Review Article

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Smart stimuli-responsive nanocarriers for the cancer therapy – nanomedicine

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Abstract: Nanomedicine is ongoing current research in the applications of nanotechnology for cancer therapy. Simply from a technology perspective, this field of research has an enormous broadening and success to date. Recently, nanomedicine has also made inroads in the treatment of cancer. Stimuli-responsive nanoparticles are an emerging field of research because its targeting capacity is of great interest in the treatment of cancer. The responsive nanoparticles are efficient in encountering different internal biological stimuli (acidic, pH, redox, and enzyme) and external stimuli (temperature, ultrasounds, magnetic field, and light), which are used as smart nanocarriers for delivery of the chemotherapeutic and imaging agents for cancer therapy. In-depth, the responsive nanocarrier that responds to the biological cues is of pronounced interest due to its capability to provide a controlled release profile at the tumor-specific site. The outlook of this review focuses on the stimuli-responsive nanocarrier drug delivery systems in sequence to address the biological challenges that need to be evaluated to overcome conventional cancer therapy.

Keywords: nanocarrier, stimuli-responsive, drug delivery, gene therapy, targeted therapy, photodynamic therapy

Abbreviations

DTT	dithiothreitol
GSH	glutathione
GO	graphene oxide
DOX	doxorubicin
CS	chitosan
FA	folic acid
P45	peptide
5-FU-5	fluorouracil
CUR	curcumin
PEI	polyethylamine
PEG	polyethylene glycol
PBLA	poly(β-benzyl L-aspartate)
TPP	triphenylphosphine
PNIPAM	poly(*N*-iso propyl acrylamide)
LCST	lower critical solution temperature
Fe_3O_4	Iron(II,III) oxide
US	ultrasound
TNP	titanium nanoparticles
PDT	photodynamic therapy
SiRNA	small interfering RNA

1 Introduction

Cancer is the second biggest populate disease to go after cardiovascular disease with the leading cause of death [1–4]. Based on the world health organization, around 26 million people will be affected by cancer and the mortality rates will increase by up to 17 million worldwide by 2030 [5]. Surgery, radiation therapy, and chemotherapy are commonly used in clinics [6]. However, it is crucial to minimize the long-lasting side effects due to the heterogeneous characteristics of cancer cells [7–11]. The recognition of nanomedicine, which is most impressive for

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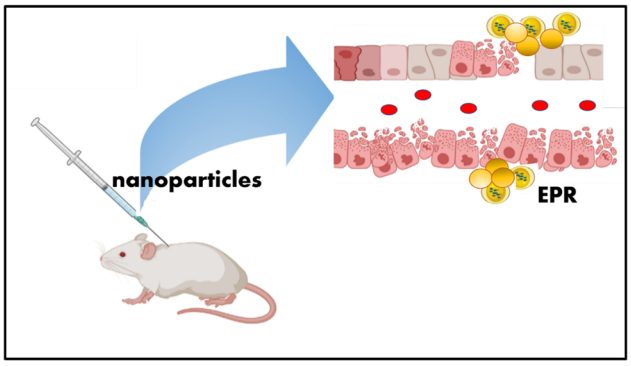

Figure 1: Schematic sketch of EPR.

cure cancer, has developed a new platform for targeted therapeutics. The mechanism of nanoparticles for targeting the tumor region is known as an enhanced permeation and retention (EPR) effect. Schematic sketch of EPR is shown in Figure 1.

Specific targeting of cancer cells is the challenge of current clinical treatment. Chemotherapy has been used as a stand-alone strategy for cancer treatment, as adjuvant therapy after surgery, and as neoadjuvant therapy before surgery [12]. Many different types of chemotherapeutic agents have been used to treat cancer, both individually and in combination. However, because these drugs are unable to distinguish between normal and cancer cells, they cause a slew of unfavorable side effects [13–17]. Targeted therapy involves the use of agents that interact with specific molecular targets that are involved in the progression and survival of cancer [18–20]. Nanoparticles otherwise ultrafine particles range from 1 to 100 nm and these particles can reveal physical and chemical properties. Nanoparticle delivery systems are broadly evaluated preclinically with other nanoparticle-constructed formulations and technologies that have been used so far in the clinic setup [21–24]. There are several methods such as oral, local, topical, and systemic (*e.g.*, intravenous) that are established by Food and Drug Administration (FDA)-approval for the delivery of nanoparticles/microparticles, upon the targeted site and preferred applications [25–31]. Therapeutic and diagnostic nanoparticles are classified into two different types: (a) inorganic nanoparticles (*e.g.*, gold, silica, and iron oxide) and (b) organic nanoparticles (*e.g.*, polymeric, liposomes, and micelles). Inorganic nanoparticles are already used in preclinical studies, for various applications [32–35]. The use of nanoparticles can compensate for several shortcomings of conventional cancer therapies. A variety of nanoparticles, including polymeric, inorganic, and lipid-based carrier systems, have been reported for drug delivery to cancer cells [36–42].

Surface modification of nanoparticles with poly(ethylene glycol) (PEG) chains can result in longer circulation time in the body by slowing the opsonization process [43]. The addition of cancer cell-specific ligands to the surface of nanoparticles confers target-specificity [44]. Folic acid (FA) and transferrin are commonly used as cancer-targeting ligands [45]. However, identifying cancer-specific surface markers for targeting is a difficult task that has spawned a separate field of study. Furthermore, many solid tumors develop a stromal layer around cancer that restricts nanoparticle contact with the cancer tissue, limiting their therapeutic potential [46]. The use of external or internal stimuli to trigger the release of the drug from the carrier is one strategy that can improve the therapeutic potential of nanoparticles carrying the therapeutic agent as shown in Figure 2. There are numerous reports in the literature on the development of modified nanoparticles for stimuli-responsive drug release [47].

However, it is now recognized that the type of carrier, size of the carrier, type of linkers used for capping agent conjugation, nature of the capping agent, cell uptake, intracellular localization, and cell type all influence the carrier's chemoresponsiveness as well as a therapeutic effect [48]. As a result, the field for investigating various types of carriers for cancer treatment remains wide open. Up to date, few clinical trials that use nanoparticles-based drug delivery systems to treat various cancer types have been revealed. This review debates the development of nanoparticles for stimuli-responsive drug delivery research and clinical developments around the globe.

2 An approach to smart delivery strategies

2.1 Internal stimuli for drug delivery systems

Here, we elaborate on the advances in internal stimuli for drug delivery systems. Different internal stimuli have been used to trigger the release of drug molecules towards cancer therapy.

2.1.1 pH responsiveness

pH stimuli trigger the drug release in response to the changes in the pH inside the body. In general, pH in normal tissues such as the brain and subcutaneous

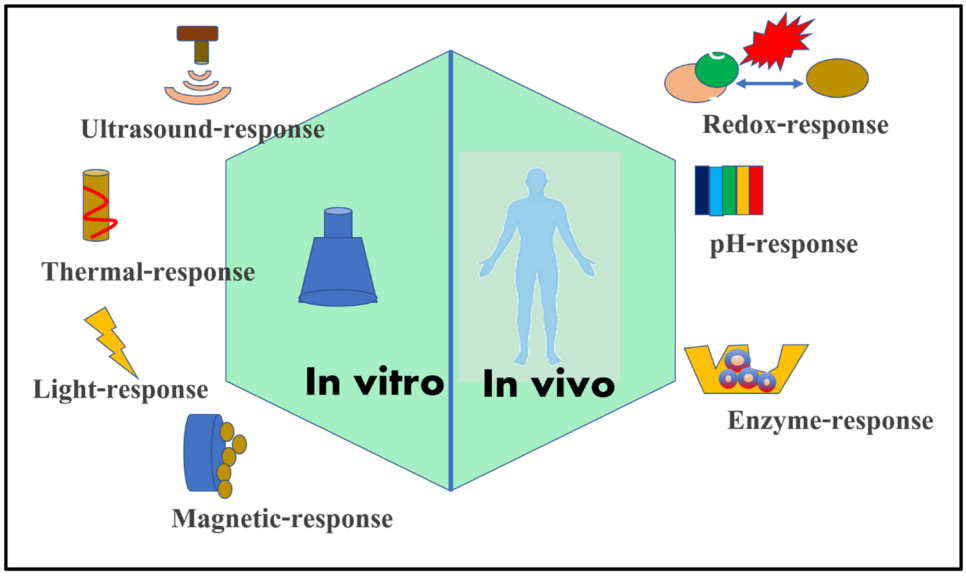

Figure 2: Schematic sketches of different types of stimuli for cancer therapeutics.

