Review Article

“Smart” materials-based near-infrared light-responsive drug delivery systems for cancer treatment: A review

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ABSTRACT

To overcome drawbacks of conventional chemotherapy for cancer treatment, stimuli-responsive drug delivery systems (DDSs) including internal and external stimuli-based cues are the potential candidates. Both internal and external stimuli-responsive behavior can be utilized for engineering of the so-called “smart” DDSs. Drug release triggered by external stimuli is more controllable and avoid individual variability. Among them, light-responsive DDSs are more promising because of spatiotemporal control. With considerable penetration features, near-infrared (NIR) light is potential stimulus with clinical implication. There are three types of NIR-responsive DDSs (NIRDDSs) based on the mechanism, i.e., (1) photothermal effect, (2) two-photon absorption, and (3) up-converting nanoparticles (UCNPs). Photothermal effect-based DDS has been extensively studied because of their tunable optical properties and flexible surface chemistry. Carbon nanomaterials, gold nanomaterials, indocyanine green, and metallic sulfides/oxides are the commonly employed photothermal agents. Two-photon absorption-based DDSs provide higher excitation and overcome the drawback of UV/Visible light-sensitive DDSs of poor penetration. UCNPs are inorganic crystalline nanoscale particles (1–100nm) that exhibit photon up-conversion, i.e., conversion of NIR excitation light into UV/Visible emission light and empower deeper penetration into biological samples due to reduced light scattering. In this review, we discussed different NIRDDSs. The emphasis was also given to their drug release mechanisms and applications in the treatment of cancer.

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1. Introduction

Cancer is one of the major health problems and is a leading cause of death [1]. In 2017, around 600,920 deaths are projected only in the United States [2], due to cancer. Conventional treatments, i.e., chemotherapy and radiotherapy, are considered not to be very effective due to lack of specificity and toxicity [3–6]. Thus, the development of targeted drug delivery systems (DDSs) for tumor treatment is a hot research area. Nanotechnology-based DDSs such as polymeric nanoparticles, liposomes, micelles, etc. are considered as potential DDSs due to enhanced permeability and retention effect, enhanced half-life, better bioavailability, and higher targeting ability by the addition of aptamers [3,7,8]. However, premature drug release and insufficient drug release at target sites are major limitations for such drug delivery [9,10]. Stimuli-responsive drug delivery systems (SRDDSs) are considered to be effective in overcoming these limitations [3–6,9–11]. SRDDS release the loaded drug under the influence of a particular stimulus. These are also termed as intelligent or smart DDSs because of on-demand drug delivery property [12]. These stimuli can be internally based on the difference in the environment of tumor tissue and normal tissue or can be external [12–14].

Internal stimuli include pH, temperature, hypoxia, enzymatic activity, and glutathione (GSH) concentration. Tumor tissue has low pH (6.5), high temperature (40–42 °C), higher GSH concentration (reductive environment) and specific enzymes overexpression (e.g., matrix metalloproteinases, cathepsin, urokinase plasminogen activators) when compared to normal tissue. So DDSs that can release the loaded drug in response to these stimuli can be used to targeting tumor tissue and have shown specificity with low toxicity [9,14,15]. However, inter-individual variability, limited control over drug release, and difficulty in preparation of such systems that can respond to such narrow limits are limitations for such DDSs [16,17]. External stimuli such as light, magnetic field, electric field, and ultrasound-responsive DDSs have been reported to be successful in overcoming igniter-individual variability as drug release is controlled external stimuli which are controllable when compared to internal stimuli [6,10,11,18]. Among these external stimuli, light is considered as an attractive external stimulus due to ease and better spatiotemporal control [19]. Among different developed light-responsive DDSs, most of them respond to UV light which has disadvantages of not only poor tissue penetration, but also harmful to cells and tissues. Due to these drawbacks, UV light-responsive systems are difficult to bring in clinical practice [10]. However, near-infrared (NIR) light with a wavelength of 650–900 nm has good tissue penetration due to limited attenuation and is also safe for cells and tissues [10,20,21]. Therefore, NIR-responsive systems are potential carriers for drug delivery in targeted site for clinical applications [22].

