

Review

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Review

Recent Advances in “pH and Redox Responsive Polymer-Nano-Composites for Cancer Therapy

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Highlights:

- This review explains the pH and redox-triggered polymer-nanocomposites to exploit the acidic pH and elevated reducing agents present in cancer cells.
- We discussed the dual-stimuli responsiveness of the polymer-nanocomposites is a key feature for integrating pH-sensitive and redox-sensitive biomaterials, respond to both pH and redox conditions, enhancing the precision and control of drug release, and ultimately improving therapeutic efficacy.
- Various fabrication methods, including nanoprecipitation, emulsion polymerization, and layer-by-layer assembly, are examined in detail.
- This review explores the prospects of pH and redox-responsive polymer-nanocomposites in cancer therapy.

Abstract: In recent years, cancer therapy has witnessed significant advancements, with a focus on personalized and targeted treatment strategies. One promising approach involves the use of stimuli-responsive biomaterials for site-specific drug release. Among these biomaterials, pH, and redox-triggered polymer-nano composites have gained immense attention due to their ability to respond to the specific tumor microenvironment, enhancing therapeutic efficacy while reducing off-target effects. Cancer cells often exhibit anomalous biochemical properties, attributed to lower cytosolic pH (acidic) and elevated redox potential through the epitomized upregulation of undesired genes. Such biological process substantially imbalance the level ions (protons) and biological thiols glutathione (GHS) in the cytoplasm as well as in the subcellular organelles. Superfluous accumulation of ions and redox imbalance is associated with proliferation, invasion, and growth of tumor. Because of high surface area, deep tissue penetration capability, higher hydrophilicity, hydrophobic interior for drug/gene efficient loading, biocompatibility and site-specific targeting efficiency, functionalized polymer nanocomposites are superior to conventional small molecular materials. Paradoxically conventional methods of drug delivery aided therapeutics accompanied with inherent drug/genes are encapsulated in biocompatible carrier or suitable transfecting agents generally suffered with low bioavailability, uncontrolled drug release, low cellular penetration, cellular internalization, toxicity, and poor drug loading efficiency. To overcome these issues, recently various multifunctional nanomaterials were developed, based on synergistic stimuli responsive aided drug release in a specified cellular or subcellular system. High therapeutic efficacy, of nanoparticles (NPs) mainly associated with surface functionalization through biocompatible polymeric materials, site-specific targeting units accompanied with stimuli responsive components. Followed by therapeutically important drug or genetic materials were loaded into NPs either in covalent or non-covalent approach. Intriguingly, combined pH and redox dual stimuli based functional materials specially based on polymeric nanocomposites for cancer therapeutics scarcely reported. This article provides the recent progress in pH and redox-responsive polymer-nano

composites for site-specific drug delivery in cancer therapy. It explores design principles, fabrication methods, mechanism of action, and prospects of these dual-stimuli responsive biomaterials.

Keywords: cancer; biological thiols; stimuli responsive; cancer therapeutics

1. Introduction

However, despite entire efforts invested in efficient developments underlying cancer mortality [2]. With regards mortality rate has been decreased in a past half decade owing to positive outcomes related from killing cancer cells in early cancer diagnosis and better understanding of improved diagnostics techniques, treatments, and advanced tumor biology [3,4]. While conventional cancer therapies have shown some effectiveness, they suffer from various limitations, including non-specific drug distribution, suboptimal pharmacokinetics, and cancer pathologies still often involve surgical intervention, intense radiation, and chemo/hormonal therapeutic drugs, which can destroy healthy cells and cause toxicity [5,6]. Therefore, developing a more effective chemotherapeutic method is crucial. Current therapeutic regimes are limited by cytotoxic drugs due to their lack of affinity for cancer cells and the hydrophobic nature of numerous anticancer drugs, which results in poor cell surface distribution [7,8]. In this context, cancer chemotherapy and detection technologies offer promising tools for reducing side effects, increasing biocompatibility, and improving therapeutic efficacy [9,10]. In prospective, smart nanomaterials, such as polymeric nano particles, liposomes, micelles, dendrimers, have demonstrated the ability to address these limitations by allowing the development of targeted drug delivery systems or active-intracellular delivery into cancerous cells [11]. This drug delivery system is supported by evidence of Nanoparticle-cell surface interactions, attributing lower cytosolic pH (acidic) and elevated redox potential to specific active targeting units [12,13].