tissues is in the span of 7.2–7.5. But the pH in tumor cells is generally more acidic (pH 6.0–7.0). The variation between the normal cells and tumor cells attributes to the development of pH-responsive drug delivery systems, which trigger the release of the cargo into the cancer cells. Otto Warburg *et al.*, a German scientist first describe the abnormal action of the cancer cells. The glycolysis process in the cancer cells completes, even in the presence of oxygen is known as aerobic glycolysis. An unusual relying on glycolysis as the only source of ATP conception is seen in many types of cancer cells is called the "Warburg effect" [49]. There are various gatekeeping molecules, which can be tagged to the surface of the nanoparticles through the pH labile groups such as ester bond, hydrazine bond, and acetal bond, which can be lysed in acidic pH [50]. The transformation from a neutral milieu to an acidic milieu could cause remarkable changes in the physical properties of the material activity. The mechanisms behind the pH-triggered targeted drug delivery at the tumor are as follows;

- Protonation caused by the internalization
- Extracellular drug release owing to dissociation
- Detachment of PEG, which promotes the endocytosis of nanocarriers followed by destabilization of endosomal membrane and hence the release of the drug [51].

Wang *et al.* [52] constructed a novel pH-responsive block copolymer, poly(ethylene glycol)–poly(ε-caprolactone)–poly(L-histidine) (PEG–PCL–PHis), synthesized, and characterized for anti-cancer drug delivery with excellent advantages such as biocompatible, biodegradable, and strong drug-loading efficiency inner core. This self-assemble micelle has a constant circulation system in blood and tissue-specific targeting on cancer cells with pH sensitivity. Moreover, the cell viability of MCF-7 cells treated doxorubicin-loaded self-assemble micelle proved the biocompatibility of the drug-loaded system and the release mechanism pathway of DOX-loaded micelles. Anirudhan *et al.* [53] developed a graphene oxide (GO) and modified it to amine-functionalized GO (AGO), which acts as a cationic polyelectrolyte. Further, chitosan (CS) was conjugated with FA through *N*,*N*-dicyclohexylcarbodiimide coupling to form FA-CS. Subsequently, itaconic acid and acrylic acid monomers are grafted to the hydroxyl group of CS using ethylene glycol dimethacrylate as cross-linker and potassium peroxydisulfate as an initiator to generate –COOH functional groups and forming chemically modified chitosan (CMCS). In addition, doxorubicin (DOX) was loaded into the FA–CMCS/AGO through π–π stacking interactions. This carrier forms the complex with DOX through π–π stacking and hydrogen bonding interactions, which enhances the increased encapsulation and loading efficiency of DOX. The encapsulated DOX into the polymeric matrix specifically transit the cargo into HeLa cells through FA receptors. This system demonstrated the pH-responsive DOX release behavior at acidic conditions. Liu *et al.* [54] developed a targeted pH-responsive conjugated with polysaccharide and constructed with boronate linkage of *N*-(2-aminoethyl)-gluconamide- and grafted hyaluronic acid (HA) loaded with anticancer drug bortezomib, which could mediate the targeted drug release behaviors at acidic pH and exhibits decreased cytotoxicity and an increased inhibition rate toward cancer cells.

Men *et al.* [55] were motivated by overexpression of CD44 receptor in tumor microenvironment on the outside of the tumor cells. Through this inspiration, they have designed and developed a pH-sensitive liposome–polymer nanoparticle (NP) consisting of lipid, HA, and poly(β-amino ester) (PBAE) by layer-by-layer (LbL) technique for targeted delivery and controlled release of DOX to augment the cancer treatment efficacy. The release profile of the DOX from multilayered nanoparticles was depending on pH. The percentage of release at low pH was notably stimulated in contrast to that at the base or normal pH, determining the promise for controlled drug release as shown in Figure 3. Further, A549 cells treated with DOX-loaded nanoparticles resulted in very low toxicity as compared to free DOX. *In vivo* efficacy of the DOX-loaded NPs showed an excellent anticancer efficacy with minimal side-effects in contrast to free DOX and PBS causing an active targeting of HA and pH-triggered drug-release profile (Table 1).

2.1.2 Redox responsiveness

Redox responsive mechanism is the second most commonly used method to pH responsiveness for constructing stimuli drug delivery systems. The substances such as vitamin E, vitamin C, and glutathione are the reducing agents that are broadly present in our humans. Out of the reducing agents present in our body, glutathione (GSH) is most involved in the metabolic process [61]. The snap switch between the oxidized and reduced forms of glutathione secures the cells from pro-oxidant stress. This consists of a tripeptide sequence of glutamic acid-cysteine-glycine. The distinct feature of the peptide is the peptide bond configured between the gamma carboxylic acid of glutamic acid and the alpha-amino group present in cysteine. The stability in circulation as GSH levels are low in the extracellular environment is about 0.002 mM. Good response to high intracellular levels of GSH is about 1–10 mM indicating that the GSH-triggered release of redox responsive nanocarriers can take place inside the tumor cells and not in the extracellular environment. An intracellular concentration of GSH in tumor tissues is at least four times higher than that in normal tissues. The ratio has been varied in different cancer cells such as head and neck, ovarian, breast, pancreatic, and lung cancer cells [62]. The unique aspect of the redox responsive nanocarrier systems is the S–S bond that is chemically cross-linked as a gating or capping molecule on the surface of the nanoparticle is cleaved upon the addition of GSH, causing the rapid drug release to the tumor cells [63]. Sauraj *et al.* [64] developed a redox responsive nanocarrier system using Xyl-SS-Cur for dual delivery of curcumin and 5-FU in human colorectal cancer therapy. Researchers have synthesized Xyl-SS-Cur through covalent conjugation of curcumin to xylan *via* the disulfide bridge. The redox-sensitive Xyl-SS-Cur facilitates the self-assembly into the nanocarrier through the encapsulation of lipophilic 5-fluorouracil-stearic acid into the hydrophobic core containing Xyl-SS-Cur NPs/5-FUSA NPs *via*

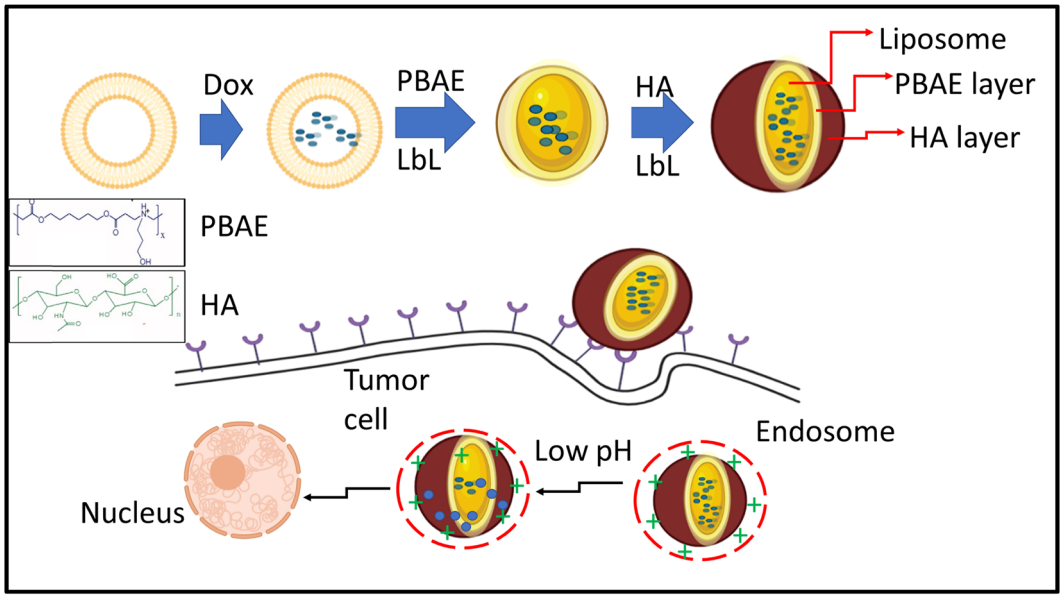

Figure 3: Schematic illustration of the development of LbL DOX-loaded NPs for targeted drug-delivery systems.