NIR-responsive systems release drug upon exposure to NIR light which is resulted by photothermal effect, leading to an increase in temperature. This increase in temperature can also cause cell death (photothermal treatment) which synergies drug action [23,24]. Other mechanisms involved two-photon conversion and UCNPs [10,24]. The later one is also used to deliver photosensitive material as a source for photodynamic therapy [25,26]. Based on these mechanisms, multi-modal carriers have also been developed which contribute to drug release, photothermal therapy, and photodynamic therapy [27,28]. This review will cover mechanism of drug release from NIRDDSs and their reported applications in the treatment of cancer by different types of drug carriers. We also discussed multimodal systems based on NIR response such as imaging, photothermal, and photodynamic therapy along with multi-responsive DDSs.

2. Design strategies and mechanisms of drug release

There are three reported mechanisms for drug release from NIRDDSs, i.e., (a) photothermal effect (PTE) (b) two-photon absorption (TPA), and (c) Up-converting nanoparticles (UCNPs) [10]. A scheme of these mechanisms is given in Fig. 1. Out of these mechanisms, photothermal effect-based drug release systems were widely explored with or without photothermal therapy. Thermo-responsive materials are employed for the preparation of such systems. These systems generate heat after absorbing NIR light, and this increase in temperature will enhance the drug release whether by phase change mechanism or by disruption of the structure of drug carriers. High temperature (hyperthermia) also has cytotoxic effect, so photothermal therapy can also be observed in such systems along with chemotherapy (chemo-photothermal therapy) [6,29,30]. Carriers for designing this kind of DDSs should have strong absorption in NIR range for efficient photothermal conversion, efficient tumor homing capacity after intravenous administration, biodegradability, and safety [31]. As already discussed, UV and visible light-responsive systems have limited clinical implications because of poor penetration and harmful effects of UV light. This problem can be overcome by using two-photon absorption, for instance, [7-(diethylamino) cauamarin-4-yl]methyl (DEACM) is a photo-cleavable group via single-photon UV light. However, two-photon absorption can also promote the same cleavage reaction of DEACM [32]. Hence, such UV light-sensitive material having ability to undergo two-photon absorption in NIR range may be extended for clinical implications. In another report, micelles composed of hydrophilic polyethylene oxide (PEO) and hydrophobic poly(2-nitrobenzyl) methacrylate) were found to have photo-induced disruption with a single photon in UV range (350 nm) or two-photon NIR (700 nm) [33]. FRET (Förster/fluorescence resonance energy transfer) phenomenon by two-photon excitation can also be used for activation of photo-labile moieties in which a fluorophore absorb two-photon and transfer energy to activate light-sensitive compounds [34]. UCNPs can convert NIR into high-energy photons in UV and visible range. These nanoparticles are usually made of lanthanides-based nanomaterials that can absorb multiple low-energy photons in NIR range and convert them into high-energy photons in a visible or UV range which can be further used to activate photochemical reaction for promoting drug release or to activate photosensitizers for photodynamic therapy (PDT). UCNPs overcome UV light-responsive drug delivery drawbacks such as poor penetration and toxicity of UV light exposure [10].
NIR irradiation

Drug carrier

Heated particle with NIR irradiation

Use of fluorophore to activate drug release through FRET

TPA activated photosensitive material

Emitted high energy photon activate photosensitive material for drug release

Emitted high energy photon activate photosensitive to generate ROS

Figure 1 – A scheme of three mechanisms of NIRDDSs.
There are three ways for the development of UCNPs for drug delivery. (i) Hydrophobic pockets which involve encapsulation of hydrophilic drug into hydrophobic pockets present on UCNPs by the hydrophobic–hydrophobic attraction between hydrophobic ligand and drug. (ii) Mesoporous silica shells coated UCNPs which offers a large surface area for drug deposition, (iii) Drugs loaded in hollow spheres with mesoporous surface [35]. PDT involves photosensitizer that produces singlet oxygen (SO) and reactive oxygen species (ROS) upon light exposure usually of high energy which has a limitation in clinical implications. Using UCNPs, emitted visible light can be utilized for activation of photosensitizer for PDT [25].

