



A Review on Stimuli-Responsive Polymers and Recent Strategies for Treating Cancer Based on Stimuli Responsive Nanocarriers

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Abstract

This review describes some commercially accessible stimuli-responsive polymers of synthetic and natural origin, and their applications in drug delivery with the help of nanocarriers and treating cancer like dosages. The polymers of natural origin such as gelatin, albumin, cellulose, and chitosan are found to exhibit both pH-responsive and thermo-responsive properties and these features of the biopolymers impart sensitivity to act differently under different pH and temperatures conditions. Stimuli-responsive biomaterials that include logic gates maintain excellent potential for detecting and responding to pathological markers as phase of medical treatments that they are not perfecting. Some virtually essential thermo-responsive polymers such as poly (N-isopropyl acrylamide) (pNIPAAm) and Pluronic F127 (PF127) of synthetic origin has been mentioned in the review. In recent years, a lot of progress has been impelled in stimuli-responsive nanocarriers, that might response to the pathological and intrinsic physicochemical factors in diseased regions to extend the specificity. Currently, various nanocarriers are designed with physicochemical changes in responding to external stimuli, like ultrasound, thermal, light, and magnetic field, as well as internal stimuli, including hydrogen ion concentration. This review has summarized the general strategies of developing stimuli-responsive nanocarriers and recent advances, presented their applications in drug delivery, treatment and tumor diagnosis with help of stimuli-responsive polymers. Owing to precise stimuli response, stimuli-responsive drug delivery systems will management drug release, thus on improve the curative effects, reduce the harm of organs and normal tissues and reduce the side effects of traditional anti-cancer medicine.

Keywords

Stimuli-Responsive Polymer; Nanoparticles, Tumor Microenvironment, Cancer Therapy; Drug Targeting.

INTRODUCTION:

Variations in physiological parameters, such as pH, enzymes, metabolites, temperature and shear force, are important parameter for development, genesis and prognosis of human diseases (for example, heart disorders, cancer, infection and neurodegeneration),

presenting as promising diagnostic biomarkers and therapeutic targets. (1,2,3). The aim of functional polymers principally centers around stimuli-responsive polymers and these polymers have attracted great attention since these will show sol-gel transitions in response to external triggers like

hydrogen. Moreover, the physical changes in stimuli-responsive polymers are reversible, and they are capable of returning to their initial state when the trigger is removed. [4] In recent years, there has been a remarkable growth within the development of stimuli-responsive polymer-based drug delivery systems with controlled drug release (CDR) and sustained release (SR) properties [5,6]. The vital feature of stimuli-responsive polymers is the critical solution temperature (CST), which might be outlined as a critical temperature at which the polymeric solution shows a phase separation that moves from the isotropic state to the anisotropic state [4] Cancer remains one among the leading causes of human death worldwide. Although significant progress has been created in cancer biology, genomics, proteomics, and clinical oncology throughout the past many decades, antineoplastic treatments are inadequate and also the overall survival of many cancer patients stays low. (7) Chemotherapy is one of the foremost normally used cancer treatments usually within the clinic. Typically, chemotherapy drugs are toxicant chemicals and administrated systemically via either parenteral or oral routes. However, these medicines usually have drawbacks, as well as poor solubility and bioavailability, unfavorable pharmacokinetics, and nonselective bio distribution, which may complicate their clinical use and cause undesirable side effects. (8,9) The nanotechnology-based medicines, that is, nanomedicines, have shown excellence in drug delivery, diagnosis, and medical aid, significantly in cancer analysis. Nanoscale drug delivery systems (NDDSs) or nanocarriers play a crucial role in nanomedicine to overcome the same drawbacks of chemotherapy medicine. Compared to traditional drug delivery systems, nanocarriers have shown greater potential in rising drug bioavailability, prolonging drug circulation time, dominant drug release, and targeting neoplasm. additionally, to activity these basic functions, the newly emerging technology and nanomaterials could provide further functions or opportunities to nanomedicines/nanocarriers for numerous functions of cancer diagnosis and treatments.(10,11) Various nanocarriers are developed, of that the foremost normally studied is the organic nanocarriers, like liposomes, polymeric micelles (PMs), and dendrimers, and inorganic nanocarriers, like carbon nanotubes, silica nanoparticles, gold nanoparticles, magnetic nanoparticles, and quantum dots. (14,15) In general, nanocarriers within vary of 10 to 200 nm

are additional possible to be accumulated in solid tumors by passively extravasation from the hyper permeable neoplasm blood vasculature [14] and also the dynamic openings [13]. Nanocarriers offer a versatile platform for loading a wide range of payloads, as well as imaging agents, nucleic acids, anticancer medicine, photosensitizers, and antibodies, etc., to enhance the diagnostic and therapeutic outcomes [16,17]. By incorporating bio active compounds inside nanocarriers, it may avoid unwanted exposure to healthy organs and enzymatic degradation, maintain drug activities, additionally as alert the half-life in blood circulation, neoplasm accumulation, and biological performance. Until now, many varieties of nanocarriers are designed for drug delivery in oncology [18,19] presently, some nanocarriers have been approved for cancer treatment in clinic, for instance, the doxorubicin-incorporated PEGylated liposome (i.e., Doxil®) is approved for handling Kaposi's sarcoma and female internal reproductive organ cancer. Nanocarriers are presupposed to deliver bio active compounds (e.g., imaging or therapeutic agents) to tumor tissues or cancer cells for achieving improved diagnostic and therapeutic effectiveness. However, it meets several barriers throughout circulation or in tumors [20], such as super molecule corona, degradation, burst release or leaking of cargos, and recognition and clearance by the reticuloendothelial system (RES) etc.

The swelling-shrinking behavior of pH-responsive polymers in response to associate external pH condition makes them appropriate for drug delivery applications [21-23]. The cationic pH responsive polymers together with chitosan, poly (N, N-diethyl amino ethyl methacrylate) (PDEAEMA) and poly (N, N-dimethyl amino ethyl methacrylate) (PDMAEMA), swell in acidic hydrogen ion concentration and shrink in basic pH, wherever the basic pH-responsive polymers like albumin and poly acrylic acid (PAA) swell in basic pH and shrink in acidic pH [24,25]. The stimuli-responsive behavior of pH-responsive polymers has been given in Figure 1, and this schematic diagram of pH-responsive hydrogels provides a concept about the sensitivity of pH-responsive polymers toward completely different external pH conditions. As shown in Figure 2, depending on the charge groups of pH-responsive polymers, and their hydrogels are found to change their swollen state in response to external pH of the media.

Figure 1. The schematic representation of thermo-responsive behaviour (LCST) of the stimuli responsive polymer hydrogel drug delivery system.

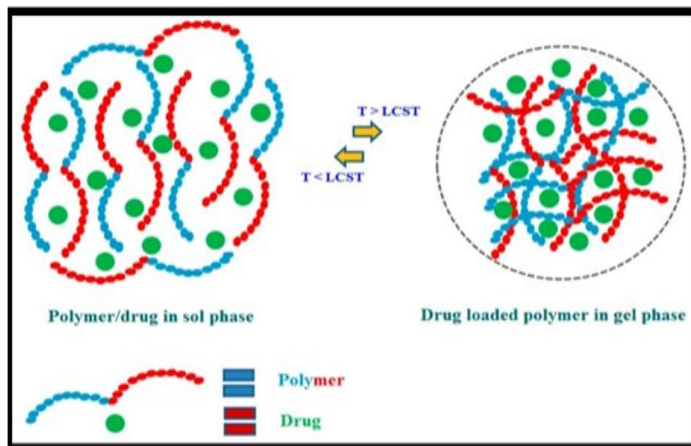
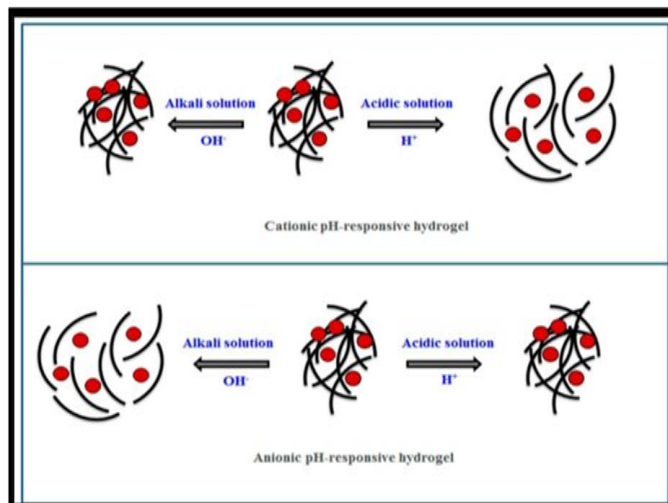


Figure 2. The schematic representation of pH-responsive behaviour of the stimuli-responsive polymer hydrogel drug delivery system.