Table 1: pH responsive DDS for mono and combination cancer therapy

Nanoparticles used	Composition	Payload for delivery	Outcome	References
Amphiphilic polymer	PEG-BHyd-dC_{12} *via* an acid-labile hydrazone bond	Paclitaxel (PTX)	• Exhibited pH-dependent drug release profile • Enhanced endosomal escape • Intracellular delivery, and enhanced anti-tumor activity	[56]
Hybrid nanoparticles	pH-responsive hybrid ATRAM-BSA-PLGA	DOX-triphenylphosphine	• Nanoparticles exhibited highly efficient pH-dependent cellular uptake • Energy-independent and -dependent internalization mechanisms • Significant cytotoxicity	[57]
Hollow mesoporous silica nanoparticle	Mesoporous silica nanoparticles tagged with folic acid, coupled with polyethyleneimine (PEI–FA)	DOX and siRNA toward anti-apoptotic genes	• pH-responsive intracellular drug and siRNA release • Lowers off-target effects, • Down regulation of anti-apoptotic protein Bcl-2 and triggered apoptosis	[58]
Black phosphorous nanoparticles	DOX-loaded BP@PDA-PEOz-BTZ platform	DOX and bortezomib	• Exhibits high encapsulation efficiency • Enhanced cellular uptake and cytotoxicity • Demonstrated photo-responsive, and fast drug release triggered by low pH	[59]
pH sensitive polymerosomes	Angiopep-2-tagged pH-responsive polymersomes (Au-DOX@PO-ANG)	DOX	• pH sensitivity and counter the tumor microenvironment • These targeted polymerosomes has ability to cross blood brain barrier	[60]

the dialysis membrane method. The Xyl-SS-Cur/5-FUSA NPs demonstrated a significant redox-responsiveness system because of the disulfide bridge causing the release of dual drug curcumin and 5-FUSA predominantly in the presence of 10 mM glutathione (GSH). The blood compatibility results determined hemolytic activity even at higher temperature Xyl-SS-Cur/5-FUSA NPs. The cytotoxicity results showed a significant reduction in the cell viability levels and an inhibition activity in cancer cells (HT-29, HCT-15). Hence, these dual drug delivery redox responsive nanocarrier systems would be potential and ideal candidates for multiple drug delivery research soon. Jia *et al.* [65] presented the two-stage rocket mimetic redox responsive system for a better tumor intracellular and tumor microenvironment. They designed a redox responsive nanocarrier, organo silica-micellar hybrid nanoparticles doped disulfide, and surface functionalized with PEG and amido-bonded polyethyleneimine (PEI), called as DOSN-PEI-SS-PEG, the disulfide tagged PEG of DOSN-PEI-SS-PEG, guards the positive charges of PEI, make sure the elongated circulation time, and inhibits the non-specific adsorption of protein. At stage 1, the long chain of PEG is broken with an extracellular concentration of GSH (2–10 μM). At stage 2, the positively charged PEI enhances the cell internalization through electrostatic interactions. This PEI allows the nanocarrier to get away from the endosomes and enters the cytoplasm through the proton sponge mechanism. In addition, the second stage of endocytosis by tumor cells is stimulated with an elevated intracellular concentration of GSH redox-responsive system by lysis of the disulfide bonds of the silsesquioxane matrix, causing the drug release. This two-stage rocket-mimic nanocarrier would be a novel approach to ameliorate the selective or target specific, *in vivo* efficacy, enhanced tumor accumulation, and safety chemotherapy.

Chang *et al.* [66] presented a novel redox-sensitive system, with polyethylene glycol-poly(β-benzyl-L-aspartate) (PEG-PBLA)-SS-paclitaxel (PPSP) prodrug conjugated with disulfide bridges, constructed, and synthesized successfully. This system was developed to improve the faster release of drug molecules to the cancer cells HepG2 and MCF-7 from the hydrophobic layer (prodrug) through lysis of the disulfide bridges upon exposure to GSH. This redox-sensitive (PEG-PBLA)-SS-paclitaxel (PPSP) system enhances the anti-tumor efficacy and biosafety. Chen *et al.* [67] reported a novel system, transferrin is a glycoprotein and an upregulated receptor present on the surface of the cancer cells. This protein is conjugated on the surface of the mesoporous silica nanoparticles *via* redox lysed disulfide bonds, which function both as a targeting and capping agent concurrently. This system (DOX@MSNs-S-S-Tf) showed a very slow release in the presence of GSH, at the high concentration of GSH, it triggers the drug release, limiting the premature leakage, and enhances the anti-tumor efficacy. The unique aspect of this system is three functions in one moiety such as targeting, capping, and intracellular uptake of cells. In summary, this protein conjugated MSNs for GSH-triggered drug delivery system would be an ideal and potential candidature for our new insights of upcoming

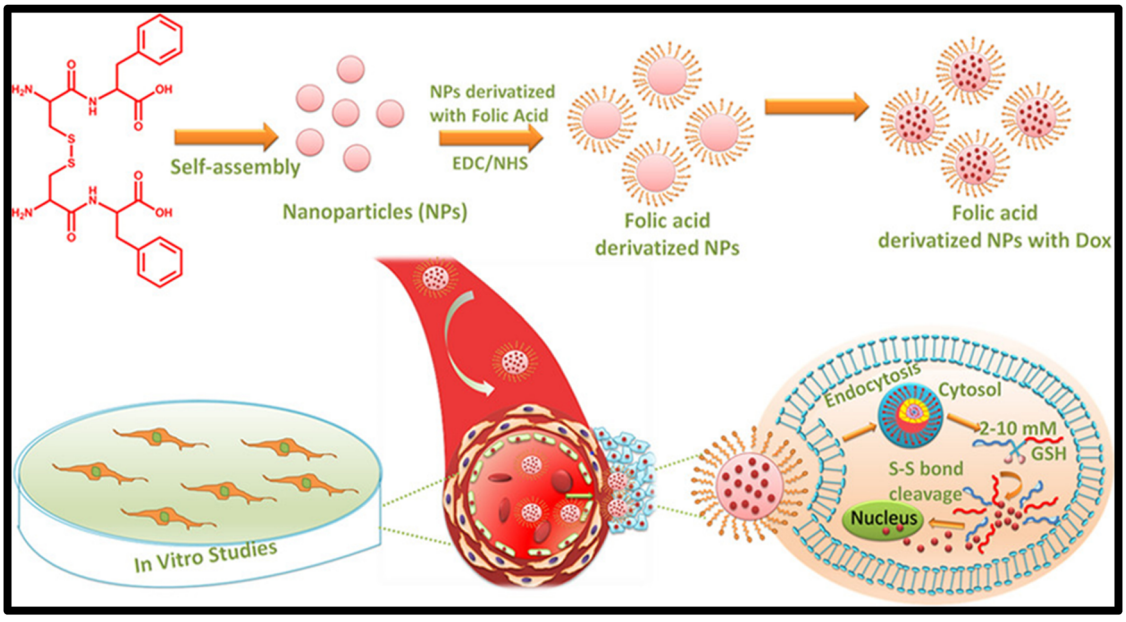

Figure 4: Schematic representation for the disulfide-linked oxidized cysteine-phenylalanine nanoparticles drug carrier.