3. Photothermal effect-based NIRDDSs

Light to heat conversion upon NIR irradiation by NIR absorbing materials can cause drug release from a thermo-responsive drug carrier. Different materials have been reported having the ability to convert NIR light into heat (photothermal property) such as carbon nanomaterials (graphene oxide and carbon nanotubes), gold nanomaterials (such as nanoparticles, nanorods, and nanocages), metallic oxides/sulfides, indocyanine green dye, melanin, polyaniline, etc. [10,36].

3.1. Graphene-based NIRDDSs

Graphene is hydrophobic in nature and its dispersion in blood is difficult. However, functionalization with polymers can enhance its dispersibility. Moreover, a DDS based on graphene oxide (GO) has been prepared by oxidation of graphene using exfoliation technique. The GO has property to bind to drugs by covalent bond due to free carboxylic and hydroxyl groups, by adsorption of drugs, by hydrophobic attraction, and by π–π hydrogen bonding [37,38]. These free functional groups can also be used for binding with targeting proteins (antibodies) to develop targeted delivery systems and with other material to form nanocomposites [39]. Such modification with nontoxic polymers enhances its biocompatibility. GO has the property to generate heat efficiently after absorbing NIR light leading to hyperthermia [40]. This property has been utilized by many researchers for drug delivery and photothermal treatment. Recently, Zeng et al. [41] have reported multifunctional nanographene oxide carriers for gene and drug delivery. A combination of chemo, gene, and photothermal therapy showed the synergistic effect to overcome drug resistance. Folate-targeted polyethylenamine (1800)-modified PEGylated nanographene (PPG) was used to load both siRNA and doxorubicin. NIR irradiation exhibited enhanced doxorubicin release when compared to without NIR irradiation. In another study, Bani et al. [42] developed nano-graphene-polyglycerol-cucurmin hybrids for chemo-photothermal therapy. Non-covalent functionalization of nano-graphene with polyglycerol increased the dispersibility of nano-graphene for a longer duration as no aggregation was reported up to several weeks. Furthermore, an increase in the release of curcumin from 6 to 29% was reported after NIR irradiation after predetermined time intervals over 48h. Synergistic effect of photothermal with chemotherapy was observed by in vitro cytotoxicity studies in MCF7 cancer cells. Graphene oxide can also be used to prepare multi-responsive systems such as responsive to both pH and NIR light. Doxorubicin-loaded nanographene oxide flakes incorporated with chitosan-PEG were synthesized by Thapa et al. [43] (Fig. 2a). These flakes showed a pH- and NIR-responsive doxorubicin release (Fig. 2b). In vivo experiments showed hyperthermic effect (32.3–43.1 °C after 5 min NIR irradiation) at tumor site when compared to control (Fig. 2c). Furthermore, synergistic activity of photothermal effect of nanographene oxide and chemotherapy with doxorubicin was observed by comparing tumor volume after treatment (Fig. 2d). Hence, nanographene/nanographene oxide can be used for drug/gene delivery to have chemo and gene therapy with photothermal therapy.

3.2. Carbon nanotube-based NIRDDSs

Biomedical applications of carbon nanotubes have been explored widely including DDS and photothermal treatment because of strong light to heat transducing ability, chemical stability, robustness, high drug binding site, and ability to penetrate through the cell membrane. However, like graphene, carbon nanotubes have dispersibility problem and cytotoxicity which can be overcome by functionalization [36,44]. In a recent report, Dong et al. [45] utilized functionalized multiwalled carbon nanotubes with TAT-chitosan (TC) conjugate for enhancing cytocompatibility. Further, they loaded doxorubicin to evaluate the prepared system as an NIR-triggered drug release system along with photothermal therapy. Maximum release of doxorubicin was observed with NIR irradiation at pH 5.5, which also indicated that release behavior was pH-dependent. TC coating decreased the release rate, but enhances cell internalization when compared to without TC-coated systems. Overall results showed the synergistic effect of chemotherapy and photothermal therapy of prepared nanosystems which efficiently ablated tumor in animal models. Yoo et al. reported the enhanced efficacy of metformin against tumor cells by hyperthermia induced by multiwalled carbon nanotubes. With metformin cell viability of HepG2 cells decreases to 24% when compared to without metformin carriers. Hydrogels are semisolid three-dimensional polymeric networks having a large volume of water/biological fluid and is considered an attractive system for drug delivery due to biocompatibility. Stimuli-responsive hydrogels underwent structural disruption leading to release of the enclosed drug [44]. In this regard, thermo-responsive doxorubicin-loaded PCL-PEG-PCL hydrogel was reported by Dong et al. [45], which was combined with carbon nanotubes to establish an on-demand drug release system. On-demand release, controllable through NIR irradiation was observed in in vivo studies. Some other reported drug delivery carriers based on carbon nanotubes are summarized in Table 1.