Polymeric nanocarriers have garnered considerable attention due to their efficient delivery of bioactive compounds in biomedical applications [14]. These carriers can be further modified to incorporate stimuli-responsive signals, triggered by either endogenous factors like pH, redox potential, or glucose levels, or exogenous factors such as magnetism, light, or ultrasound, enabling precise control over drug release in specific conditions [15–20]. Various strategies have been developed to prepare these stimuli-responsive signals in polymeric nanomaterials, whether synthetic or bio-based polymers. This is especially important to overcome limitations associated with the release of hydrophobic drugs, including poor absorption, limited bioavailability, and formulation challenges [21,22]. Polymer nanoparticles play a significant role in therapeutic settings by safeguarding delicate drugs until they reach their intended delivery site. However, there are numerous physicochemical and biological obstacles that hinder the targeted delivery of cargos, drug solubilization, biocompatibility, and site-specific delivery to cells and tissues, making therapeutic delivery challenging [23,24]. To address these challenges, engineered or smart nanopolymer systems have been developed to possess physicochemical properties that respond to dual stimuli, such as pH/magnetic fields, pH/redox potential, pH/temperature, double pH changes, temperature/reduction, pH and diols, and temperature/enzymes [25,26]. These nanoparticles are designed to undergo chemical alterations in response to various biological stimuli. One of the key challenges in cancer treatment and diagnosis lies in engineered gene/drug delivery systems that can specifically target diseased cells without harming normal healthy tissues/cells, particularly within the tumor microenvironment (TME). Achieving this requires precise and controlled delivery of anticancer agents [27,28]. In contrast, polymer nanoparticles with stimuli-responsive properties offer various approaches, including emulsion polymerization, layer-by-layer assembly, and self-assembly [29], to address these challenges and enhance drug delivery in a targeted manner.

To explore controlled and targeted drug delivery stimuli-responsive biomaterials have emerged as a promising solution, offering the potential for personalized and site-specific cancer therapy. Stimuli-responsive biomaterials are meticulously designed to sense and respond to specific cues

within the tumor microenvironment, enabling the precise release of therapeutic agents at the site of action. This targeted drug delivery approach aims to maximize the therapeutic effects on cancer cells while minimizing damage to healthy tissues, ultimately reducing overall toxicity, and enhancing treatment efficacy. By harnessing the unique characteristics of cancer cells and their surrounding microenvironment. Among the diverse range of stimuli-responsive biomaterials, pH, and redox-responsive polymer-nanocomposites have garnered considerable attention for their dual-stimuli responsiveness and potential as future-generation biomaterials. Hence, these novel polymer-nanocomposites are engineered to respond to changes in pH and redox conditions, which are characteristic features of the tumor microenvironment [30]. The slightly acidic pH in tumor tissues, resulting from an increased metabolic rate and inefficient vascularization, serves as a distinctive trigger for pH responsiveness. Simultaneously, the elevated levels of reducing agents, such as glutathione (GSH), within cancer cells offer an opportunity for redox responsiveness. The design principles of pH and redox-responsive polymer-nanocomposites revolve around incorporating pH-sensitive and redox-sensitive elements into the polymer matrix. These elements enable the biomaterials to undergo controlled changes in structure and physicochemical properties in response to changes in pH and redox conditions, facilitating on-demand drug release. As a result, pH and redox-responsive polymer-nanocomposites offer the unique advantage of dual-stimuli responsiveness, further enhancing their precision and effectiveness in drug delivery for cancer therapy.

This review article aims to provide a comprehensive overview of the recent advancements in pH and redox-triggered polymer-nanocomposites for site-specific drug release in cancer therapy. The review will explore the design principles and fabrication methods of these biomaterials, elucidate the mechanisms of their action in response to pH and redox stimuli, and discuss in vitro and in vivo studies that showcase their potential in cancer treatment. Furthermore, the review will analyze the challenges and future perspectives of these innovative biomaterials, underscoring the importance of continued research and development in this exciting field. The emergence of pH and redox-responsive polymer-nanocomposites marks a significant stride towards personalized and targeted cancer therapy, offering hope for improved patient outcomes and a brighter future in cancer treatment.