Table 2: Redox responsive DDS for mono and combination cancer therapy

Nanoparticles used	Composition	Payload for delivery	Outcome	References
Disulfide-linked oxidized cysteine-phenylalanine nanoparticles	Folic acid-CFO-Dox-nanoparticles	DOX	• Increased cell uptake of FA tagged nanoparticles • Significant reduction in cell viability compared to plain drug	[69]
PAEs/RNA complex nanoparticles (PAEN)	Bioreducible poly(*b*-amino esters) (PAEs), poly[bis(2-hydroxylethyl)-disulfide-diacrylatetetraethylenepentamine] (PAP)	iMdr-1-shRNA, iSurvivin-shRNA	• Demonstrated low IC50 of DOX in multidrug resistance cells, down-regulated P-gland reduced tumor size of survivin, *in vivo*	[70]
Anti-carbonic anhydrase IX antibody on the surface of mesoporous silica nanoparticles *via* disulfide linkages	Doxorubicin@MSNs-CAIX	DOX	• Doxorubicin@MSNs-CAIX would facilitate cell internalization with response to glutathione trigger • It suppresses the tumor growth efficiently	[71]
Mesoporous silica nanoparticle	Amino-gated alkyl chains with disulfide bonds modified on the surface of nanoparticle by the reaction of *S*-(2 aminoethylthio)-2 thiopyridine hydrochloride (SATH) and thiol-modified nanoparticles (MSNPSH)	Negatively charged ssDNA, DOX	• Increased cellular internalization and significant apoptosis induction	[72]
Biodegradable polymeric NPs	Solid poly(disulfide amide) (PDSA)/cationic lipid core and a lipid–PEG shell	siRNA	• GSH-triggered intracellular siRNA release • Potent gene silencing	[73]

research. Zid *et al.*, [68] developed DOX-loaded hexagonal mesoporous silica nanoparticles to confirm the redox responsive system, cysteamine-based ligand was grafted on the surface of the SBA 15. Further, to prove the premature leakage of thioglycolic acid-functionalized ZnS nanoparticles (ZnS–COOH NPs) as pore capping agents. These cysteamine-grafted SBA 15 was bonded by peptide to thioglycolic acid groups of ZnS–COOH NPs. *In vitro* results of this system demonstrated that the cleavage of the disulfide bond through the addition of thiol reducing agents caused the drug to release and kill the cancer cells resulting in significant cytotoxicity effects. Schematic representation for the disulfide-linked oxidized cysteine-phenylalanine nanoparticles drug carrier is shown in Figure 4 (Table 2).

2.1.3 Enzyme responsiveness

Enzyme responsive drug delivery system is well developed and functions in many biochemical effects inside the body. There are many enzymatic reactions such as esterase's produce ester hydrolytic reactions; glycosidases induce the hydrolysis of glycosidic bonds; peptidases invoke the breakdown of proteins into amino acids, and so on. The attractive feature of the enzyme is to provide the biodegradation of biomacromolecules and other important enzymes that are up-regulated in cancer cells would be advantageous for emerging of an enzyme-responsive drug delivery system [74]. Naz *et al.* [75] presented an enzyme-responsive drug delivery system by constructing mesoporous silica nanoparticles for multiple targeted anti-cancer activities. This mesoporous silica nanoparticle acquires both CD44 and triphenylphosphine (TPP) for mitochondria targeting effects and is further encapsulated with DOX then by capping with tumor-targeting molecules HA through electrostatic interactions. The HA capped on the surface of the mesoporous silica nanoparticles impart a powerful sealing ability in normal cells and improved selective uptake by cancer cells through CD44 receptor-mediated endocytosis pathway. These systems would be great for exhibiting enzyme responsive systems *via* the degradation property of HA in cancer cells as shown in Figure 5.

β-gal enzyme upon exposure to elevated concentration and go along with the emission produced by the fluorescence turned on, the DOX is released to the tumor cells. The *in vitro* and *in vivo* results showed a significant therapeutic potent on GalDOX specifically in ASGP overexpressed HT-29 cells and significant retardation of tumor growth was observed in the xenograft mice model [76]. Zhou *et al.* [77] developed an enzyme-responsive drug delivery system involving mesoporous silica nanoparticles covalently conjugated with extracellular matrix biomacromolecules such as collagen I and HA enhances

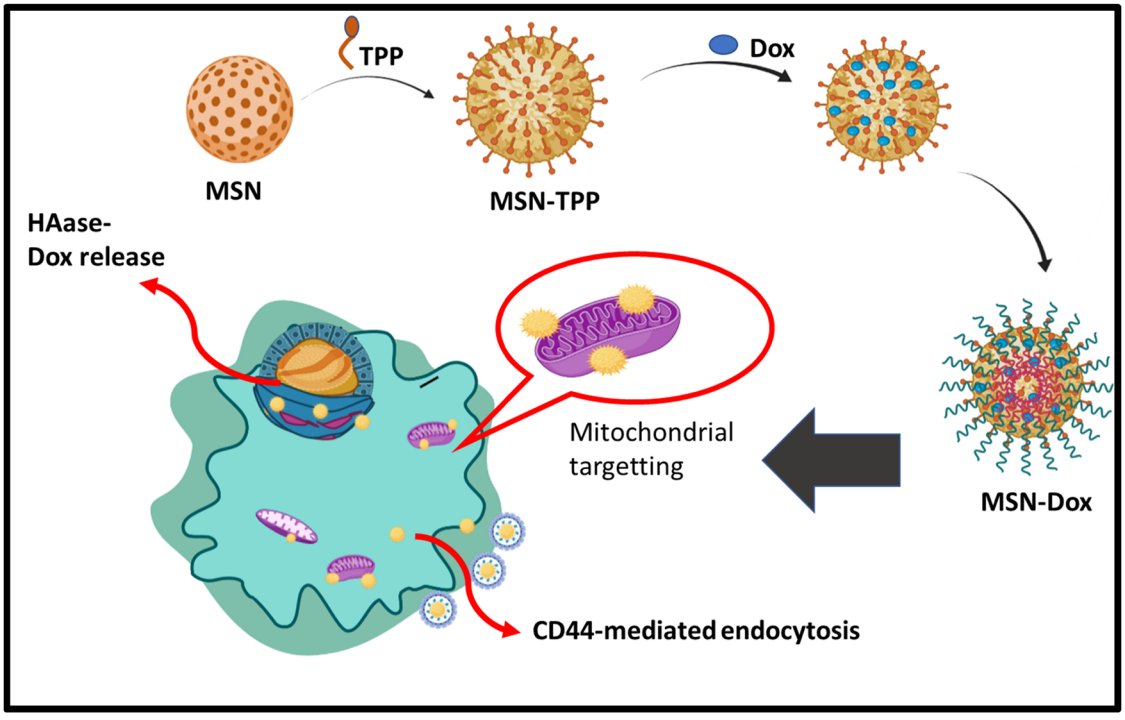

Figure 5: Schematic representation of enzyme responsive system.

Table 3: Enzyme responsive DDS for mono and combination cancer therapy

Nanoparticles used	Composition	Payload for delivery	Outcome	References
Theragnosticnanohybrids	GO capped with poly(ethylenimine)-*co*-poly(ethylene glycol) (PEI–PEG) *via* MMP2 cleavable PLGLAG peptide linkage	DOX, DNA	• Significant drug toxicity against tumor cells • Coherent transfection in contrast to that with PEI25k	[78]
Dendrimers (PAMAM)	γ-Glutamyl transpeptidase (GGT)-triggered transcytosis of the dendrimer–camptothecin conjugate	Camptothecin	• Increased anti-tumor activity in mouse models	[79]
Gold nanocluster	Fabricated gold nanocluster@bovine serum albumin (AuNC@CBSA-ICG), indocyanine green	Indocyanine green	• Hyaluronidase-dependent drug release • Suppress tumor growth on mice breast cancer model	[80]
Dendrimers	Dendritic thiolated hyperbranched polyglycerol	Maleimide-bearing DOX prodrug, maleimide-bearing methotrexate prodrug	• Exhibit high cytotoxicity against human cancer cells	[81]

biocompatibility and limits premature leakage. Drug release was attained by biodegradation provoked by hyaluronidase (HAase) and matrix metalloproteinases 2 (MMP-2), which are over-expressed in cancer cells. The *in vitro* studies enhance the biocompatibility and targeting of the cells. The *in vivo* results demonstrated that this system would retard the tumor growth and reduces the side effects to the normal cells (Table 3).