3.3. Nanomaterial-based NIRDDSs

In recent years, numerous materials have been used to construct different drug delivery carriers using nanoscale-level including nanoparticles, nanorods, nanocages, nanocubes, etc. [51–53]. Nanomaterials with special reference to gold-
Figure 2 – (a) Single-pass gas-phase self-assembly of nanodimensional graphene oxide (nGO)-incorporated doxorubicin (DOX) (nGO@DOX) flakes from incorporation of nGO flakes and DOX droplets and subsequent solvent extraction from the hybrid droplets. The assembled nGO@DOX flakes were incorporated with chitosan-polyethylene glycol (cPEG) in the liquid phase before application in anticancer activity analysis. (b) In vitro release profiles of DOX at different pH conditions (P < 0.01). (c) In vivo photothermal imaging upon NIR laser irradiation on tumors of mice pretreated with saline or nGO@DOX-cPEG. cPEG, chitosan-polyethylene glycol; Cy5.5, cyanin 5.5; DOX, doxorubicin; nGO, nanodimensional graphene oxide; NIR, near-infrared. (d) Tumor volume after IV administration of different samples (control, DOX, nGO@DOX-cPEG, and nGO@DOX-cPEG). Reproduced from Ref. [43], an article licensed published by Nature Publishing Group under a Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.

Table 1 – Carbon nanotube-based NIRDDSs.

<table>
<thead>
<tr>
<th>System</th>
<th>Functionalization</th>
<th>Drug loaded</th>
<th>Modality/(ies)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanostructures</td>
<td>PEG-NH₂, ssDNA-caged aptamer</td>
<td>Doxorubicin</td>
<td>Dual-targeted NIR-responsive drug delivery, photothermal therapy</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Poly(dimethyl) ammonium chloride</td>
<td>Doxorubicin</td>
<td>NIR-responsive DDSs</td>
<td>[47]</td>
</tr>
<tr>
<td>Microcapsules</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prodrug on single-walled carbon nanotubes</td>
<td>PEG</td>
<td>Doxorubicin</td>
<td>pH/NIR dual responsive drug delivery, photothermal therapy</td>
<td>[48]</td>
</tr>
<tr>
<td>Single-walled carbon nanotube-based nanocarriers</td>
<td>Poly(ethyleneimine), NGR</td>
<td>Doxorubicin</td>
<td>pH/NIR dual responsive drug delivery, photothermal therapy</td>
<td>[49]</td>
</tr>
<tr>
<td>Mesoporous silica-coated carbon nanotubes</td>
<td>PEG</td>
<td>Doxorubicin</td>
<td>NIR-responsive drug delivery, photothermal therapy</td>
<td>[50]</td>
</tr>
</tbody>
</table>

oriented nanoparticles tend to convert NIR light to heat efficiently even several times higher when compared to photothermal dyes due to surface plasmon resonance phenomenon. Secondly, readily attachment of antibodies and other biological macromolecular agents makes it a potential candidate for therapeutic applications [10,51]. Furthermore, they are biocompatible and chemically inert [52]. Among different gold nanomaterials, gold nanoparticles, and nanorods are potential ones due to proficient large-scale production, high optical absorption coefficient, and tunable absorption
of gold nanomaterials for chemo-photothermal therapy (Table 2).