1.1. Polymeric Nanomaterials

Polymer nanoparticles includes with organic and inorganic nanoparticles [31]. Widely used in theragnostic agents due to valuable significant efficacy and the plethora benefits in cancer treatments [32]. Several subtypes of polymeric NPs are developed for specific triggered drug delivery to tumor. The mainly NPs are classified as polymeric micelles, dendritic polymers, polymeric nanospheres, polymeric conjugate complex [33,34]. The structural and typological diversity of polymeric nanoparticles employed in different applications is shown in **Figure 1**. The general structural makeup of polymeric nanoparticles is shown graphically in this section (a) [31]. It provides a crucial comprehension of the fundamental architectural components that these nanoparticles have in common. This covers the polymer matrix as well as any other elements or alterations that support its functional and responsive qualities. The wide variety of polymeric nanoparticles used in various scientific and medical situations is discussed in more detail in section (b) [34]. The structural forms of these nanoparticles include brush polymers, micelles, dendrimers, nanofibers, nanoparticles, polymersomes, and nanogels. Because of their distinct qualities, each of these forms can be customized for a particular need. The advantageous of polymeric composite materials have properties as drug carriers imposed to low solubility drugs solubilization, provides potentials to tumor targets, controlled drug release and ability to reach specific active targeting in tumor diagnosis [35,36]. Considering polymeric micelles are spherically shaped, size ranges from 10 to 100 nm. The simplicity of polymeric micelles formation held via spontaneous self-assembly of hydrophobic and hydrophilic copolymer molecules [37]. Drug encapsulation nano carriers provides physical mixing formation rather than the chemical conjugation. Hydrophobic shell/micelles act as drug reservoirs while hydrophilic shells ensure solubilization of micelles in aqueous solution- [38,39].

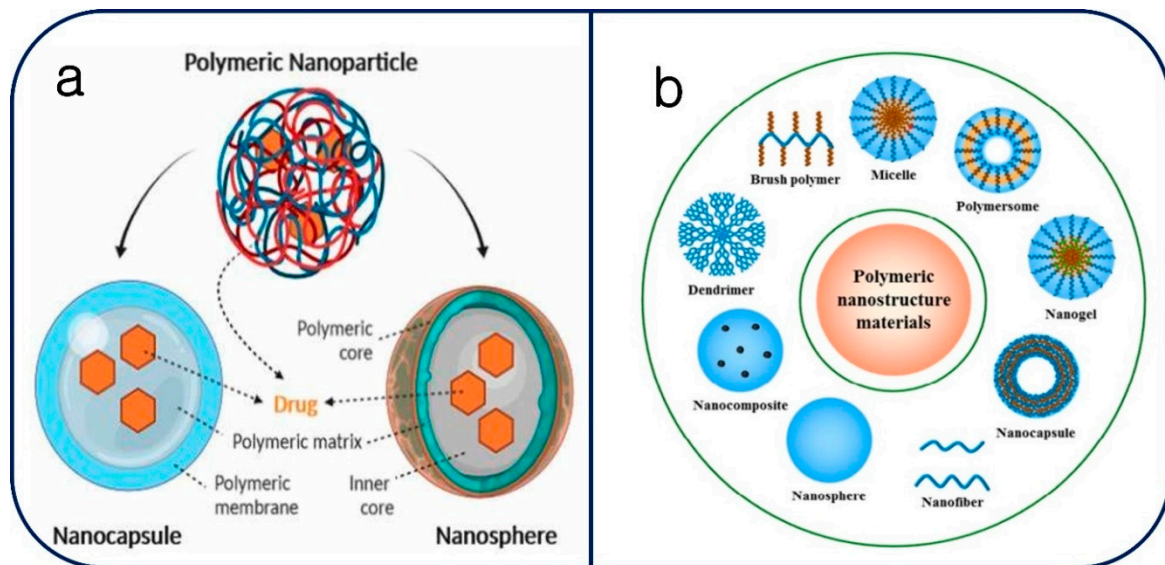


Figure 1. (a) Polymeric nanoparticle structure [31] (b) Various Polymeric nanoparticles includes, nanofibers, dendrimers, brush polymers, nanoparticles, polymersomes, micelles, nanocapsuals, and nanogels [34].

The polymer composite nanocarriers must possess.

- (1) Remain stable in blood until they reach TME
- (2) Improve the hydrophilic property and delayed recognition in immune system, allowing it for enhanced targets to desired cells/tissues after the reticuloendothelial system (RES) and mononuclear phagocyte system (MPS) surface activity.
- (3) these are gathered in TMS while allowing to pass through irregular vasculature tumor condition.
- (4) to respond for stimuli-controlled drug release to loaded therapeutic contents.
- (5) ability to modifying surface functionalization.
- (6) tumor-interstitial fluid penetration occurred in TMS.
- (7) to reach specific active targeting site to carry out drug phenomena [40–42].