2.2 External stimuli for drug delivery systems

The external stimuli are man-designed stimuli, which are induced or signals from outside the body to stimulate the drug delivery systems. Recent advancements on the external stimuli developed by researchers have achieved a controlled release manner. There are quite a few parameters behind the interior body known as "external stimuli" such as magnetic fields, ultrasound, and light. In contrast with the "internal-stimuli" acts within tumor microenvironment like pH value, temperature, and redox as described earlier, the external stimuli-responsive drug delivery systems would introduce contrast agents to image, that of nanoparticles located in the target tissues, cells, or organelles, further triggers the nanocarriers outside the body through particular stimuli at a specific time. Hence, the controlled release is an increased spatiotemporal and has a great potential for clinical applications.

2.2.1 Magnetic field responsiveness

Magnetic systems are broadly utilized in targeting as well as imaging. As magnetic-responsive nanotherapeutics is a noninvasive signal, an externally applied magnetic field can damage the moving particles and increase the accumulation of anticancer agents in tumors by a magnetic field that would be employed for *in vivo* applications, this could have greater advantages for targeted cancer therapy as compared with intrinsic stimulus-responsive nanotherapeutics [82]. Furthermore, core/shell magnetic nanoparticles showed a collection of unique magnetic properties. The large surface-to-volume ratio of magnetic nanoparticles support a large number of active sites for conjugating a biomolecule, thus provides precise design and engineering to gain their smart functions by exploiting a localized external magnetic field, prolonged circulation in the bloodstream, targeting the damaged tissues, and therapeutic delivery [83]. Kong *et al.* [84] demonstrated a novel lipid–polymer hybrid nanoparticles encapsulated

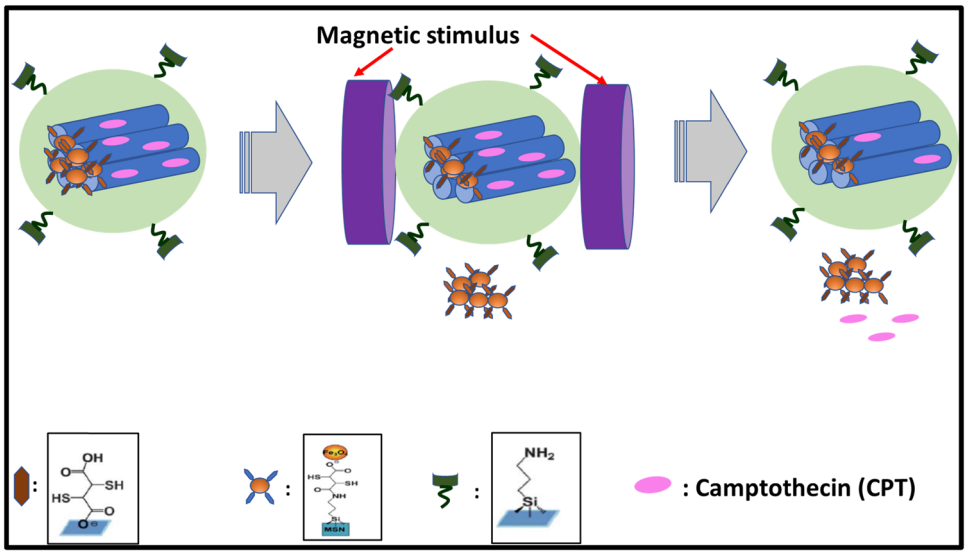

Figure 6: Schematic illustration of magnetic field responsive system.

with magnetic beads and anti-cancer drug camptothecin for breast cancer therapy. The drug release was stimulated by external RF magnetic field actuation. In the presence of RF magnetic field actuation induces the heat by Fe_3O_4 in the inner side of the polymeric cores, which relaxes the polymer matrices and triggers the drug release, causing the elevated significant cytotoxicity *in vitro* results toward breast cancer cells.

Guisasola *et al.* [85] constructed a new system of magnetic field responsive systems that can control the release of drug molecules and proteins upon an altering on and off the magnetic field. Mesoporous silica nanoparticles were encapsulated with iron oxide and surface functionalized with temperature below lower critical solution temperature (LCST) based polymer called PNIPAM. The release was stimulated by altering the on and off switch of the magnetic field. As the temperature of the polymer increased above LCST upon the alternative magnetic field on and off switch, hence the drug is released on the conformational change of the surface-coated polymer. Chen *et al.*, [86] presented a magnetic field responsive based drug delivery using (MSN@Fe3O4) capped with amine group with 2,3-dimercaptosuccinic acid-functionalized Fe_3O_4 nanoparticles *via* chemical amidation. Upon the induction of the magnetic field, nanocaps were detached by lysing the chemical bonds, resulting in faster drug release. These release profiles were controlled by the duration of strength and time. Hence, these MSN@Fe_3O_4 nanocarriers also play a role in T2 magnetic resonance contrast agents that could be useful for molecular imaging. Schematic representation for the rocket-mimetic mechanism of DOSN-PEI-SS-PEG drug carrier is shown in Figure 6 (Table 4).

2.2.2 Ultrasound responsiveness

Ultrasound is one of the most commonly used exogenous stimuli methods in cancer therapy. The unique advantages of ultrasound responsiveness are safety and deeper penetration into tissue, which is a non-invasive method. In the drug delivery systems, ultrasound has the pressure waves at frequencies of 20 kHz or greater is a most important factor for local stimulus concerning site-specific delivery and spatial release control of drugs tempt an increasing awareness on the cancer therapy [91]. Paris *et al.*, [92] developed an ultrasound responsive system based on mesoporous silica nanoparticles capped p(MEO2MA)-*co*-THPMA on the surface connecting US-cleavable hydrophobic tetrahydropyranyl moieties, confer an LCST below physiological temperature. At 4°C, the polymer in the state of coil-like confirmation, allows the drug to be encapsulated inside the pores of the silica. As the temperature elevates to 37°C, the polymer transforms to the collapsed state and the drug molecule continue to be inside the pores. On exposure to the ultrasound irradiation, hydrophobic tetrahydropyranyl moieties are cleaved and the polymer turns to the hydrophilic nature and thereby increases in LCST temperature above 37°C. This exhibits the conformational change of the polymer, allowed to open the gates of the pores to release the encapsulated drug as shown in Figure 7.

Kim [93] and his group members developed a DOX-loaded titanium nanoparticles surface coated with poly (methyl vinyl ether-*alt*-maleic anhydride) pPBA through the generation of the boronic ester bond, forming pPBA@TNP-DOX nanoparticle to enhance the tumor-targeting *via* the

Table 4: Magnetic field responsive DDS for mono and combination cancer therapy

Nanoparticles Used	Composition	Payload for delivery	Outcome	References
Iron oxide-double emulsions nano capsules	Polyvinyl alcohol shell inside iron oxide nanoparticles (core shell), IVO24, a peptide targeting cancer cells, capped to double emulsion capsules	Paclitaxel, DOX	• Controllable drug release • Intensified dual magneto-chemotherapy and magneto-hyperthermia *in vitro* and *in vivo*	[87]
Magnetic nanoparticles	Amine groups attached to the carboxylic functional groups coating magnetic nanoparticles (fluid MAG-CMX)	DOX	• Tumor retardation rate of CMX–DOX NPs under a magnetic field was significantly higher than the control group	[88]
Polymersomes	Superparamagnetic iron oxide nanoparticles (USPIO; γ-Fe_2O_3)	DOX	• Upon magnetic field triggers an increased intracellular drug release	[89]
Lipid-coated magnetic nanoparticles	Magnetic lipid microcapsules (MLMs) containing lipid-coated magnetic nanoparticles	5-(6)-Carboxyfluorescein	• Effectively reduces the aggregation • Improved stability and biocompatability	[90]

synergy between PBA and sialylated epitope of cancer cells. When it is exposed by ultrasound, the drug molecule could be released from pPBA@TNP-DOX on breaking of boronic ester bonding mediated by ultrasound-mediated ROS generation. This system suggests that pPBA@TNP-DOX could be ideal for ultrasound responsive drug delivery (Table 5).