3.4. Indocyanine green dye-based NIRDDSs

Indocyanine green (ICG) is an NIR absorbing dye, and only US-FDA approved NIR organic dye. Absorption and emission range fall in the NIR region of about 740–800 nm [64]. Due to its ability to switch absorbed NIR light to heat, it is widely explored for photothermal therapy and developing NIRDDSs based on photothermal effect [65]. However, some of its properties limit its applications such as poor aqueous solubility, aqueous degradable, rapid clearance from the body (half-life of about 2–4 min), agglomeration in an aqueous medium, photostability, non-specific protein binding, and lack of targeting [64,66]. Using nanotechnology, several attempts have been made to surmount these limitations, for instance, poly(lactic-co-glycolic acid) (PLGA) encapsulating ICG nanoparticles are reported to not only increase stability in an aqueous medium, photo, and thermal stability, but also increase half-life [67]. In another study, colloidal poly(e-caprolactone)-coated silica nanocomposite encapsulating ICG were reported to enhance photo and aqueous stability of ICG [68]. Moreover, functionalization of nanoparticles encapsulating ICG with targeting molecules can be used to target tumor cells, e.g., anti-HER2 antibody for targeting HER2-positive breast cancer [69], anti-
<table>
<thead>
<tr>
<th>Gold nanomaterial</th>
<th>Delivery system</th>
<th>Drug-loaded</th>
<th>Modality(ies)</th>
<th>Evaluation method</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold nanoshell</td>
<td>Gold nanoshell-coated chitosan liposomes</td>
<td>Resveratrol</td>
<td>pH-NIR responsive drug delivery, chemo-photothermal therapy</td>
<td>In vitro HeLa cells</td>
<td>[56]</td>
</tr>
<tr>
<td>Gold nanorods (GNR)</td>
<td>GNR@mesoporous silica/poly(N-isopropylacrylamlde-co-N-hydroxymethyl acrylamide) nanocomposites</td>
<td>Doxorubicin</td>
<td>Thermo/NIR-responsive drug delivery, chemo-photothermal therapy</td>
<td>In vitro U87 cells</td>
<td>[57]</td>
</tr>
<tr>
<td>Gold nanocages</td>
<td>Biotin-PEG-modified gold nanocages</td>
<td>Doxorubicin and quercetin</td>
<td>NIR-responsive drug delivery</td>
<td>In vitro MCF7/ADR</td>
<td>[58]</td>
</tr>
<tr>
<td>Gold nanoshells</td>
<td>Phospholipid liposomes</td>
<td>Betulinic acid</td>
<td>NIR-responsive drug delivery, chemo-photothermal therapy</td>
<td>In vitro 143B cells and HeLa cells</td>
<td>[59]</td>
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<tr>
<td>Gold nanorods</td>
<td>GNR-embedded Diblock copolymer [PEG-b-poly(2-hydroxyethyl acrylate)-lipoic acid–folic acid] micelles</td>
<td>GW627368X</td>
<td>Redox/NIR-responsive drug delivery, chemo-photothermal therapy</td>
<td>In vivo studies on S180 bearing Swiss albino mice, in vitro studies on SiHa, ME180, HaCat, and 3T3</td>
<td>[53]</td>
</tr>
<tr>
<td>Gold nanorods</td>
<td>Dopamine-adipic acid dihydrazide-hyaluronic acid trifunctionalized gold nanorods</td>
<td>Doxorubicin</td>
<td>CD44-targeted NIR-responsive drug delivery, chemo-photothermal therapy</td>
<td>In vivo studies on tumor-bearing mice, in vitro studies on MCF-7 cells</td>
<td>[60]</td>
</tr>
<tr>
<td>Gold nanorods</td>
<td>N-isopropylacrylamide (NIPAM) and methacrylated poly-β-cyclodextrin (MPCD)-based PEG-GNR nanocomposite hydrogel</td>
<td>Doxorubicin</td>
<td>pH-NIR responsive drug delivery, chemo-photothermal therapy</td>
<td>In vivo studies on MCF-7 and HeLa cells, in vivo evaluation on S180 tumor-bearing mice</td>
<td>[61]</td>
</tr>
<tr>
<td>Gold nanorods</td>
<td>Poly(sodium 4-styrene sulfonate) gold nanorods</td>
<td>Doxorubicin</td>
<td>NIR-responsive drug delivery, chemo-photothermal therapy</td>
<td>In vivo evaluation performed on MCF-7, in vivo studies using Dalton lymphoma ascites bearing Swiss albino mice</td>
<td>[62]</td>
</tr>
<tr>
<td>Gold nanorods</td>
<td>Carbon core-shell based GNR nanocapsules</td>
<td>Doxorubicin</td>
<td>NIR-responsive drug delivery, chemo-photothermal therapy, fluorescence imaging</td>
<td>In vitro studies on MCF-7</td>
<td>[63]</td>
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<table>
<thead>
<tr>
<th>Carrier system</th>
<th>Functionalization</th>
<th>Drug-loaded</th>
<th>Modality(ies)</th>
<th>Evaluation</th>
<th>Ref.</th>
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<tr>
<td>Cell membrane capsules</td>
<td>–</td>
<td>Doxorubicin</td>
<td>NIR-responsive drug delivery, photothermal therapy</td>
<td>In vivo studies on tumor-bearing mice, in vitro evaluation performed using HepG2 cells</td>
<td>[74]</td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>Chitosan-N-arginine conjugate</td>
<td>Doxorubicin</td>
<td>Chemo-photothermal therapy</td>
<td>In vitro studies on MCF7/ADR breast cancer cells</td>
<td>[75]</td>
</tr>
<tr>
<td>Nanoparticles</td>
<td>1,2-Distearyl-sn-glycero-3-phosphoethanolamine-N-maleimide (polyethylene glycol 2000) [DSPE-PEG], PLGA DSPE-PEG2000</td>
<td>Doxorubicin</td>
<td>NIR-responsive drug delivery, photothermal therapy</td>
<td>In vivo studies on tumor-bearing Balb/c nude mice. In vitro evaluation of MCF7 and MCF7/ADR cells</td>
<td>[76]</td>
</tr>
<tr>
<td>Hybrid bicelles</td>
<td>DSPE-PEG2000</td>
<td>Doxorubicin</td>
<td>Chemo-photothermal therapy, fluorescence imaging</td>
<td>In vivo studies on 4T1 tumor-bearing Balb/c nude mice. In vitro evaluation of MDA-MB-231 cells</td>
<td>[77]</td>
</tr>
<tr>
<td>Liposomes</td>
<td>DSPE-PEG2000</td>
<td>Doxorubicin</td>
<td>In vivo studies on MCF7 tumor-bearing Balb/c nude mice, in vitro evaluation performed using MCF7 cells</td>
<td>[78]</td>
<td></td>
</tr>
</tbody>
</table>
Figure 4 – (A) DOX-release profiles in the presence and absence of NIR laser at pH 5.0 and 7.4. (B) Cytotoxicity at different concentrations of PCNA-hydrogel leachate. The composite exhibited no cytotoxicity and the NIH 3T3 cells proliferated as well as when treated with the negative control. (C) In vivo persistence and histology sections from subcutaneous rat tissue after implantation of PCNA-hydrogel composites for different periods. Images in panels a (e), b (f), c (g), and d (h) were captured at 7, 14, 28, and 35 days, respectively (scale bar: 200 μm). Reproduced from Ref. [55], an article licensed published by Nature Publishing Group under a Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/. 