Classification of Stimuli-Responsive Polymer and Their Application.

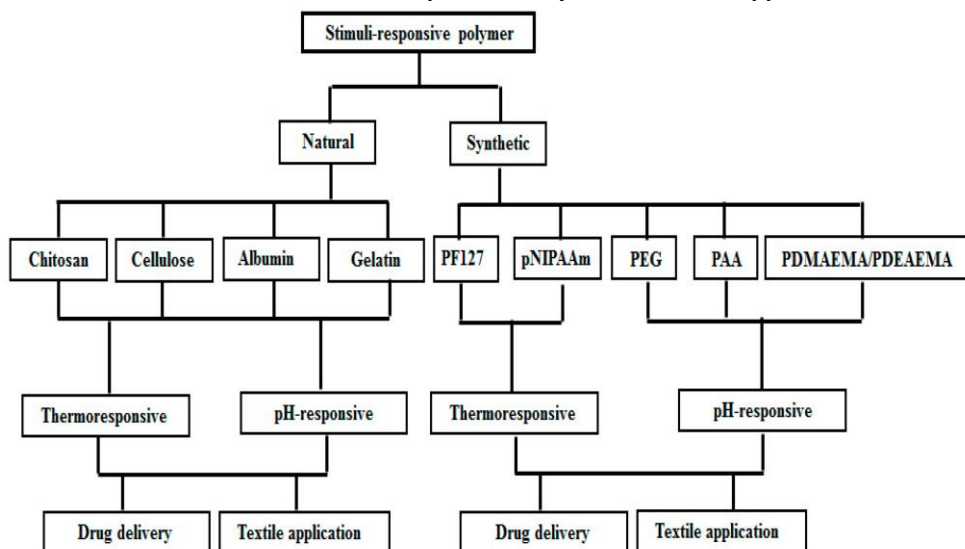


Table 1. Chemical nature, type of stimuli-responsiveness, and biomedical applications of stimuli-responsive polymers.

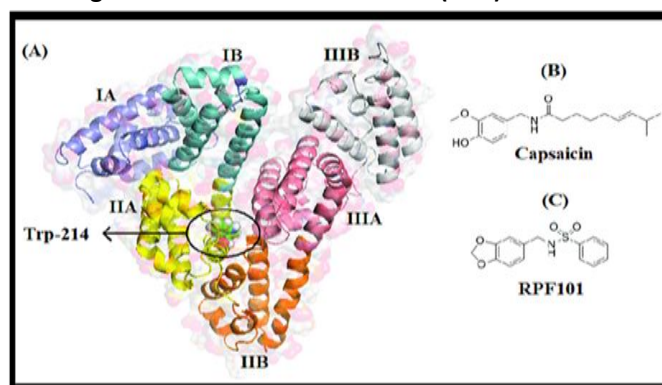
Polymer	Chemical Nature	Type of Stimuli-Responsiveness	Biomedical Applications
Chitosan	Natural (polysaccharide)	Thermo-responsive pH-responsive	Drug delivery, tissue engineering, textile application
Cellulose	Natural (polysaccharide)	Thermo-responsive pH-responsive	Drug delivery, tissue engineering, textile application
Albumin	Natural (polypeptide)	Thermo-responsive pH-responsive	Drug delivery, tissue engineering, textile application
Gelatin	Natural (polypeptide)	Thermo-responsive pH-responsive	Drug delivery, tissue engineering, textile application
PF127	Synthetic	Thermo-responsive, <i>in-situ</i> gel formation	Drug delivery, textile based transdermal therapy
pNIPAAm	Synthetic	Thermo-responsive, <i>in-situ</i> gel formation	Drug delivery, textile application
PEO	Synthetic	pH-responsive (neutral)	Drug delivery, textile application
PAA	Synthetic	pH-responsive (anionic)	Drug delivery, textile application
PDMAEMA/PDEAEMA	Synthetic	pH-responsive (cationic)	Drug delivery, textile application

2.1 Natural Stimuli-Responsive Polymers

2.1.1 Albumin

The anionic colloidal gel forming albumin can show pH-responsiveness by swelling in basic pH medium and shrinking in acidic pH [27,28]. Albumin, that could be a natural spherical protein usually found in plasma, is capable of showing a stimuli-responsive property in response to external stimuli like (hydrogen ion concentration) pH and temperature. [26]. The pH responsive colloidal gel developed by radical polymerization of methacrylate bovine albumin and N-isopropylacrylamide was used as a

drug delivery system for caffeine and theophylline. The pH-responsive colloidal gel developed from BSA with hydroxyethyl methacrylate and carboxylic acid monomers were used as a drug delivery system for anti-neoplastic drug flutamide [28]. BSA-based pH responsive colloidal gel fashioned by radical polymerization was applied as a drug delivery system for oral delivery [29]. The drug delivery system supported the pH responsive colloidal gel from alginate and albumin was used for delivery of prednisolone [30]

Figure 3. Human serum albumin (HSA) structure.


2.1.2 Chitosan

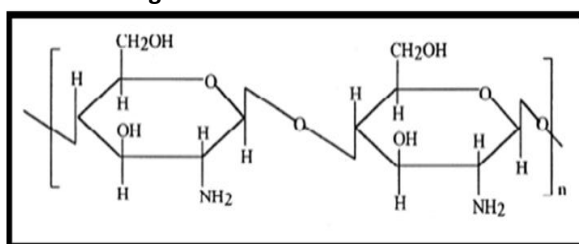
Chitosan due to its primary amine teams forms a cationic colloidal gel network in water, and it shows hydrogen ion concentration-responsive behavior by swelling in acidic pH scale ($\text{pH} < \text{pKa}$) and shrinking in basic pH ($\text{pH} \geq \text{pKa}$) [31]. Chitosan as a natural stimuli-responsive polymer is capable of showing

both pH scale responsive and thermo-responsive properties [32,33] The colloidal gel fashioned from chitosan, propanoic acid, (2-dimethylamino) ethyl methacrylate via in situ radical polymerization showed pH-responsiveness with increased mechanical stability and was used as a drug delivery system for controlled delivery of albumen and 5-

fluorouracil in cancer medical aid [36]. The thermo-responsive colloidal gel made from cross-linked chitosan and pNIPAAm via emulsion polymerization was applied as a drug delivery system for antibacterial levofloxacin [34]. The thermo-responsive colloidal gel created by attachment Pluronic onto chitosan was used as associate injectable cell delivery system for cartilage regeneration [35] The drug delivery systems made from chitosan show relevance to drug delivery applications particularly for cancer medical care and

skin treatment because of their, biodegradability, biocompatibility, and low toxicity [26]. The pH-responsive hydro gel network was found to release a lot of drugs in simulated gastric (fluid) than simulated intestinal fluid [37]. The pH-responsive colloidal gel made from poly(N-vinyl-2-pyrrolidone) and chitosan within the presence of 74 neutralized Polyacrylic acid (PAA) was used for healing. It showed completely different extent of swelling depending on the pH of external media [38].

Figure 4. structure of Chitosan

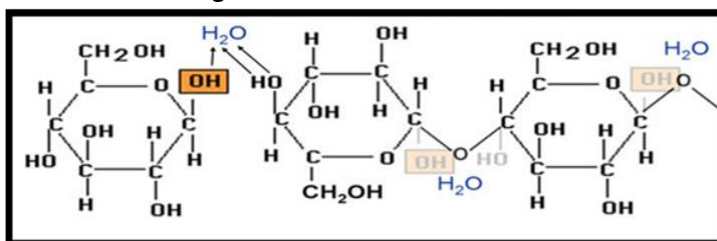


2.1.3 Cellulose

The stimuli-responsive hydrogels made of cellulose have been becoming widespread for the last few years because of their biocompatibility and non-toxicity. The pH-responsive colloidal gel of cellulose was developed by merely combination liquid solutions of cysteamine dihydrochloride and cellulose acetoacetate at room temperature and, moreover, this cellulose-based hydrogel showed dual cellulose, that is the most abundant natural polymer on earth, is formed from glucose monomers and capable of forming colloidal gel using their useful hydroxyl groups [40,41] The thermo-responsive colloidal gel made up of pNIPAAm and methyl cellulose showed gel formation close to the body temperature and also the mechanical strength of the

hydrogel was improved [43]. The thermo-responsive colloidal gel from methyl cellulose and PF127 was used as a drug delivery system for anti-cancer drug docetaxel and also the system showed additional sustained drug release than free docetaxel [44]. The thermo-responsive colloidal gel from methyl cellulose and kappa-carrageenan showed double thermal gel-sol-gel transition upon heating and was used for developing the drug delivery system [45]. Methyl cellulose, which is the useful material developed from cellulose, is water-soluble and might show a thermo-responsive property with the sol-gel transition within the temperature range of 60 to 80^o C [26,42]. responsiveness via reversible sol-gel transitions in response to each pH and redox triggers [46].