2.2.3 Temperature responsiveness

There are many exogenous stimuli used for drug delivery systems, among those temperature-responsive drug delivery systems afford potential advantages compared to other counterparts because of their flexibility in design, regulating the phase transition temperatures, passive targeting capability. The localized hyperthermia from 42.5 to 43.5°C helps to evade cancer cells by inducing high temperature to tumor tissues. On the other way, these stimuli on hyperthermia would enlarge the blood vessels and modify the perforation of tumor cell membranes, thereby enhancing the anti-tumor drug delivery. Temperature responsive properties are seen in the polymers such as poly(*N*-isopropyl acrylamide) (PNIPAM). These temperature-responsive polymers have a LCST factor. When the room temperature is lesser than the LCST, these polymers become soluble and move to the swelling state because of the hydrogen bonds present between the polymer chain and water molecules. As the temperature increases, the hydrogen bonds break, leading to insolubility and collapse of the polymer. This mechanism would help in developing the temperature-responsive drug delivery system [98].

Temperature responsive drug carrier Fe_3O_4/PNIPAM/5-Fu@mSiO_2-CHI/R6G was developed by Shen *et al.* [99]. They studied a drug carrier using different temperatures *in vitro*. In this system, Fe_3O_4 magnetic nanoparticles, as a source of magnetic used for the treatment of hyperthermia. This hyperthermia treatment of Fe_3O_4, Fe_3O_4/PNIPAM/5-Fu@mSiO_2, and Fe3O4/PNIPAM/5-Fu@mSiO_2-CHI/R6G was demonstrated using a magnetic field. The thermo-responsive drug delivery could be controlled by the magneto-caloric function of the magnetic field. These systems would release a drug ideally at 45°C, which was due to the advantage of smart thermoresponsive polymer PNIPAM. Demirci *et al.* [100] developed an iron oxide nanoparticle coated with dextran to destroy the retinoblastoma cells in a significant manner as compared to normal cell counterparts. Magnetic hyperthermia stimulated apoptosis seen in Y79 cells basically through the intrinsic pathway initiated by FAS and TNF-a signaling. These iron oxides-coated dextran nanoparticles would be a promising strategy for thermo-chemotherapy. Zamora-Mora *et al.* [101] in 2017 reported

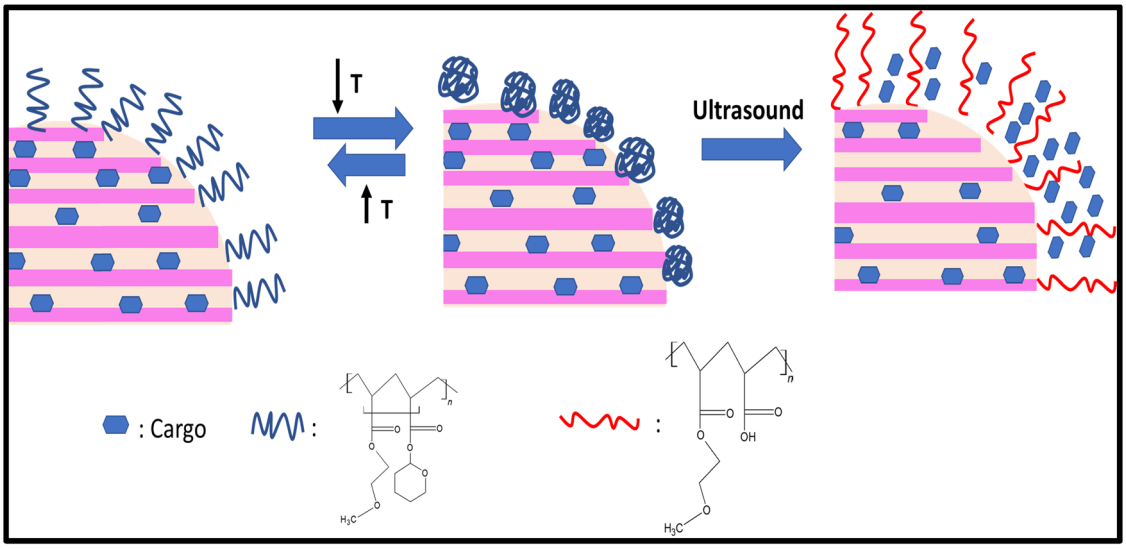

Figure 7: Schematic illustration of Ultrasound responsive systems.

tripolyphosphate salt (TPP) cross-linked with chitosan nanoparticles (CSNPs) for combined delivery of MHCT and 5-fluorouracil (5-FU) in human glioblastoma A-172 cells. The dual functionality of these magnetic CSNPs with core-shell morphology showed a dose-dependent reduction in cell viability levels of glioma cells on AMF application as compared to fibroblasts cells counterparts showing no reduction in viability levels. Magnetic core–shell nanoparticle (MCNP) activated drug delivery of a mitochondria-targeting proapoptotic amphipathic tail-anchoring peptide (ATAP) in association with MHCT for malignant brain cancer cells as shown in Figure 8 (Table 6).

2.2.4 Light responsiveness

Light-stimulated drug delivery system is one of the exogenous systems, most applied stimulus because of its non-invasive nature [105]. The main impact of light-responsive drug delivery systems is their temporal and spatial property which controls the release behavior accurately upon

Table 5: Ultrasound responsive DDS for mono and combination cancer therapy

Nanoparticles used	Composition	Payload for delivery	Outcome	References
Lipid microbubbles	Paclitaxel-loaded lipid microbubbles	Paclitaxel	• Has ultrasound-mediated drug delivery with low-frequency US transducer • Able to visualize and track in the iliac artery which is good for identification restenosis	[94]
Micelle	Perfluoropentane or perfluoro-15-crown-5-ether	DOX	• Ultrasound triggered intracellular and nuclear trafficking. Megahertz continuous wave or pulsed ultrasound with 33% duty cycle at 3.4 W cm^{-2} nominal power density	[95]
Alginate hydrogels	Cross-linked polymers with respect to ultrasonic irradiation can stimulate drug release on-demand	Mitoxantrone and macromolecules such as siRNAs	• Ultrasound triggered system enables the digital drug release • Ultrasound mediated release effectively reduces the tumor growth *in vivo*	[96]
Nested nanobubbles-	Nested-nanobubbles containing outer liposomal shell-loaded	Calcein	• The use of continuous wave and exposure to ultrasound trigger the drug release	[97]

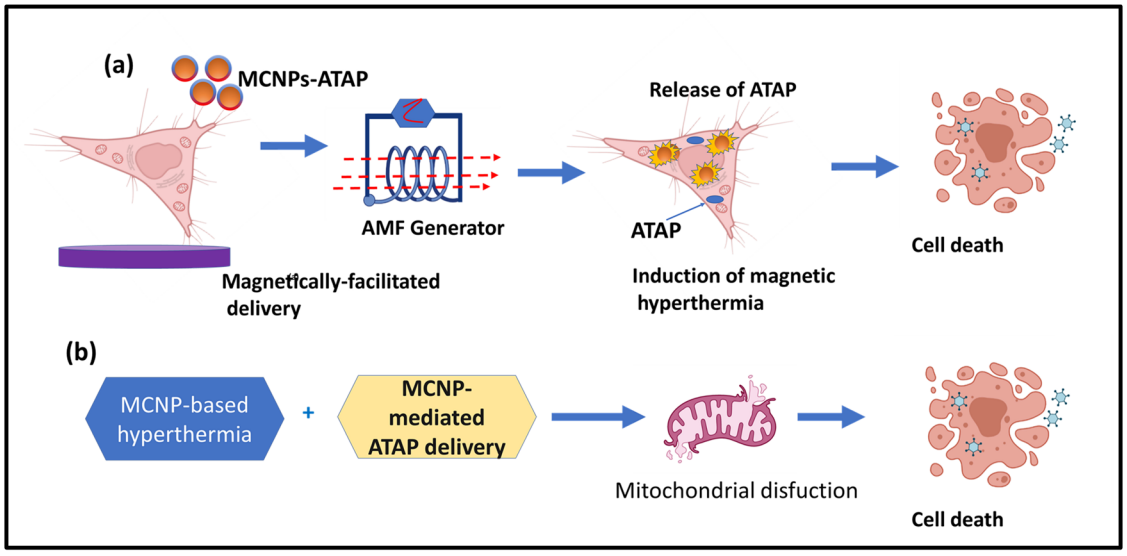

Figure 8: Schematic representation of temperature-responsive systems.