EGFR antibodies against EGFR-rich tumor [70], and floated grafted nanoparticles [71]. In addition, many NIR-responsive DDSs employing ICG for its photothermal property have also been reported (Table 3). Self-co-assembled nanoparticles of ICG and Epirubicin (EPI) were prepared by Li et al. [72] for chemo-photothermal therapy and dual modal imaging, i.e., near-infrared fluorescence (NIRF) imaging and photoacoustic imaging (PA). Hydrophilic epirubicin hydrochloride was transformed into hydrophobic EPI by removal of HCl. Then nanoparticles were prepared by drop-wise addition of an organic solution of ICG and EPI in aqueous solution with stirring and ultrasonication. In vitro studies indicated good physical stability with no significant particle diameter change for up to 7 days and photothermal effect to reach 57 °C after 5 min laser irradiation when compared to 48 °C with ICG alone. Further, accelerated drug release was found at pH 5.0 due to protonation of EPI and after NIR irradiation. In vitro cellular uptake studies in 4T1 and MCF-7 cells showed enhanced uptake of nanoparticles and retention. In vivo treatment of 4T1 breast cancer-bearing BALB/c nude mice with ICG/EPI nanoparticles with NIR irradiation showed a reduction of tumor volume and relative tumor volume to normal in 20 days with no toxicity as depicted by biochemical and histopathological studies. In another report, anti-HER-2/ICG-DOX_PEF-PLGA diblock copolymeric nanoparticles (HIDPPNPs) were developed by Lee et al. [73] through solvent evaporation method followed by conjugation with antibody using carbodiimide linker. Prepared targeted nanoparticles showed twofold increase uptake by HER-positive breast cancer cells when compared to HER negative cells. Cytotoxicity studies performed on MDA-MB-453 showed HIDPPNPs with a 3 μM concentration of DOX had maximum cytotoxicity efficacy after NIR light irradiation.

