلاج السرطان، والليبوسومات الحساسة لدرجة الحرارة المستخدمة في العلاج بالحرارة. وقد أظهرت الأنظمة الهجينة التي تجمع بين المواد العضوية وغير العضوية وعدًا بتحسين التحكم في إطلاق الدواء وقدرات الاستهداف.

استنتاج: تمثل أنظمة توصيل الدواء الذكية قفزة نوعية في الطب الدقيق، حيث تقدم آليات لإطلاق الدواء بشكل مستهدف ومتحكم فيه، مما يعزز النتائج العلاجية ويقلل من الآثار الجانبية. على الرغم من التطورات الواعدة، لا تزال هناك تحديات مثل القدرة على التوسع، والسلامة، والعقبات التنظيمية. يجب أن يركز البحث المستقبلي على التغلب على هذه العقبات لتسهيل التبني السريري الواسع لهذه الأنظمة المتقدمة.

الكلمات المفتاحية: أنظمة توصيل الدواء، تكنولوجيا النانو، البوليمرات الذكية، المواد المستجيبة للمحفزات، التطبيقات السريرية، العلاج المستهدف.