stimulation light exposure at a specific time and position. There are different lights with different wavelengths. As of now, the drug delivery systems use ultraviolet light, visible light, and near-infra-red light. There are three major mechanisms on how these light-induced drug delivery systems work, such as isomerization, bond cleavage, and disaggregation of the nanocarrier on exposure to light. The wavelength of the ultraviolet ranges from 10 to 400 nm, lower than that of the visible light but greater than that of X-rays. The most commonly used chromophores are azobenzene, coumarin, spiropyran, pyrenylmethyl, *o*-nitro benzyl are UV light-responsive groups. Wang and Wu [106] demonstrated mesoporous silica nanoparticles nano valves surface capped with tetra-ortho-methoxy-substituted azobenzene (mAzo) and β-CD and loaded with DOX for a controlled release from the mesopores. Azobenzene has the light-inducing property that would trigger the drug release to the tumor cells on red light irradiation as shown in Figure 9 (Table 7).

2.3 Dual and multiple stimuli-responsiveness

Dual and multiple stimuli stars have been playing a potential role in biomedical materials on controlled

Table 6: Temperature-responsive DDS for mono and combination cancer therapy

Nanoparticles used	Composition	Payload for delivery	Outcome	References
Polypeptides	Polyaspartamides with isopropylamide and hydroxyalkylamide pendant groups	DOX	• The phase transition temperature (Tp) of the copolymers phase transition temperature could be varied by modulating the pendants composition • Exhibited a temperature-responsive release	[102]
Core-shell nanoparticles	Hollow poly(*N*-isopropylacrylamide) (PNIPAM) nanogels surface modified with silica nanoparticles	DOX	• Lower density of cross-linking showed an elevated controlled release • Determines a higher toxicity toward Hela cells	[103]
Thermo-responsive barrier gel	Injectable thermo-gelling poly (diethylaminoethyl methacrylate) (PDEAEM)-Pluronic F127 (PL)-PDEAEM pentablock copolymer (PB)	Paclitaxel, DNA	• Magnified transfection efficiency • Anti-cancer activity of paclitaxel *in vitro*	[104]

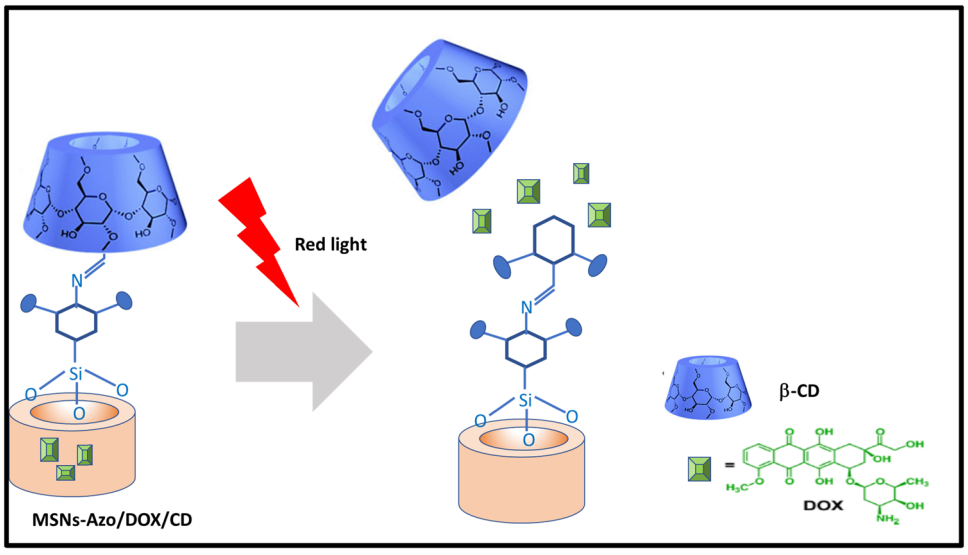

Figure 9: Schematic representation of light-responsive systems.

drug delivery systems. An *et al.* [110] developed multistimuli-responsive nanoparticles, mesoporous silica nanoparticles end-capped with PEG-*a*-PCL-SSP(NIPAM-*co*-DMA) and loaded with an anti-cancer agent (paclitaxel, PTX) and a photothermal cyanine dye (cypate), which stimulate pH/reduction–responsive drug release upon exposure to disulfide bridges, resulting in the lysis of the acetal bonds, on exposure to NIR-light-irradiation enhance the temperature increase, photostability, and intracellular reactive oxygen species of cypate. Reactive oxygen species induced drug transportation from lysosomes to the cytoplasm, which results in the synergistic effect and causes effective thermo-chemotherapy as shown in Figure 10.

They have also developed multistimuli composed of polymer, Dex-*g*-PpIX-*g*-PBA-SS-CPT (DPPSC), fabricated using dextran(hydrophilic) grafted protoporphyrin IX (PpIX) and loaded with anticancer drug camptothecin (CPT) and also conjugated with Dextran *via* the disulfide bridge holds the pH-responsive linker (hydrophobic). Dextran is a polysaccharide that has the property to prolong the blood circulation time of self-assembled micelles of the polymer, increases tumor accumulation through the enhanced permeability and retention effect. After the micelles get inside the tumor tissue, on a short time of light irradiation PpIX gets activated and enhances the endocytosis process. Further, the puncture of the endocytic membrane on exposure to PDT long time irradiation activates reactive oxygen species, causing the micelles to get away from endosomes and lysosomes and get into the cytoplasm. In the acidic lysosomal environment,

Table 7: Light responsive DDS for mono and combination cancer therapy

Nanoparticles used	Composition	Payload for delivery	Outcome	References
Dendritic micellar nanoparticles	Diazonaphthoquinone, light 808 nm; NIR irradiation; 365 nm, UV irradiation	DOX	• Exhibited a light-responsive release of DOX	[107]
Polymeric drug conjugates	Porphyrin-based polymeric drug conjugates PSDTD-m	Porphyrins	• Controlled release was achieved through reactive oxygen species cleavable linkage for anti-cancer efficacy and photodynamic therapy	[108]
HA-based nanocarriers	HA-photosensitizer conjugate (HA-TK-Ce6)	Ce6-Chlorin e6	• Laser irradiation at 660 nm produces ROS during a photodynamic (PDT) therapy to cleave the TK linker next to Ce6, demonstrating in light-stimulated TKHCENPDOX breakage and selective DOX release in the tumor cells.	[109]