The nano particles able to place in tumor Interstitial space allowed for long fluid circulation properties through passive mechanism of which accumulation leads to enhanced surface permeability and retention effect. In case of active targeting, the polymeric nanoparticles need to be modified by such targeting agents in the surface area to enhance tumor efficiency and minimizes caused side effects [43]. polymeric micelles NPs are developed using synthetic polymers or bio polymers. Polyamine, polyether, polyamide, and polyester are known to be Synthetic polymers and polypeptide, polysaccharides, polynucleotide are classified as bio polymers. Depending on their structure, variability and biocompatible enables the flexibility to design engineered polymeric micelles in synthetic polymers. While bio polymers show high-defined structure and considered as more biocompatible nature compared to synthetic materials due to reduced contamination in produced side products [44,45].

2. Role of Tumor Micro-Environment

The formulated Nanoparticles allowed to physicochemical and biological roadblocks which imposes requirements of size, biocompatibility, penetration, surface activity materials for preventing unspecific targets and introducing the specific binding materials to targets. Recently polymeric dual stimuli responsive nano particles acquired more and more attraction towards drug delivery due to their physicochemical unique properties which significantly improve their bioactivity of specific delivered agents for certain diseases tumor treatment [46]. Physicochemical properties exhibit surface ligands based on drug delivery systems in molecular, cellular level to enhancing versatility of

multifunctional nano particles [47]. Including these surfer ligands constructed with various internal stimuli and external stimuli factors such as temperature, magnetic, ultrasound, light etc. [48,49] and these studies can demonstrate in both in vivo as well as in vitro. The Physicochemical properties takes place in a simultaneous way at pathological site in intercellular compartment [50]. This kind of compartment system developed to study specific signals from solid tumor microenvironment [51]. In subcellular system tumor targeting, tumor diagnosis and tumor imaging undergoes multifunctional activities with all three-work load done by single move enhancing multimodal approach towards tumor disease [52]. In addition to this the extracellular environment shows more acidic (pH-6.5) nature in than blood circulation [53]. Here are a few significant variables that impact the tumor microenvironment's role.

- A **NPs size:** The diameter of NP therapeutic should be range from 10-100 nm and with surface combatant either positive or negative charge can lead great clearance to accessibility when dosed into either tumor or circulatory system [54]. Provide emerging treatment of NPs through fenestrations within tumor vasculature permitting for direct-cell access [55]. The lymph compartment of tumor vasculature in mouse model furnished the macromolecules leaking out from blood vessels this is well known as enhanced permeability and retention (EPR) effect [56]. Enables the chemotherapeutic agents as Conjugate polymeric NPs-drug into cancer tissues (ensure deeper penetration) may have favorably biased along with several mechanisms includes particle size [57]. If mentioned size range is correct NPs are restricted from normal vasculature (usually requires size below 2 nm); however, these NPs are still capable to access liver compartment in humans.
- B **NPs surface properties:** The NPs depends on high surface-to-volume ratio as compared to larger particles so control of surface properties will be crucial with their behavior in local environment. Usually, NPs surface properties includes with hydrophobic and hydrophilic, pH & charge, PEGylation or other coating, surface functional group (-SH, -NH₂, -COOH), surface charge, binding interaction [58–60].
- C **NPs composition:** The variety of NPs such as organic NPs (Liposomes, dendrimer, carbon tubes, polymers) and inorganic NPs (QD, magnetic NPs, GNPs, micelles) with dimensions less than few hundred nanometers have been recently shown emerging platforms for diagnostic treatment in drug delivery system. Especially, polymeric micelles, dendrimer, liposomes have been broadly explored for selectively targeting drug delivery of anti-cancer agents. In recent years nano scale composite with RNA (siRNA) as delivery vehicle also been developed for effective therapeutic approach in cancer treatment [61,62].
- D **NPs targeting agents:** NPs surrounded with anticancer drugs have been conjugated with different targeting molecules such as aptamers, antibodies, peptides present in Stem cells. Once this encapsulated drug released within cell or enter tumor. Thus, stimulating pH-redox responsive utilized by NPs for sit-specific drug release to enhance accumulation in tumor-site to bring physiological effects by active and passive mechanisms. On condition that destroy only cancer cell before leaving stem cell [63,64].