3.5. Other materials-based NIRDDSs

Several other materials having ability to convert NIR light into heat have also been investigated for fabrication of NIRDDS and photothermal therapy such as different metallic sulfides/oxides, organic conjugated molecules, and melanin. A few reported applications of these materials in connection with NIRDDS/photothermal therapy are summarized in Table 4.
### Table 4 - Various types of DDSs based on photothermal agent, their notable characteristics, and applications.

<table>
<thead>
<tr>
<th>Photothermal agent</th>
<th>Delivery system</th>
<th>Drug-loaded</th>
<th>Characteristics</th>
<th>Applications</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper sulfide (CuS)</td>
<td>CuS@mesoporous silica-PEG core–shell nanoparticles</td>
<td>Doxorubicin</td>
<td>Size of nanoparticles is about 37 nm with colloidal stability due to PEG. 200 μg/ml concentration showed a temperature rise from 20 to 40.4 °C of water after 360 s irradiation. No toxic effect up to 500 μg/ml in HeLa cells indicating biocompatibility of nanoparticles</td>
<td>NIR-responsive drug delivery combined with photothermal therapy</td>
<td>[79]</td>
</tr>
<tr>
<td>CuS</td>
<td>Hollow material copper sulfide nanoparticles conjugated with hyaluronic acid (HA) Meso-2,3-dimercaptosuccinic acid (DMSA) functionalized nanoparticles</td>
<td>Doxorubicin</td>
<td>The average size of DOX-loaded nanoparticles was 113.8 ± 6.9 nm, significant increased cellular uptake found in MCF7 cells due to CD44 receptor targeting by HA, ROS generation Average size of DOX-loaded NPs was 102.02 ± 0.597 nm with photothermal conversion efficiency of about 21.85%, NIR triggered cellular uptake, ROS production with NIR irradiation</td>
<td>Targeted/NIR-responsive drug delivery with photothermal therapy</td>
<td>[80]</td>
</tr>
<tr>
<td>Ferric oxide (Fe3O4)</td>
<td>Polyacrylic acid-coated PPY/florescent mesoporous silica core–shell nanoparticles</td>
<td>Doxorubicin</td>
<td>The average size of NPs was 150 ± 5 nm with the photothermal efficiency of 31.3% having the ability to cause hyperthermia (42° C) at 0.250 mg/ml. Excellent cellular uptake</td>
<td>pH/NIR-responsive drug delivery with photothermal therapy, imaging</td>
<td>[81]</td>
</tr>
<tr>
<td>Polypyrrole</td>
<td>Polystyrene Nanosheets</td>
<td>Doxorubicin</td>
<td>High drug loading capacity, ROS generation ability, biocompatible (4T1, HeLa, L929, and A549 cells)</td>
<td>Chemo-photothermal therapy, PDT, NIR-responsive drug release system NRDD, photothermal therapy</td>
<td>[82]</td>
</tr>
<tr>
<td>Black phosphorus</td>
<td>Chitosan functionalized MoS2 Nanosheets</td>
<td>Doxorubicin</td>
<td>Average size was about 80 nm with the photothermal efficiency of about 24.37%. Biocompatible (studied in KB and Panc-1 cells)</td>
<td></td>
<td>[83]</td>
</tr>
</tbody>
</table>