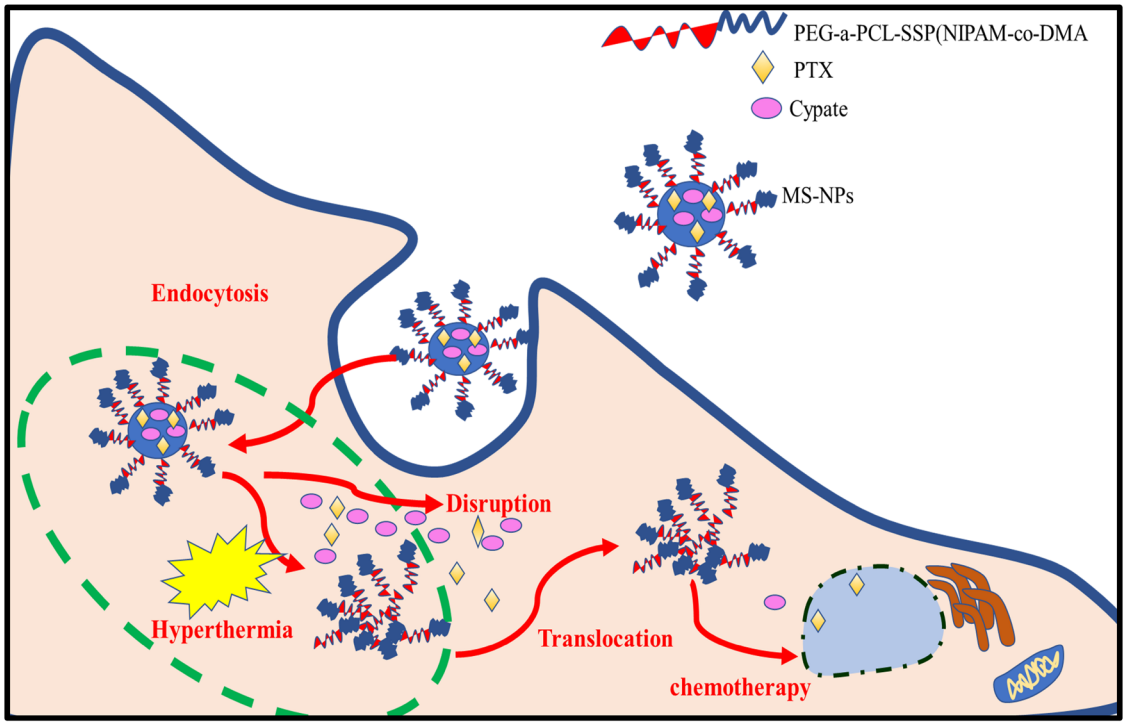

Figure 10: Schematic illustration of multiple stimuli-responsive systems.

the hydrolysis of the boric acid ester linkage at low pH enhances the release of the prodrug (PBA-SS-CPT) from the nanoparticles. Once it enters the cytoplasm, the prodrug CPT converts into the free CPT through GSH responsiveness. Therefore, the drug enters the nucleus for an effectively combined chemo phototherapy with minimized side effects [111]. Researchers have also developed a dual stimulus by supramolecular polymer nanocarriers CPAP (CDPEG), hydrophilic and hydrophobic (Azo-PCL). PEG was grafted onto the surface of b-CD through disulfide linkages to form CD-PEG, and Azo-PCL were poly(ε-caprolactone) chains with azobenzene groups grafted at one end. CD-PEG and Azo-PCL were combined by the host–guest interaction between azobenzene and b-CD. The PCL chains with hydrophobic core loaded the hydrophobic drug DOX. The nanocarriers CPAP-loaded DOX detaches and triggers the drug release with an exposure of glutathione and light irradiation at 365 nm. These results demonstrated that CPAP nanocarrier would be the potential for killing the cancer cells by preventing the normal cells with adverse side effects [112]. Ko *et al.* [113] developed a novel dual stimuli-responsive graphene quantum dots grafted multifunctional carbon nanoparticles (DS-CNPs). These nanoparticles further functionalized with PEG and HER to form the ester/amide bonds (pH-dependent and GSH responsive disulfide bonds). Further DOX was encapsulated in DS-CNPs (DL-CNPs) as the size of the nanoparticles larger than 200 nm are preferred intravenous injection, gathers in the breast cancer region through EPR effect. Once endocytosis of DL-CNPs occurs, HER and DOX get released on exposure to pH and high concentration level of GSH. DOX gets inside the nucleus and causes apoptosis by interrupting DNA. HER also functions to suppress tumor growth.

2.4 Stimuli-responsive nanocarriers in clinical translation

There are few advancements made for stimuli-responsive nanocarrier systems from bench to bedside in the clinical trial and various formulations. They are also the barriers behind the clinical translations along with the progress such as

- The differences between animal tumor models and tumors in patients, as tumors in patients, are more heterogeneous and complicated. The most primary factors that should be inscribed are toxicity, biosafety, and biodegradability of the nanocarriers.
- *In vivo* function of the stimuli-responsive should be stable.

Table 8: Stimuli-responsive nanoparticles in clinical trials

Stimulus	Nanocarriers	Type of cancer	Drug	Status	Reference
pH	Polymeric micelles	Solid tumor, sarcoma, and metastatic sarcoma	Epirubicin	Phase I/II	NCT03168061
Thermosensitive liposomal	Thermo DOX	Breast cancer, primary liver cancer	DOX	Phase II/III	NCT00826085
Magnetic	Iron oxide magnetite	Prostate cancer	Iron oxide nanoparticles	Phase I	NCT02033447
	Iron and carbon	Hepatocellular carcinoma	DOX	Phase II	NCT00034333
Genexol®-PM	PEG-PLA	Recurrent breast cancer	PTX	Phase IV	NCT00912639
		Breast cancer		Phase III	NCT00876486
		Ovarian cancer		Phase II	NCT00877253
		Non-small-cell lung cancer		Phase II	NCT01023347, NCT01770795
NK012	PEG-PGlu	Refractory solid tumors	SN-38	Phase I	NCT00542958
Nanoxel®M	PEG-PLA	Head and neck squamous cell carcinoma	Docetaxel	Phase II	NCT02639858
NC-6004	PEG-PGlu	Head and neck neoplasms	DDP	Phase I	NCT02817113

- The efficacy and accumulation of the tumor of stimuli-responsive nanocarriers must be evaluated in the clinical trial.
- The route of administration and dose of the stimuli-responsive nanocarrier must be considered. The most commonly used routes are intravenous injection (i.v.), intraperitoneal injection (i.p.). Hence, the clinical transfer of the stimuli-responsive nanocarriers and formulations should be optimized from sessions of a clinical trial [114,115].

Hence, stimuli-responsive nanoparticles and polymers in clinical trials as presented in Table 8.

3 Conclusion

Very broad research has been carried out on stimuli-responsive drug delivery systems. As we desired to elaborate this review, the design of the stimuli-responsive drug delivery systems is not that easy process and it requires multidisciplinary knowledge of materials, chemistry, and biology. A unique aspect achieved by the stimuli-responsive systems is high drug loading capacity, *in vitro* drug release profiles, biocompatibility, and safety concerns on the efficacy of small molecule drugs. These stimuli-responsive nanocarriers can be tagged along with antibodies toward tumor immunotherapy [116,117]. A clinical stage of the stimuli-responsive system is arriving at the near future, interdisciplinary cooperation. Finally, the term "nanomedicine" will establish applications for novel and superior diagnostic, therapeutic, and preventive measures.

4 Future perspectives

Nanocarriers are a wonder of nanoscience, playing an important role in anti-cancer delivery and biomedical applications. To minimize the adverse events in conventional chemotherapy, stimuli-responsive drug delivery systems have been developed. Though there are exogenous and endogenous stimuli applied for the controlled drug release system into the tumor-specific release. Still, there are many challenges ahead to overcome in the stimuli-responsive drug delivery system. Therefore, stimuli-responsive research is a promising strategy for cancer treatment in chemotherapy. Hence this responsive system is under ongoing research to overcome the major challenges

such as lack of multistimuli systems, immature tumor-targeting effects, biodegradation, and toxicity issues, developing combinational therapy for cancer treatment.

The future challenge is to evolve drug delivery systems acting to biomarkers with small concentration ranges and fabricate drug delivery systems with promptly activating factors. And also integrating multiple functions to drug delivery systems for occurring at the same time such as detection, diagnosis, and therapy of a disease with a nanoparticle. These stimuli-responsive systems - nanomedicine has paid great attention in the scientific community, however toward the academic lab research. The clinical translation of these systems are likely challenging, yet certainly not impossible.

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