Figure 5. Structure of Cellulose.



2.1.4. Gelatin

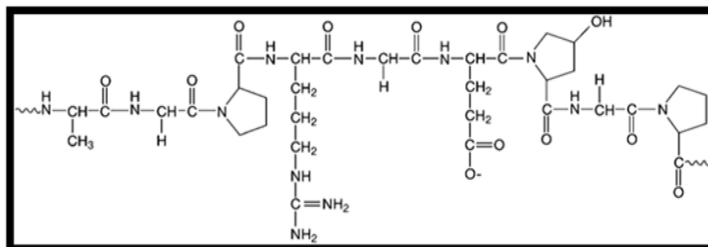
The nanogel made of gelatin, sodium methacrylate, and N, N-ethylene bis acryl amide showed a pH-responsive character, and it was developed by a solvent-free emulsion polymerization method with sun flower seed oil as a continuous phase [47] Gelatin, which is an animal origin natural protein, can show thermo-responsive properties and is

commercially available in different forms such as nanoparticles, fibers, and, hydrogels [48]. The tunable thermo-responsive gelatin hydrogel showed volume transition near the body temperature, and it was reported to be a promising drug delivery system [49]. The injectable thermo-responsive hydrogel made of chitosan and gelatin showed sol-gel transition near the body temperature and it showed

compatibility with human tissue [50]. The gelatin-based pH-responsive hydrogel was developed by grafting β -cyclodextrin to gelatin (Gel), which is

followed by cross-linking with hydrogel and the oxidized dextran was used as a drug delivery system for anti-cancer drug 5-fluorouracil [51]

Figure 6. Chemical Structure of Gelatine.



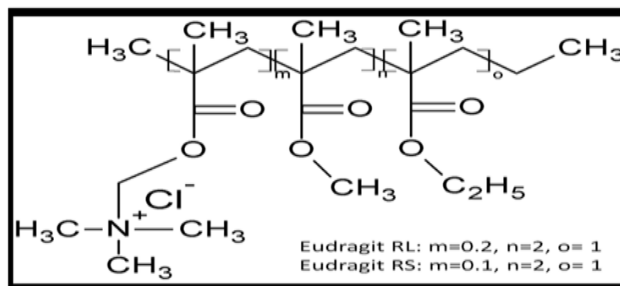
2.2. Synthetic Stimuli-Responsive Polymers.

2.2.1. Poly (N, N-dialkylamino ethyl methacrylate) and Eudragit

Eudragit prepared by the polymerization of acrylic and methacrylic acids or their esters was first introduced commercially in 1950 by Röhm GmbH & Co. KG—Germany. Eudragit RL and Eudragit RS are anionic co-polymers of acrylic and methacrylic acid esters having quaternary ammonium groups and used as anionic pH-responsive polymers for mainly oral delivery of the drug [52] poly(N, N-diethylamino ethyl methacrylate) (PDEAEMA) and Poly(N, N-dimethylaminoethyl methacrylate) (PDMAEMA), which are both cationic pH-responsive polymers and swell in acidic pH ($pH < pK_a$) due to the protonation

of their tertiary amine groups [53] The pH-responsive hydrogel made of block co-polymer of poly (dimethylsiloxane) and PDMAEMA was applied to deliver antineoplastic drug doxorubicin and the block co-polymer (poly(dimethylsiloxane)-b-PDMAEMA) was synthesized by atom transfer radical polymerization (ATRP) [54]. The pH-responsive hydrogel made of PDMAEMA and poly (vinyl alcohol) was used for drug delivery applications [55]. The pH-responsive nano-hydrogel was synthesized by co-polymerization of PDEAEMA with hetero-bifunctional PEG bearing a 4-vinylbenzyl group at one end and a carboxylic acid group at the other side end. The nano-hydrogel was used as a drug delivery system for anti-neoplastic drugs doxorubicin [56].

Figure: 7 Chemical structure of Eudragit® RS PO and Eudragit® RL PO.



2.2.2. Pluronic F127

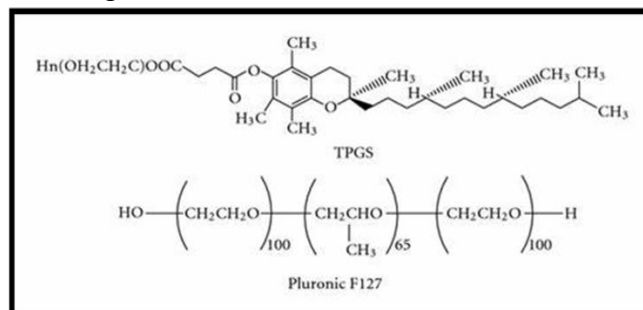
PF127 is approved by the 'U.S. Food and Drug Administration' (FDA) to be employed in biomedical areas particularly for drug delivery tissue engineering, and also the administration of the PF127-based drug delivery system, which may be intranasal, subcutaneous, oral, ocular, vaginal, and rectal. [45] (PF127) is a nonionic triblock polymer of poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) and, being a thermo-responsive synthetic polymer, PF127 form type the hydro gel close to the body temperature [46]. The thermo-responsive colloidal gel manufactured from PF127 and hyaluronic acid showed gel formation at a

body temperature of 37°C and was used as a drug delivery system for an individual's somatotrophic hormone [47]. The thermo-responsive colloidal gel manufactured from hyaluronic acid grafted PF127 showed in situ gel formation and was applied for delivery of model anti-neoplastic medication cisplatin and carboplatin [48]. The drug delivery system made from thermo-responsive colloidal gel of glycol chitosan and PF127 by photo-polymerization was applied for delivery of doxorubicin anti-cancer medication [49]. The thermo-responsive colloidal gel made of chitosan and PF-127 was applied as a drug delivery system for model anti-cancer drug 5-fluorouracil [50] The thermo-responsive colloidal gel

of pNIPAAm and spiropyran formed by a facile and versatile surface-initiated controlled polymerization technique (SI-ARGET-ATRP) showed the potential of

dimensional changes on cotton fabric upon temperature stimulation or a irradiation with visible light [51]

Figure:8 chemical structure of Pluronic f127.



2.2.3. Polyacrylic Acid

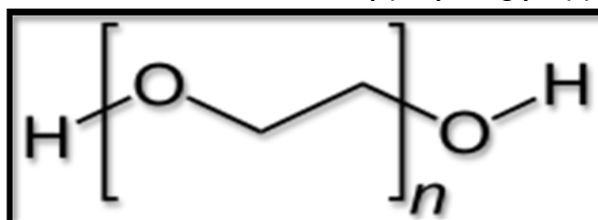
The pH-responsive PAA-based colloidal gel cross-linked by poly (l-glutamic acid)-g-(2-hydroxyl meth acrylamide) showed pH-dependent swelling-shrinking behaviors and was used for the delivery of the model macro molecule BSA [52]. Polyacrylic acid (PAA), that is associate anionic synthetic compound, will, can pH-responsive colloidal gel, swells/dissolves at hydrogen ion concentration [pH] on top of its pKa, and remains collapsed at acidic pH (pH < pKa) [53]. This hydrogen ion concentration responsive behavior of PAA attributes to oral delivery of the drug by the PAA-based drug delivery system [54]. The hydrogen ion concentration and thermo-responsive micelles developed from the block polymer of pNIPAAm (pNIPAAm-b-PAA) and PAA was used as a drug delivery system for anti-cancer drug doxorubicin [55]. The pH-triggered oral drug delivery system was developed by capping mesoporous silica SBA-15 with pH-responsive polymer PAA via a facile graft-onto strategy, and it was wont to deliver antineoplastic drug doxorubicin for the treatment of carcinoma [67]. The pH-responsive biodegradable hydrogels made up of four forms of pH-sensitive poly (l-glutamic acid) and PAA derivatives as a cross-linker

were applied for oral delivery of hypoglycemic agent [insulin] [68].

2.2.4. Poly (ethylene glycol) (PEG)

The drug delivery system manufactured from PEG and cholesterol-modified poly (monomethyl itaconate) showed a pH-responsive property and was used for controlled and targeted unharness of the model drug piroxicam, that was employed in tumor-targeting therapy [69]. Poly (ethylene glycol) (PEG) could be a water-soluble synthetic polymer with no-toxicity and excellent biocompatibility, and shows a pH-responsive property in response to an external pH modification [70]. The pH-responsive colloidal gel manufactured from the gel, β -polyaspartylhydrazide and PEG by-product was applied as a drug delivery system for anti-cancer drug doxorubicin [71]. The pH-responsive hydrogel from PEG and poly (itaconic acid) was developed using UV free radical polymerization with tetra ethylene glycol as the cross-linking agent and Irgacure 2959 because the initiator, and it was used as a drug delivery system for oral delivery of the drug [72] pH-responsive nanoparticles manufactured from PEG-poly(l-histidine)-poly(l-lactide) were used as drug carriers for antineoplastic drug doxorubicin [73].