In addition, **Figure 2.** summarizes the main components of the complex and dynamic milieu that makes up the tumor microenvironment within the tumor tissue [62]. The diversity of the tumor microenvironment can be attributed to the varied genetic and phenotypic traits exhibited by tumor cells. Stromal components, such as fibroblasts, extracellular matrix proteins, and other supporting tissues, are also a part of the tumor microenvironment. These components are essential for giving the tumor structural and nutritional support. Since immune cells can play both pro- and anti-tumor functions in the tumor microenvironment, their presence is an important factor. The invasion of immune cells into the tumor tissue is depicted graphically in this figure. The microenvironment surrounding tumors frequently displays aberrant collagen networks and vasculature. The disorder in collagen and blood artery architecture can affect drug delivery effectiveness, metastasis, and tumor growth. Gaining an understanding of these elements and how they interact is essential to appreciating the potential and difficulties that the tumor microenvironment in our experimental

setting presents. It offers important new information about the possible interactions between these components and the overall tumor response that may result from our experimental interventions.

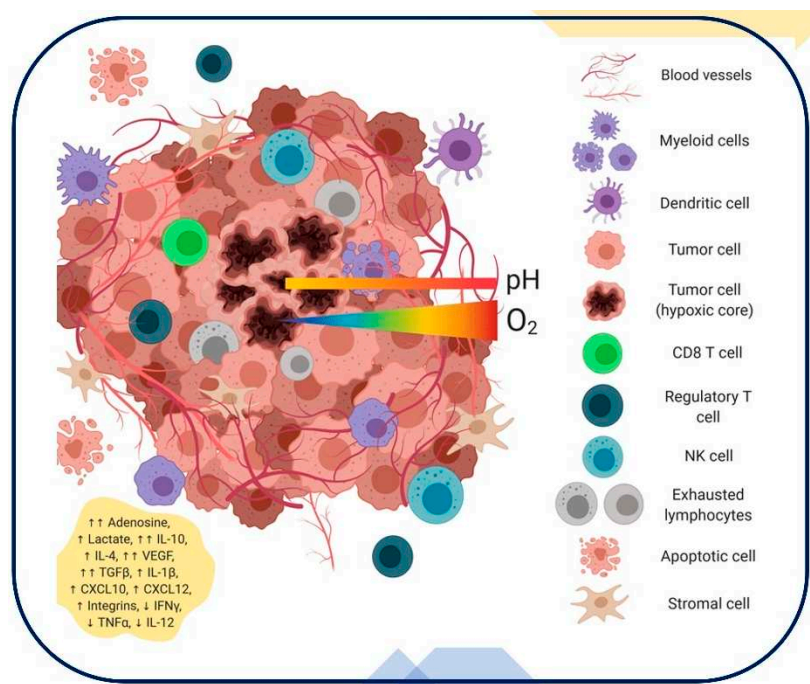


Figure 2. Tumor Microenvironment Components: Heterogeneous Tumor Cells, Stromal Elements, and Immune Cells in a Dysregulated Vasculature and Collagen Network [62].

An overview of the genetic tumor microenvironment and its critical role in improving the efficacy of oncolytic viruses (OVs) for cancer therapy is given in **Figure 3** [64]. It clarifies key tactics and elements for maximizing the efficacy of OVs in the treatment of cancer. To increase selectivity for cancer cells, Section (A) discusses methods for better tumor targeting, including serotype switching, tumor-targeted peptides, glycoprotein integration, single-chain antibodies, and tumor-specific promoters. The importance of virulence gene deletion to improve safety in OV treatment is emphasized in Section (B). Strategies to increase antitumor efficacy are covered in Section (C). These strategies include the use of immunostimulatory molecules, suicide genes, ECM-degrading enzymes, and anti-vasculature compounds. The information in Section (D) explains how to use markers like GFP, Rluc, NIS, and NET markers to track the dynamics of OV replication.