4. **Two-photon absorption-based NIRDDSs**

One of the drawbacks of light-responsive DDSs is that many such systems required UV or visible light for activation which has the limitation of poor tissue penetration. Two-photon absorption in NIR range provides an opportunity to resolve this issue, as NIR light has better tissue penetration and safety profile [10]. For instance, azobenzene moieties undergo reversible cis–trans isomerism under UV irradiation (300–380 nm) which can alter structures having these moieties. Such structural changes have been utilized to design on-demand UV light-responsive DDSs [84]. To utilize these systems clinically, some efforts have been made to activate such moieties by employing NIR light. For instance, Croissant et al. [34] developed two-photon triggered drug release system-based mesoporous silica nanoparticles with fluorophore nanovalves. For this, they developed a novel paracyclophane-based fluorophore which could absorb two photons in NIR region and transfer energy through FRET to azobenzene part of valves, which upon cis–trans isomerization open valves to release enclosed drug (camptothecin). Camptothecin-loaded nanoparticles irradiated with a laser of 760 nm with maximum power showed 30% cell death, while without irradiation no significant cell death observed, indicating the success of the developed particles. Previously, the same research group also reported two-photon excitation-based nanoimpellers for drug release lying on the same principle of FRET [85]. Recently, novel nitrogen-doped and surface-passivated carbon nanodots for NIRDDSs based on two-photon absorption principle were reported by Ardekani et al. [86]. Prepared carbon nanodots exhibited NIR-responsive doxorubicin release along with photothermal cell killing in vitro evaluation using MCF7 cells. Carbon nanodots can also be used as a donor of FRET for activating photosensitizers to promote PDT [87].

5. **Up-converting nanoparticles**

UCNPs can convert NIR light into high-energy UV/visible light. This emitted high-energy light has recently increased interest for utilization in the development of nanomaterials based on UCNPs for drug delivery, PDT, and biomedical imaging. Lanthanide/rare earth metals are commonly employed for up-conversion of energy. High-energy photon emitted by up-conversion can be used to promote photochemical reaction on the surface or within polymer-coated UCNPs passing up drawbacks of high-energy light [7]. Liu et al. [88] reported NaYF4:TmYb core–shell UCNPs coated with mesoporous silica. Azobenzene groups were installed in mesoporous silica, and nanoparticles were further functionalized by TAT.
protein for enhancement of cellular uptake and loaded with anticancer drug (doxorubicin). Conversion of azobenzene to trans-configuration upon UV light absorption leads to the release of the drug. Irradiation of NIR light at 980 nm leads to the emission of UV light from UNCPs which was absorbed by azobenzene group triggering drug release. Cytotoxicity studies on HeLa cells showed good cytocompatibility of nanoparticles without the drug. However, the significant cell killing ability was reported with DOX-loaded nanoparticles with NIR irradiation. UV/visible up-converted light can also be used to activate photosensitizers to generate ROS for PDT. Hu et al. [89] developed nanodumbles composed of UNCPs (NaYF₄:Yb:Er) covered with amphiphilic lipid (octadecyl-quaternized polyglycolytic acid) and polystyrene-block-poly(acrylic acid) for enhancement and attachment of photosensitizer (zinc (II) phthalocyanine). NIR irradiation and the presence of photosensitizers were found necessary for ROS generation to promote cytotoxicity. In another study [90], NIR responding multifunctional nanoimpellers for simultaneous chemo and PDT was developed. Nanoimpellers were composed of NaYF₄:Yb, Tm@0.6(NaYF₄:Yb, Er) upconverting nanocrystals coated with mesoporous silica (mSiO₂) conjugates with Rose bengal (RB) and 4-phenylazobenzoyl (azo) loaded with doxorubicin (Fig. 5). NIR light (980 nm) was reported to activate nanoimpellers upconverting nanocrystals for emission of high-energy photon that was absorbed by the azo group and RB, resulting in drug release and ROS generation. Cytotoxicity showed the synergistic effect of PDT and chemotherapy.

6. Concluding remarks

In this review, we have covered different mechanistic approaches of NIR-responsive DDSs. NIR light is a promising external stimulus due to its tissue penetration and unharmful. Photothermal and PDT are often found in conjunction with such delivery systems having a synergistic antitumor effect. Due to prevailing resistance to chemotherapy, external stimuli triggered drug delivery with synergistic photothermal, and PDT is found potential approach when compared to conventional therapy. However, biocompatibility/biodegradability of nanomaterials (especially inorganic nanoparticles) used in such delivery systems must be considered for clinical implications.

7. Conflicts of interest

The authors declare that they have no conflict of interest.
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