Figure: 9. Chemical Structure of Poly (ethylene glycol) (PEG).



3. Classification of Stimuli-Responsive Nano Delivery Systems OR Nanocarriers

Ideal drug delivery systems (DDS) are expected to satisfy the requirements of excellent

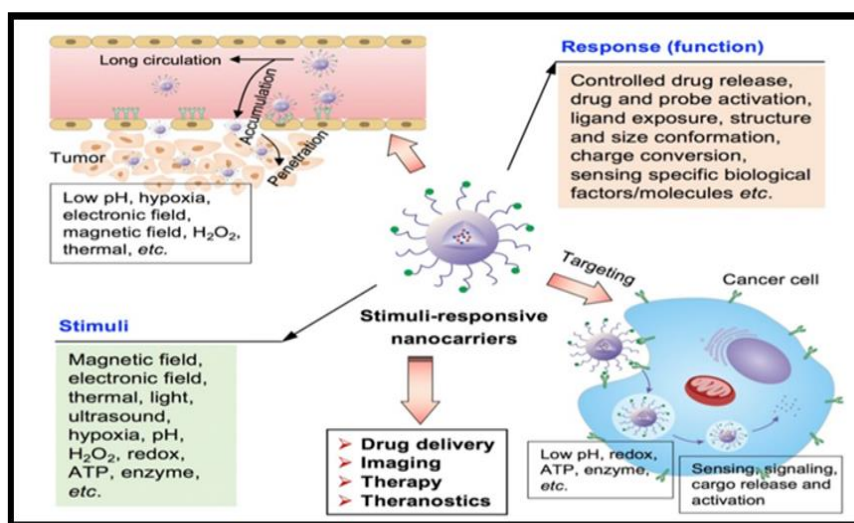
biocompatibility, high drug loading and controlled release capability [74,75]. Nano-technology can management the biological changes below the 100 nm scale, and provide assessments for the

monitoring, diagnosis, and treatment of diseases at the cellular level [76,77]. Since the concept of stimuli-responsive nano delivery system was first planned within the 1970s, there has been a lot of related researches and applications [78-82]. The concept of immediate-responsive drug delivery the same as a switch (open/close) is designed to simulate the response of living organs by constructing stimuli-responsive carrier system to acknowledge the dynamic method of body's changes of a microenvironment and organic chemistry reactions, therefore, on achieve sustained and controlled release of drugs. In different words, based on the particular intracellular and extracellular physiochemical stimulations, stimuli-responsive nanocarriers will modify their structures by suggests that of hydrolysis, protonation, isomerization and polymerization, getting to

accelerate the discharge of active components in special physiological environments [83].

Endogenous stimuli are mainly derived from the pathological changes and physiological, such as enzyme concentration, pH and redox potential gradient [84-88]. Exogenous physical stimuli mainly include, ultrasound, light, magnetic field, and temperature. [89,90]. The compound stimuli-responsive delivery system consists of two or more than two stimuli-responsive factors [91-94]. Additionally, perfect drug delivery systems can control drug release by responding to stimuli signals that exist in the tumor microenvironment and extracorporeal physical stimuli [83,95]. According to the sources, physiological properties, structures and biochemical properties of stimuli signals, the irritation-responsive nano delivery systems can be classified into exogenous, endogenous and multi-stimuli responsive delivery systems [96-98].

Figure :10. The stimuli-responsive nanocarriers for drug delivery to tumours towards precision imaging, effective therapy and theragnostic. The nanocarriers could penetrate and accumulate tumors, and target cancer cells for achieving different applications and functions by responding to the internal and external stimuli.



3.1 Exogenous Stimuli-Responsive Drug Delivery Systems.

Exogenous physical stimuli mainly include light, temperature, magnetic field and ultrasound. When these stimuli signals act on exogenous stimuli-responsive nanocarriers, they will trigger drug release rapidly [99-103]. With the external stimuli, it facilitates enhancing the accumulation of nanocarriers in desired regions with outer forces (e.g., magnetic field), controlled release, intracellular drug delivery, as well as activated imaging and therapy. There are several advantages of applying external-stimuli for drug delivery to tumors: (1) it could precisely control the location and intensity of

given external stimuli (e.g., magnetic field, laser irradiation); (2) the external stimuli could be added or removed depending on the treatment requirement; (3) multiple external stimuli could be overlaid for achieving multifunction in cancer theragnostic; (4) the possibility to provide multi-times or continuous (e.g., several hours or days) stimuli for drug delivery and therapy. However, the externally-directed triggers would be impractical for treating and accessing the metastatic lesions, when their location is uncertain.

3.1.1 Temperature-Responsive Delivery Systems

The temperature-sensitive nanocarriers have also been widely applied for drug delivery and dealing

with cancer. Temperature-responsive carriers generally involve liposomes, nanoparticles and polymer micelles, etc. When the ambient temperature is higher than the critical solution temperature (CST) of polymer, the polymer chain dehydrates and the hydrophilic hydrophobic equilibrium breaks, resulting in the changes of the carrier's structure and the release of the contents packed in the system [104]. The thermal-sensitive nanocarriers is generated with materials that could undergo physicochemical properties variation associating with temperature change [105,106]. In 2017, Liu et al. (2017) loaded the salmon calcitonin and oxidized alginate complex (sCT-OCA) on the temperature-sensitive three-block polymer, poly (lactic acid-glycolic acid)-polyethylene glycol-poly (lactic acid-glycolic acid) (PLGA-PEGPLGA), and the sol-gel phase transformation occurred at 37 °C in vivo (Figure 2). With the degradation of the hydrogel and the decomposition of the complex sCT-OCA, the calcitonin was sustained release slowly from the in-situ gel system [107]. The temperature sensitive materials are mainly including poly (N isopropylacrylamide) (PNIPAM) [108,109], poly (N-inyisobutyramide) (PAMAM) [110], poly(2-oxazoline) (POxs) [111], and poly [2-(2-methoxyethoxy) ethyl methacrylate] [PMEOMA], etc. Besides, another strategy for achieving thermal-sensitivity is to incorporate thermal-unstable materials inside nanocarriers. For instance, the NH₄HCO₃ incorporated liposome could generate CO₂ after giving local hyperemia (42°C) to make liposome swollen and collapse [112], leading to drug release for efficient intracellular drug delivery.

3.1.2. Light-Responsive OR Ultrasound-Responsive Nanocarriers Delivery Systems.

Under specific wavelength of exogenous light (such as ultraviolet, visible or near infrared, etc.), light-responsive drug delivery systems can change the stability or break down the structure of responsive nanomaterials to appreciate the precise release of drugs [113-117] Ultrasound could be a type of high-frequency sound waves, which could affect nanocarriers for controlled drug release at diseased sites (i.e., tumors). The intensity of ultrasound may be adjusted for various applications. At a low ultrasound frequency (< 20kHz), it might be applied for imaging, while it could be applied for disrupting nanocarriers to release cargos or enhancing the permeability of neoplastic cell membrane at a high

ultrasound frequencies (> 20 kHz) [118]. The ultrasound-responsive nanocarriers may be applied for tumor ultrasound imaging, which is safe, low cost and providing images with high spatial resolution and widely applied in clinic. The gas and contrast agent (e.g., perfluoro pentane) incorporated nanocarriers [119].

The technology of near infrared (NIR) laser has finer penetration, and minor damage to tissues. Meanwhile, plasma materials with NIR absorption characteristic can convert light energy into energy, to make up a stimuli-responsive delivery system [120]. as an example, when the gold nanoparticle was loaded with doxorubicin (DOX), the discharge rate of drugs increased under the 808 nm illumination [121]. Compared with the free drug, light-responsive delivery systems have a decent ant neoplasm activity. Until now, several microbubbles are commercialized, like Albunex, Optison, Definity, Imagent, Levovist and Sonazoid etc. [122]. However, the massive size (1-10 μm), short half-life, and low stability of microbubbles limit their access to vascular compartments in tumor tissues and deep penetration. Several size switchable microbubbles (i.e., from microbubbles to nanobubbles) [123], or nanocarriers are engineered for ultrasound imaging [124], ultrasound triggered drug delivery [125-127], and ultrasound triggered cancer theranostics (Table 2), including nanobubbles [128], calcium carbonate (CaCO₃) nanoparticles [129], liposome [130], nanodroplets [131], vesicles [132] and nanoparticles [133], etc. Generally, the ultrasound-sensitive nanocarriers are incorporating gas or contrast agents [134], including air, N₂ and perfluorocarbons, etc., or generating gas within the biological environment [135-137], like CaCO₃ nanoparticles [138]. as an example, the phase changeable, polymeric nanodroplets may be generated for tumor imaging and doxorubicin release due the collapse of microbubbles when responding to the low-intensity focused ultrasound [131]. Moreover, the ultrasound-responsive property may be applied for intracellular delivery of bioactive compounds and enhancing the tumor accumulation (e.g., siRNA, DNA). Because ultrasound could increase gap in tumor vasculature wall (i.e., disrupting of vascular integrity) to facilitate extravasation of drug delivery systems to malignant tissues, in addition as enhance cellular uptake by cancer cells [140-142].