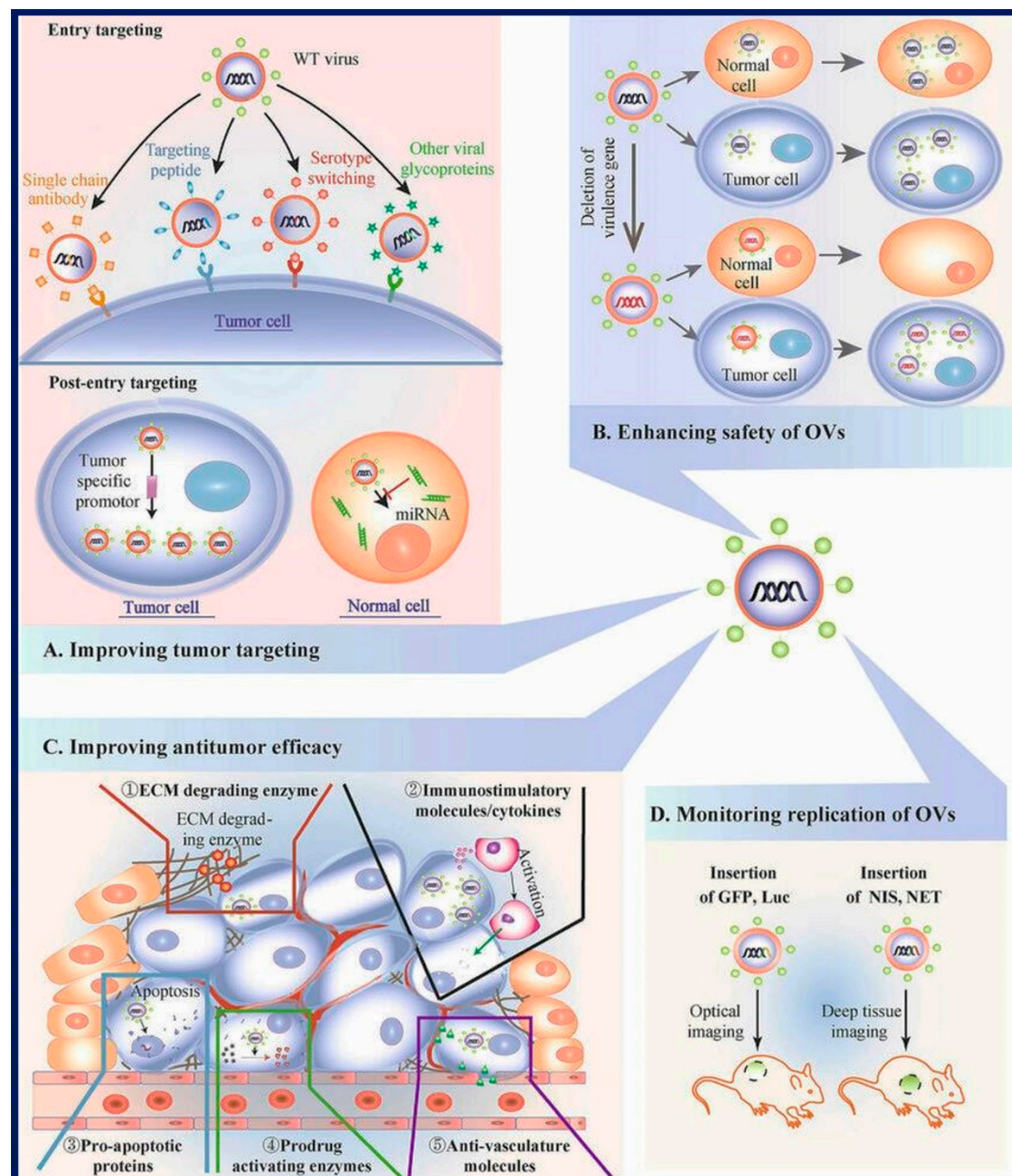


Figure 3. Schematic overview of the genetic Tumor micro-environment for Enhancing Oncolytic Virus (OV) Performance in Cancer Therapy. (A) Strategies for Improved Tumor Targeting such as Serotype Switching, Tumor-Targeting Peptides, Glycoproteins from Other Viruses, Single-Chain Antibodies (scAb), Tumor-Specific Promoters, miRNA Target Sequences. (B) Enhancing Safety through Virulence Gene Deletion (C) Amplifying Antitumor Efficacy like, Insertion of Immunostimulatory Molecules/Cytokines, Suicide Genes (Pro-Apoptotic Proteins and Prodrug-Activating Enzymes), ECM-Degrading Enzymes, Anti-Vasculature Molecules. (D) Monitoring OV Replication Dynamics (GFP, Rluc, NIS, NET) [64].

2.1. Tumor Redox Micro-Environment

Redox potential marked differences between intracellular and extracellular levels. The synthetic polymers or biopolymers linked or formulated with redox-sensitive bonds which allows to the formation of redox-sensitive materials in the intracellular compartments such as mitochondria, cytosol, and cell nucleus. The glutathione (GSH) level inside tumor microenvironment is range about 0.5×10^{-3} M due to elevated concentration of GSH and reductive moieties inside tumor cell. In addition, tumor tissue containing GSH level is four times elevated than the normal tissue. It has also