Table:2. Representative ultrasound-responsive nanocarriers.

Nanocarriers	Ultrasound-sensitive strategy/materials	Cargos	Applications
Converting microbubbles	Converting porphyrin microbubbles to nanoparticles by ultrasound	Porphyrin and perfluorocarbon gas	Ultrasound imaging
CaCO ₃ nanoparticles	The CaCO ₃ could generate CO ₂ in the acidic tumor microenvironment	Doxorubicin	Tumor ultrasound imaging, drug release and tumor therapy
Nanobubbles	CO ₂ gas-generating polymeric nanoparticles	-	Ultrasound Imaging
Liposome	Perfluorocarbon for ultrasound-sensitive	Doxorubicin, gold nanospheres	Cancer imaging, photothermal-chemotherapy
Liposome	Containing NH ₄ HCO ₃ to generate gas in tumors	Docetaxel and NH ₄ HCO ₃	Dual ligand targeted triplex therapy, and ultrasound imaging
Nanorattles	Perfluoropentane for ultrasound-sensitive	Perfluoropentane	Ultrasound and photoacoustic imaging, photothermal therapy
Nanodroplets	Perfluorocarbon	ZnF ₂ Pc, IR dye, perfluorocarbon	Tumor multimodal imaging and therapy
Gas vesicles	Genetically encoded gas nanostructures from microorganisms	Gas	Ultrasound and multimodal imaging, molecular biosensors

3.1.3. Magnetic Field-Responsive Delivery Systems

Magnetic field responsive nanocarriers are usually liposomes, micelles, super-molecule aggregates formed by implanting the paramagnetic or superparamagnetic materials into polymer scaffolds [143]. The magnetic-responsive nanocarriers have been engineered, as the magnetic nanoparticles has intrinsic tropism to magnetic field for tumor targeting, while it also could generate local hyperthermia under an alternating the magnetic field for cancer ablation and triggering drug release. Until now, several magnetic-responsive nanocarriers have been formulated (Table 4), including magnetic nanoparticles [144,145], liposomes [146], superparamagnetic iron-oxide nanoparticles (SPIONs) [147], polymeric micelles [148], albumin Nano capsules [149], magnetic nanocarriers [150,151] and magnetic nanogels [152], etc. Among inorganic, nanomedicines, magnetic nanoparticles (MNPs) have been investigated most widely for treatment and diagnosis of cancer. Magnetic nanoparticles have involved considerable interest due to their outstanding magnetic properties, biocompatibility, and biodegradability [153]. Generally, nanocarriers are incorporating magnetic materials for achieving magnetic-sensitivity, which are mainly including iron oxide nanoparticles (e.g. Fe₃O₄ nanoparticles) [154], iron oxide hybrid nanoparticles (e.g., graphene/Au/Fe₃O₄ hybrids) [155]. The incorporated magnetic materials also could be applied for tumor imaging by magnetic resonance imaging (MRI) [147,156,157]. Besides magnetic materials, the contrast agents [158], anticancer drugs [156], plasmids [159], antibodies [153] and photosensitizer [146], could also be incorporated inside the magnetic-sensitive nanocarriers for achieving multiple functions or multimodal therapeutic effects. Moreover, the nanocarriers could be engineered for passive tumor

targeting through the EPR effect [161], as well as be installed with targeting moieties (e.g., folic acid) for active targeting cancer cells [162]

Guisasola et al. (2018) prepared an iron oxide magnetic nanoparticle embedded in a mesoporous silica matrix, which can provoke the release of anti-tumor drug DOX trapped inside the silica pores. In vivo and in vitro experiments showed that significant tumor growth inhibition was achieved in 48 hours after treatment [163]. Moreover, magnetic materials could also be applied into nuclear magnetic resonance imaging to realize the integrated diagnosis and treatment of diseases [164-169]. The interaction between magnetic flux facilitates and magnetic nanocarriers the magnetic-guided accumulation of nanocarriers in tumors, while a typical approach is to locate a permanent magnetic flux in malignant tissues. For example, much higher level of SPIONs and doxorubicin-loaded nanocarriers in tumors are achieved with external magnetic field-guided tumor targeting, resulting in effective tumor ablation [151]. Besides primary tumors, the magnetic responsive nanocarriers have also demonstrated high potential for treating metastatic tumors (e.g., lung cancer) [170]. Further, the magnetic-sensitive Nano-carriers could also be applied for tumor theranostics [171], because it could probe tumors by MRI or other imaging modalities, and non-invasively and remotely eradicate tumors with the generated hyperthermia within the alternating flux of magnet [172]. as an example, the PEGylated MoS₂/Fe₃O₄ nanocomposites (MSIOs) made through a two-step hydrothermal method, have demonstrated high potential for tumor diagnosis by T₂-weighted photoacoustic tomography imaging and MR imaging, and magnetic-targeted effective photo-thermal ablation of tumors [173]. while, it further allowed both T₂ and T₁ weighted MR imaging of tumors by

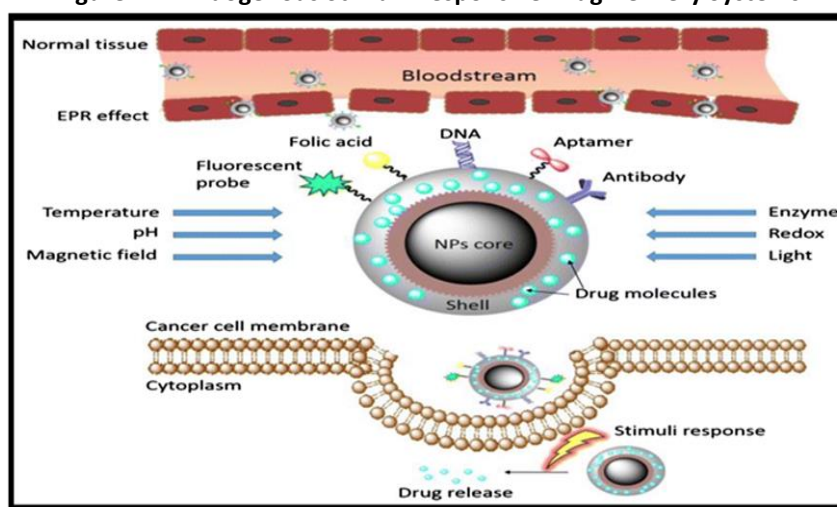
doping multifunctional nanoflowers into the core of Fe₃O₄@MoS₂ nanocomposite [174].

3.2. Endogenous Stimuli-Responsive Drug Delivery Systems.

The stimuli-responsive nanocarriers are sensitive to some specific endogenous stimuli, like the pH of various tissues and organs [175-177], the particular expression of enzymes within the tissues of normal physiological condition and disease [178,179], and therefore, the changes of cells' redox potential [180-184]. At the cellular level, endogenous stimuli can trigger targeted drugs to release into endosomes or promote the nanocarriers to escape from lysosomes to cytoplasm. At the extent of tissue, endogenous

stimuli-responsive nanocarriers can make use of the changes of cancer cells micro environment or other pathological conditions (hypoxia, infection, and inflammation, etc.) to hold out targeted drugs release [185]. The internal triggers are intrinsically existed in cancer microenvironment or inside tumor cells. However, they typically show poor specificity and heterogenous distribution in tumors, which can affect the efficacy of internal stimuli-sensitive nanocarriers. During this section, recent advances in nanocarriers responding to internal stimuli, mainly including hypoxia, pH, redox and enzymes, for tumor theragnostic are focused.

Figure: 11. Endogenous Stimuli-Responsive Drug Delivery Systems.