demonstrated that tumor tissues significantly show more reduction conditions (reducing thiol group) and hypoxic than normal cells or healthy cells. Therefore, various redox- responsive micelles nanomaterials are developed with having the ability to enhance trigger the release of their therapeutics agents in respective surface. These are usually located between the hydrophobic and hydrophilic segment with responsive agents such as disulfide bond (-S-S-), thioether bond (-S-), Di selenide bond (-se-ss-) and thiol group (-SH-) also provides the redox responsive site-specific drug release [65–67]. Further developments marked the difference between the GSH level of tumor microenvironment and normal tissues of which this brings promising platform/interest to design prodrugs (polymeric micelles nano particles). Hence disulfide exhibits self-assembled NPs with development of glutathione (GHS) in extra cellular and intra cellular compartment. The oxidized form of thiol group (-SH-) having the ability to generate disulfide linkage formation between peptide molecules in peptide synthesis, this disulfide occurs as side chain or middle of polymeric molecules. It gets cleaved in presence of GHS leads to ensuing drug release property and shows degradation of polymeric micelles [68,69]. The **Figure 4** provided a clear schematic depiction of the synthesis and subcutaneous colorectal cancer growth in mouse models. It describes how a Glutathione inhibitor and Composite Hydrogel-mediated Sonodynamic Therapy affect the progression of subcutaneous colorectal cancer in mice models as well as intracellular GSH synthesis.

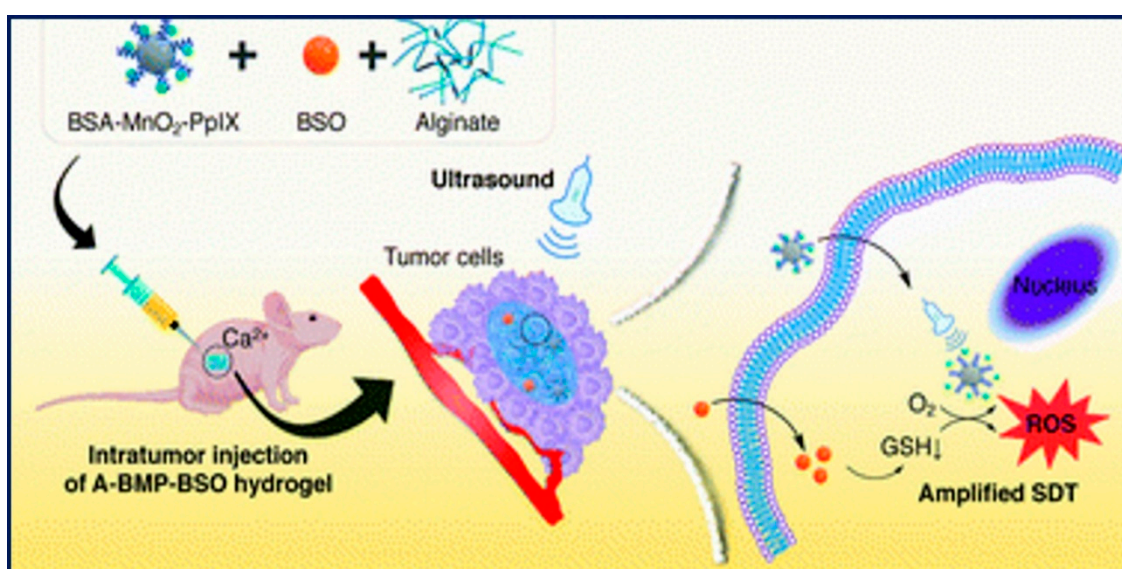


Figure 4. Impact of GSH Inhibitor and Composite Hydrogel-Mediated SDT on Intracellular GSH Synthesis and Subcutaneous Colorectal Cancer Growth in Mouse Models [69].

Sun et al. were reported the redox-responsive micelles for selectively triggered deliver of the drug in tumor microenvironment for the treatment of laryngopharyngeal carcinoma. To enhance the antitumor efficacy of Nanoparticles redox-responsive amphiphilic polymer has been developed by formulating heparosan and deoxycholic acid which fabricated through di- sulphide bond. The polymer micelles get self-assembled with favorable cargoes loading capacity containing doxorubicin (DOX). In addition, self-assembled nanoparticles can be disassembled by reductive cleavage of di- sulphide and triggered drug release capabilities in the intracellular compartment. The heparosan@deoxycholic acid micelles (HSDMs) shows the GSH triggered drug release with nearly 100% release rate. The FaDu Cancerous cell allowed to internalize HSDMs via clathrin-mediated endocytosis. Hence the DOX@HSD of FaDu cancer cells achieve the triggered drug delivery system over normal cells. [70]