3.2.1. pH-Responsive Delivery Systems

The pH-responsive nanocarriers are extensively exploited, because of the character of low pH inside the organelles (e.g., lysosomes and endosomes) of cancer cells and in tumor cells microenvironment. In general, the pH in cytoplasm, blood and normal tissue region is nearly around pH 7.0 to 7.4, while it exhibits approximately pH 6 to 4 in endosomal/lysosomal organelles, and pH 6.5 to 6.8 in tumor cells microenvironment [186]. Thus, the pH-responsive in tumor cells microenvironment can be applied for controlled drug release or prodrug activation, while keep the "stealth-effect" of nanocarriers in normal regions (e.g., within blood circulation) without leaking of cargos. This would decrease the danger of exposure normal organs (e.g., heart) to the toxic cargos (e.g., doxorubicin), and specifically deliver them to tumors for achieving high therapeutic performance. Until now, several forms of pH-sensitive nanocarriers, including CaCO₃ nanoparticles [187,188], calcium phosphate (CaP) nanocarriers [189-191], inorganic nanoparticles or crystals [192,193], polymer-drug conjugates [195],

nanogels [196-198], polymeric micelles [199-201], liposomes [202], and dendrimers [204], etc., are exploited for imaging, intracellular drug delivery, charge conversion, and controlled drug release in tumor- microenvironment [203,205]. According to the changes of pH gradient inside and outside the cells, the development of the delivery systems mainly includes the subsequent two categories: One is that the changes of conformation or dissolution behaviors of the polymer under different pH conditions [206-209]. The other is that the delivery systems may disintegrate due to the fracture of acid-sensitive groups within the nanocarriers, resulting in targeted delivery on specific sites [210-213]

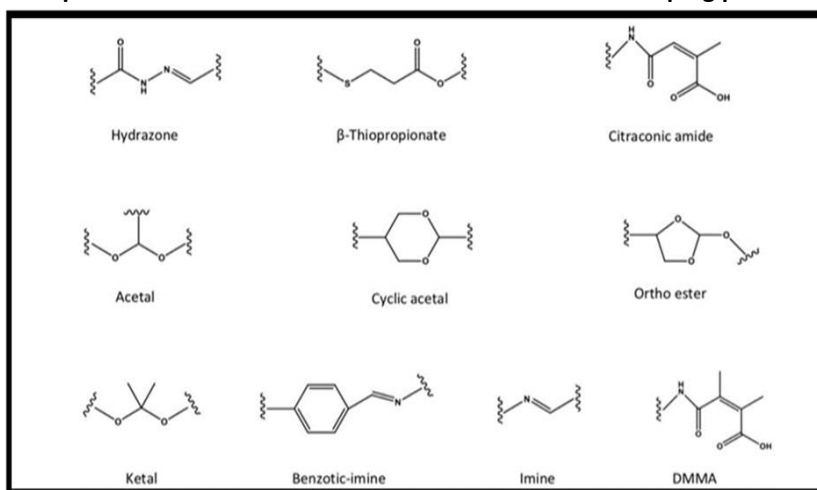
Meanwhile, several pH-sensitive polymers have been synthesized for fabricating nanocarriers with pH-responsibility [81], including poly(2-(pentamethylenediamine) ethyl methacrylate) (PC6A), poly(2-(hexamethyleneimino) ethyl methacrylate) (PC7A), poly(β -amino ester) (PAE), polysulfadimethoxine (PSD), poly(L-histidine) (PHis), poly(4-vinylbenzoic acid) (PVBA), 2,3-dimethylmaleic anhydride (DMMA), poly(N,N-diethylamino-2-

ethylmethacrylate) (PDEAEMA), poly(N'-(N-(2-aminoethyl)-2-aminoethyl) aspart amide) [PAsp (DET)], poly(2-diisopropylaminoethyl methacrylate) (PDPA), poly (N, N-dimethyl amino ethyl methacrylate) (PDMAEMA), poly [(2-N morpholino) ethyl methacrylate] (PMEMA), poly(4-vinylpyridine) (P4VP), poly (glutamic acid) (PGlu) [82], poly(L-

aspartic acid) (PAsp), poly (methacrylic acid) (PMAA), and poly(2-vinylpyridine) (P2VP) (Figure 12).

Meanwhile, certain pH-sensitive chemical bonds have also been applied for drug conjugation, confirmation/ size change and charge conversion, etc. (Figure 14), which facilitate pH-triggered drug release, and disassociation of nanocarriers inside cancer cells or in tumor microenvironment [220]

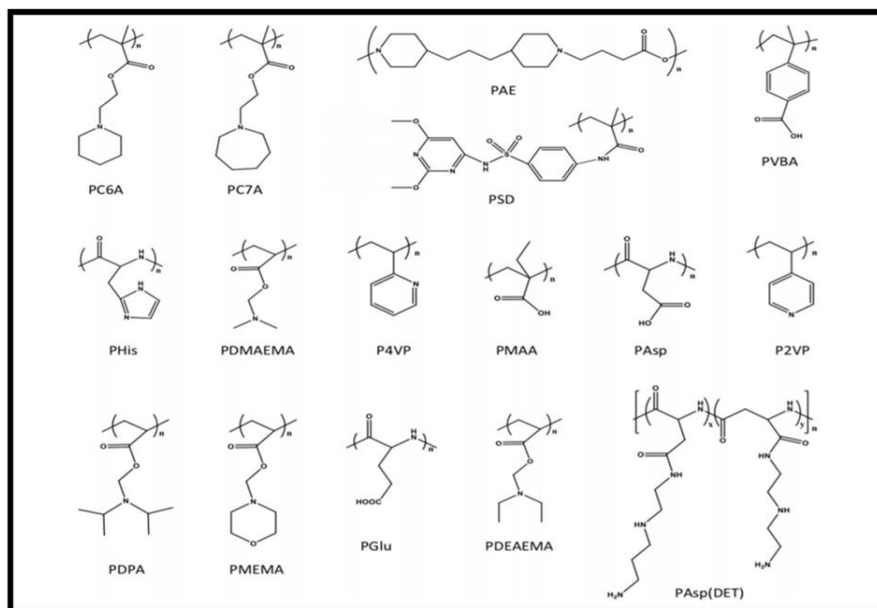
Figure 12. The pH-responsive chemical bonds have been utilized for developing pH-sensitive nanocarriers.



Lately, researchers have successfully developed nanoparticles containing pH sensitive precursor drugs, which might be used for the combined delivery of hydrophobic anti-cancer drugs [218]. as an example, the polyethylene glycol (PEG) nanoparticles loaded with curcumin (CUR) were modified by transferrin (Tf) to make a polymer (TfPEG-CUR NPs). Doxorubicin was then loaded on the polymer to create Tf PEGCUR/ DOX NPs, which was used to transport DOX and CUR at the identical time. The drug release from Tf-PEG-CUR/ DOX NPs was studied at 37°C under pH 7.4 and 5.0 in vitro. The results showed that DOX and CUR release was significantly accelerated under mildly acidic environments. for example, 79.2 and 57.6% of DOX was released from NPs in 24h at pH 5.0 and 7.4, respectively. it absolutely was observed that Tf-PEG-CUR/DOX NPs displayed beneficial physicochemical characteristics, including high encapsulation efficacy, narrow particle size distribution, uniform particle size, and sustained drug release [219]. Compared to cytoplasm with an almost neutral pH (pH 7.2), the pH in endosomal/ lysosomal organelles was around pH 6 to 4. Generally, nanocarriers enter into tumor cells through the pathway of endocytosis, which needs endosome/ lysosome escape to avoid further

degradation in late lysosomes with low pH. Currently, several intercellular pH-triggered nanocarriers are engineered for liberating cargos inside cancer cells [220]. The pH-triggered charge conversion nanocarriers have also been engineered for intracellular drug delivery, where the neutral or negative charged nanocarriers could communicate be charged by responding to low pH in endosomes/ lysosomes for disrupting endosomes/ lysosomes, because of the protonation of the cationic materials [198,222]. The pH-triggered charge conversion can be obtained with certain chemical groups, like citraconic anhydride, 2,3-dimethylmaleic anhydride (DA), cis-aconitic anhydride, carboxy dimethyl maleic anhydride (CDM) and cis-4-cyclohexene-1,2 di carboxinic anhydride, etc. The charge conversion strategy facilitates intracellular delivery of antibodies [223] siRNA [225,226], and DNA [227], proteins [222,224] as well as enhancing the tumor accumulation of nanocarriers [228], etc. In recent study, the pDNA loaded nanocarriers (HA-NPs) were innovated by using PAsp (DET) for formulating cationic PAsp (DET) /pDNA condensate, and endosome escape, as well as installing hyaluronic acid (HA) for active targeted gene therapy of cancer [229]

Figure 13. The intracellular or tumour microenvironment pH-responsive polymers have been applied for engineering pH-sensitive nanocarriers.



3.2.1 Hypoxia-Responsive Nanocarriers

The poorly vascularization inside solid tumors is likely to form hypoxia (oxygen level is low), which plays an important role in cancer (malignant tumor) progression, such as loco regional spread and distant metastasis [230]. The promoted malignant tumor phenotype by hypoxia has negative impact on prognosis and therapy and leads to resistance to standard therapy (e.g., chemotherapy, radiotherapy). Therefore, several strategies have been utilized for treating hypoxic tumors cells, mainly including increasing the oxygen (O₂) level and using hypoxia activatable prodrugs, etc. [231]. Several types of nanocarriers have been engineered/ designed for drug delivery to hypoxic tumors (Table 5) [232], including liposomes [233], albumin nanoparticles [234], silica nanoparticles [235], up conversion nanoparticles (UCNPs), layer-by-layer nanoparticles [236], nanovesicles [237], polymeric micelles [238], cell membrane coated metal organic framework (MOF) [239], solid-state sensors [240], polymeric probes [241], and polymer hybrid CaP nanoparticles [242], etc. Meanwhile, different cargos could be loaded inside the hypoxia-activation nanocarriers, anticancer drugs (e.g., doxorubicin), siRNA and photosensitizers (e.g., ICG), ranging from imaging agents (e.g., contrast agents), prodrugs (e.g., dihydrochloride), etc., demonstrating high performance in hypoxic tumor imaging and effective therapy by overcoming various types of drug resistance [243].

The tumor hypoxia could be targeted with hypoxia-responsive and some pH-sensitive nanocarriers,

since hypoxic tumor regions are generally associated low pH (hydrogen ion concentration) due to the glycolysis of glucose and production of H⁺ and lactate [244]. The major strategy is utilizing hypoxia-sensitive nanocarriers, which are generally constructed with hypoxia sensitive materials or derivatives, e.g., nitroimidazole [248-253], 2-nitroimidazole [238-240], metronidazole [243], nitrobenzene derivatives [238], azobenzene [251-253] and Iridium (III) complexes, etc. Hypoxia could trigger cargo release from the hypoxiasensitive nanocarriers, e.g., the incorporated antibody (i.e., Cetuximab) could be released from the silica gel nanoparticles in hypoxic tumors due to the cleavage of the hypoxiasensitive cross-linkers i.e., Azo monomer [254]. In another study, the nanocarriers were prepared with light-sensitive conjugated polymers and hypoxia-sensitive 2-nitroimidazole for generating ROS and local hypoxia after laser irradiation, to trigger doxorubicin release for enhanced synergistic anticancer efficacy [256]. The hypoxia-sensitive nanocarriers also facilitate molecular level imaging of tumors and metastasis. For example, the nanoscale probes with oxygen level-sensitive Iridium (III) complexes have demonstrated high potential for optical imaging of metastatic lesions and tumors [241]. Besides, some nanocarriers could delivery hypoxia-activatable prodrugs [e.g., banoxantrone (AQ4N) and tirapazamine (TPZ) etc.] to hypoxic tumors for enhanced therapy, while some photosensitizers could be co-loaded to generate hypoxia by laser irradiation for prodrug activation. For example, the

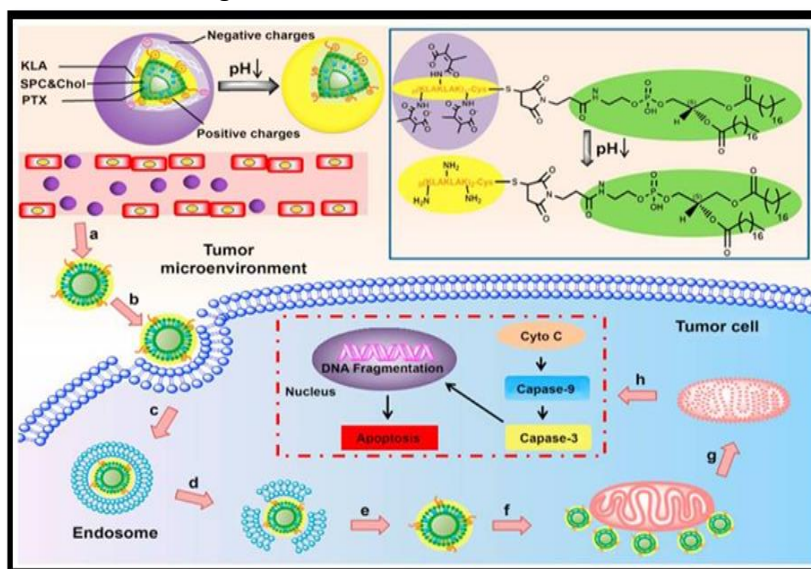
TPZ and ICG-incorporated liposomes with iRGD as targeting moieties could target hypoxic cancer cells, while the irradiation of ICG by NIR laser could produce extra hypoxia activate TPZ for enhanced therapy [255]

3.2.3. Enzyme-Responsive Delivery Systems.

Enzymes play a crucial role in biological reactions, while the unregulated expression of certain enzymes in neoplastic conditions can be triggers for enzyme-responsive drug delivery. Some enzyme responsive nanocarriers are engineered for achieving controlled release of cargos in cancer cells and tumors cells [257-258], prodrug activation, likewise as morphology change, mainly including magnetic nanoparticles [259], mesoporous silica nanoparticles [260], liposomes [288,289], dendrimers [264], and polymeric micelles [265]. Etc. As shown in Table 6, nanocarriers could response to many upregulated enzymes in tumor microenvironment and cancer cells [263], which are mainly including cathepsin B [266], transferases (e.g., creatine kinase) [263], oxidoreductases (e.g., peroxidases) [267], and hydrolases, like matrix metalloproteinases (MMPs) [268-270], human recombinant caspase 3 [271], proteinase K [272,273], trypsin [275,276], and intestinal protease [277] etc. So far, some nanomaterials have been used for constructing enzyme-responsive drug delivery systems, including polymers, phosphor esters and inorganic materials, etc. [278-282]. In the pathological conditions of inflammations or tumors, ester bonds or peptide structure of the stimuli-responsive nanocarriers may fracture due to various enzymes, so that the loaded drugs will release at targeted sites to exert therapeutic effects [283,284]. Relative researches showed that N-(2-hydroxypropyl) meth acrylamide

(HPMA) copolymer was water-soluble, non-charged, and non-immunogenic, which was developed for site-specific delivery of anti-cancer drugs [285,286]. The enzyme-sensitive nanocarriers can be utilized within the following aspects: (1) Activating prodrugs, probes and ligands by cutting the enzyme-sensitive bonds between the bioactive compounds and protective groups; (2) Direct cleaving the conjugation between nanocarriers and drugs; (3) Degradation or disassociation of nanocarriers through enzyme-triggered cleavage of polymer backbones, charge conversion of nanomaterials and disassembly of nanoparticles; (4) Enzyme-triggered physical disruption of nanocarriers; (5) Enzyme-triggered controlled release of cargos. For achieving enzyme-sensitive function, several factors should be considered for rational design nanocarriers: (1) the influence of physiological conditions and also the physicochemical properties to the enzyme-sensitivity; (2) the popularity and accessibility of enzymes to the sensitive groups/substrates in nanocarriers; (3) the edge of the substrates that responding to enzymes, which should make sure the enzyme-triggered reaction; the particular enzyme-triggered (triggered by enzyme) cargo release allows drug delivery to cancer cells and avoids cargo exposure during circulation, which could maintain the activity of bioactive compounds, while avoid causing sides effects to normal organs. For triggered by enzyme drug release, the cathepsin could cleave the hydrolyze peptide bonds in gemcitabine conjugated dendrimer carriers inside lysosomes to liberate gemcitabine and cationic dendrimers, resulting in lysosome escape and intracellular gemcitabine delivery [243].

Figure. 14. Tumour Microenvironment.



Duan et al. designed a biodegradable amphiphilic block HPMA copolymer-gemcitabine (GEM) conjugate-based nanoscale and stimuli-sensitive drug delivery vehicle. An enzyme-sensitive oligopeptide sequence glycyphenylalanylleucyl glycine (GFLG) was introduced to the most chain with hydrophobic and hydrophilic blocks via the reversible addition-fragmentation chain transfer (RAFT) polymerization. Then GEM was conjugated to the copolymer via the enzyme-sensitive peptide GFLG, and also the amphiphilic copolymer-GEM conjugate could self-assemble into compact nanoparticles. It absolutely was demonstrated that the conjugate-based nanoparticles could accumulate and be retained within tumors, leading to significant increased antitumor efficacy compared to free GEM [287].

3.2.4 Redox-responsive nanocarriers.

Vitamin C (ascorbic acid), glutathione (GSH) and Vitamin E (tocopherol) are the reductive substances that widely exist within the human body [288-291]. According to the characteristics of those substances, some redox responsive nanocarriers are developed and applied in ultrasound imaging and controlled release and targeted delivery of genes, proteins and anti-tumor drugs (anti-neoplastic drugs) [292-295]. The redox-responsive nanocarriers are widely applied for drug delivery due to the significantly different reduction potentials and capacities in tumors, e.g., the glutathione (GSH) level inside cancer cells (2-10 mM) is remarkable more than that in normal regions (2-10 μ M). Until now, several redox sensitive nanocarriers are engineered (Table 7), including nano capsules, mesoporous silica nanoparticles [296], polymer-drug conjugates [297], polymersomes [298], gold nanoparticles [299], polymeric micelles [300-302], nanogels [303], and hybrid nanoparticles [304], polymeric vesicles [305], etc. The disulfide bonds can be cleaved into sulfhydryl groups by GSH [306], while the diselenide bonds (Se-Se) also are sensitive to redox potential [307], but with lower bond energy than that of disulfide bonds [308]. Moreover, the H₂O₂-responsive nanocarriers have also been developed for tumor therapy [309,310], multidrug resistant tumors [313] and including for treating hypoxic tumors [311]. Zhao et al. (2015) developed a redox responsive Nano-capsule through surface modification technology, which could load two functional molecules, one was encoded in the capsule's shell by di-sulfide bonds, and the other was physically encapsulated in the core of the capsule. Trigger of the redox reaction could induce the cascading release of the loaded drug [312].

The redox-sensitive nanocarriers could trigger cargo release inside cancer cells [314], as some bioactive compounds were conjugated to nanomaterials through the disulfide bonds [297,315] and the drug-loaded cavities in some nanocarriers (e.g., mesoporous silica nanoparticles) were sealed by disulfide bonds [296]. The redox-sensitive strategy could also be applied to detach the surface shell [316], and cross-link the core to increase the stability of nanocarriers [317,318]. In another strategy, the cationic vesicles were formed by chelating of Fe³⁺ with amphiphilic pillararene, exhibiting GSH-triggered release of incorporated doxorubicin and siRNA from the collapse vesicles, as a result of GSH-induced reduction of Fe³⁺ to Fe²⁺ inside cancer cells [305]. Besides, the redox-responsive function could trigger the disassociation and degradation of nanocarriers inside cancer cells, as some nanocarriers were cross-linked by redox-sensitive bonds to increase the stability [317,139]. The disulfide bonds cross-linked polymer nano capsules could be disassociated by responding to GSH and dithiothreitol (DTT) [308]. Meanwhile, nanocarriers prepared by polymers with diselenide bonds (Se-Se) could also respond to environmental redox-potential (i.e., GSH, H₂O₂) for controlled disassociation of nanoparticles and release of cargos [305]. Moreover, the redox-responsive nanocarriers facilitate intracellular delivery of bioactive compounds into cancer cells to overcome the cellular barriers, such as siRNA [300] and sodium borocaptate (BSH) [297], etc. For one example, the BSH-polymer conjugates have been engineered by conjugating with disulfide bonds for tumor boron neutron capture therapy (BNCT), because of the poor cellular uptake of clinically approved 10B-compounds (e.g., BSH) and the limited effective distance almost within diameter of cancer cells [320]. The BSH-polymer conjugates have significantly promoted the intracellular delivery of BSH, slightly extended the half-life in blood circulation and highly enhanced the tumor accumulation for deep penetration in tumor tissues and significant tumor by BNCT.

4. Multimodal-responsive nanocarriers.

In addition, nanocarriers have additionally been designed with multiple stimuli-responsive functions, facilitating multistage drug delivery, similarly as achieving higher specificity and effectivity. As an example, nanocarriers responding to both intracellular pH (Hydrogen ion concentration) and GSH are developed for promoted intracellular drug delivery [321]. In another study, the developed Pt drug delivery nanocarriers may respond to intracellular GSH for disassociation, and response to

intracellular low pH for controlled drug release [322-328]. Indeed, the multiple stimuli-responsive nanocarriers hold high potential in achieving long circulation, deep penetration in neoplasm tissues, high neoplasm accumulation, internalization with cancer cells and endosome escape, etc. Thus, many multiple stimuli-responsive nanocarriers are designed for delivery cargos to tumors [329].

In one example, the multiple stimuli-responsive nanocarriers may be discharged into small nanoparticles by responding to the low pH in tumor microenvironment, then the platinum prodrugs within the small nanoparticles were activated by GSH for promoted treating and penetrating the poorly porous pancreatic tumors [330]. In another example, the nanocarriers created by made polymer–drug conjugates (PBEAGA-CPT) conjugates might response to both transpeptidase (GGT) and GSH are developed, that might convert to be positive charged nanomaterials by responding to GGT for incorporation with cancer cells and by responding to GSH within cancer cells to release CPT. The multimodal responsive polymer-drug conjugated nanocarriers have demonstrated high effectivity in extravasation, transcytosis, incorporation with cancer cells and deep neoplasm penetration, leading to effective suppression of subcutaneous HepG2 tumors. In general, it's sophisticate for developing multiple stimuli-responsive nanocarriers, and additionally difficult to keep up the multiple functions in biological systems. Thus, nanocarriers with single or dual stimuli responsive functions are additional targeted [331]

5. Clinical translation of the stimuli-responsive nanocarriers.

The advances in stimuli-responsive nanocarriers have led to clinical translation of several formulations. As shown in Table 8, there are six nanocarriers responding to magnetic, temperature, pH and secretory phospholipase A2 (sPLA2), are under clinical translation. Two magnetic-sensitive iron based nanocarriers, iron oxide magnetite, and doxorubicin-loaded iron and carbon (MTC-DOX), are under clinical trial for treating cancers. The iron oxide magnetite was conducted Phase I clinical trial to evaluate safety, retention and distribution after injection, which final score is for treating prostate cancer in men by thermal ablation. Three clinical trials have been applied for MTC-DOX, including Phase II and III studying the safety, tolerance and efficacy (survival time) on treating unresectable hepatocellular carcinoma (NCT00034333); Phase I and II evaluation of prohibiting hepatocellular carcinoma progression after injection with external magnet (NCT00054951); and Phase I and II studying

on liver metastasis (NCT00041808). Besides, the thermal-sensitive doxorubicin incorporated liposomes (ThermoDox) have been applied for the following three clinical studies: Phase I and II studying the maximum tolerated dose, safety, pharmacokinetics and hyperthermia effects in patients with recurrent regional breast cancer (NCT00826085); Phase I investigation of doxorubicin release from liposome by focused ultrasound in liver tumors (NCT02181075); and MRI and high intensity focused ultrasound (HIFU) combined study to determine doxorubicin release in pediatric refractory solid tumor (NCT02536183)

The clinical trial of Thermo Dox has also been designed to evaluate the safety and efficacy by combining with HIFU on several tumors (Phase II, NCT01640847), e.g., painful bone metastases, breast carcinoma, non-small cell lung cancer, small cell lung cancer and adenocarcinoma; as well as study the efficacy on treating hepatocellular carcinoma combined with standardized radiofrequency ablation (Phase III, NCT02112656). Moreover, the pH-responsive, epirubicin-loaded polymeric micelles (NC6300) have entered Phase I and II study (NCT03168061) for evaluating the dose, activity and tolerability in patients with soft tissue sarcoma. In previous preclinical clinical study, NC6300 could reduce the cardiotoxicity of epirubicin by conjugating to polymers through pH-sensitive bonds (i.e. Hydrazone) [327], and exhibited better therapeutic effect (10 mg/kg based on epirubicin) on treating hepatocellular carcinoma [328]. The preclinical evaluation has provided positive evidences for further clinical evaluation. In addition, the secretory phospholipase A2 (sPLA2)-sensitive, cisplatin incorporated liposomes (LiPLaCis) have entered Phase I and II to study the safety, tolerability and sensitivity on patients with advanced breast cancer and metastatic breast cancer (NCT01861496).

CONCLUSION:

Some stimuli-responsive polymers have made a major contribution within the area of drug delivery. The stimuli-responsive polymers of natural origin like chitosan, cellulose, albumin, and gelation are capable of showing both pH-responsive and thermo-responsive characters. Some synthetic thermo-responsive polymers like pNIPAAm and PF127 are capable of in situ gel formation, and their drug delivery applications have earned extremely high commercial importance. The pH-responsive polymers are useful for developing drug delivery system. during this review, some natural polymers (chitosan, cellulose, albumin, and gelatin) with both pH responsive and thermo-responsive characters are

discussed and their drug delivery applications are mentioned. Six categories of stimuli-responsive polymers are discussed. While the endogenous stimuli (redox, pH and enzyme)-responsive drug delivery systems depend upon the abnormal environments in diseased tissues to attain specificity, the exogenous stimuli (thermal, photo and ultrasound)-responsive drug delivery system requires a prior knowledge on the location of the target site to understand specificity. However, stimuli responsive drug delivery systems for clinical used are still desirable, and more works in evaluations, materials development, formulation and are needed. The nanocarriers bring novel strategy for delivery bioactive compounds to tumors. The stimuli-sensitive nanocarriers provide high specificity and multiple functions in drug delivery, including controlled release, alerted tumor accumulation, switch "ON-OFF" activities, as well as promoted diagnostic and therapeutic accuracy and efficacy. The stimuli-responsive systems could be widely applied for diagnosis, probing, sensing and therapy tumors and other diseases, such as cardiovascular diseases, etc.

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