Peng Mi et al. have reported that Environment or protection of tumor cell mainly due to reduction and oxidation states of glutathione (GSH) and NADPH/NADP⁺ which both have different reducing capacities and environment. At molecular level of GHS exhibits high concentrations as compared to NADPH/NADP⁺ shows subsequent disulfide bonds and excess reactive oxygen species (ROS) reactions leading to reach intracellular high GHS concentration about 10mM, while

extracellular environment ranges 2 to 20 μM in the drug delivery system [71]. Recent developments of pH and redox dual-responsive nanohydrogels *In vitro* has been carried out. The DOX drug release approach up to 95.7% whereas disulfide linkage lead as nanohydrogels redox agent and get degraded using PPT and GSH (reducing agents) it further leads to degradation-trigger drug release. Hence exhibits non-toxicity to HEK 293 cells helping in excellent moves for killing cancerous cell or glioma tumor in cancer therapy [72]

2.2. Tumor pH Micro-Environment

The pH variation provides significant role to internalize the NPs into cells for allowing via vessels for acidified cells. The tumor cells containing pH response signal attributes lesser acidified pH as compared to normal tissues. For effective controlled drug delivery intentionally designed pH responsive polymeric nano materials which changes the cellular level charge and hydrophilicity depending on the pH micro-environment system [73]. Two types of polymers are commonly used cationic and anionic polymer for specific drug delivery. For anionic polymers are more used pH-responsive polymers such as poly (glutamic acid) (PGA), poly (ethyl acrylic acid) (PEAA), poly (methacrylic acid) (PMAA), and poly (acrylic acid) (PAA) [74]. If anion polymeric tumor cells show transition hydrophilic to hydrophobic then pH-decreased which leads to destabilization or deformation of polymers cause swelling or changes in solubility leads drug release and polymer disassembly, hence for cationic changes from hydrophobic to hydrophilic [75]. For example, at lower pH, DOX (anti-cancer drug) loaded with conjugated polymer micelles and cross-linked polymer ion core. The Protonation formulated with Carboxylic groups as nano carrier, at tissue level nano carrier get accelerated and release DOX due to lower electrostatic attractions in both protonated acid and DOX formulation groups [76].

Whereas cationic pH-responsive polymers show positive charges in cellular compartment having the advantage of cellular uptake. It includes poly (β -amino ester), poly (β - amino ester), poly(L-histidine) (PH is) etc. are commonly de-protonated at basic pH level and protonated at acidic pH level. Min et al. Developed MPEG-poly (β -amino ester) polymeric characterized biodegradable and pH-responsive polymers which is useful in cancer treatment, herein hydrophilic PEG with PbAE (biodegradable) results in PEG-PbAE copolymers formed by self-assembly. It provides triggered drug delivery and shows sharp pH dependent biomaterials at tumor level having pH 6.4 [77]. Considerable pH variation is repeatedly used for design of suitable stimuli responsive Nanomaterials. To account for abnormally quick metabolism and cells proliferation. Because a great amount of end products developed by tumor tissues and cause cytotoxic effect to neighboring tissue. While acid pH commonly ranges between 5.7– 6.9 [78]. Thus, variety of prodrugs have designed to deliver drug or gene into tumor penetration and get controlled drug release facilities at targeted site in cancer diagnosis [79–81]. In the **Figure 5** outlined the mechanisms of pH activation and micellar self-assembly. The mechanism through which the medication DOX is released by micelles when they self-assemble in response to GSH in the biological system is depicted in Figure 5A. and schematic representation of the pH activation of nanoparticles in the tumor microenvironment is shown in Figure 5B. With regards Chang et al. have been developed a polymeric micelle consisting with design copolymer and N- Boc-histidine [82]. The capped N-Boc-histidine enhance the biodegradability as well as biocompatibility of the micelles and Doxorubicin was loaded into micelles (act as anticancer drug). Especially the normal tissues contain pH -7.4, as in cancer microenvironment the acid pH have significantly triggered doxorubicin drug release at pH -6.2. The acid pH polymer nanocarriers released doxorubicin drug at lower circulatory toxicity than free drugs. The anticancer drug should be released in acidic pH microenvironment into tumor cell. Fetch the good intercellular drug release and minimize the extracellular action in tumor diagnosis. In another study, Hu et al. reported reduced cytotoxicity of pH-triggered doxorubicin drug release polymeric micelles due to high internalizations of NPs into tumor [83]. In addition, Yu et al. Develop polymeric micelles contain PbAE, which alter size, surface charge and drug resistant antitumor site [84].

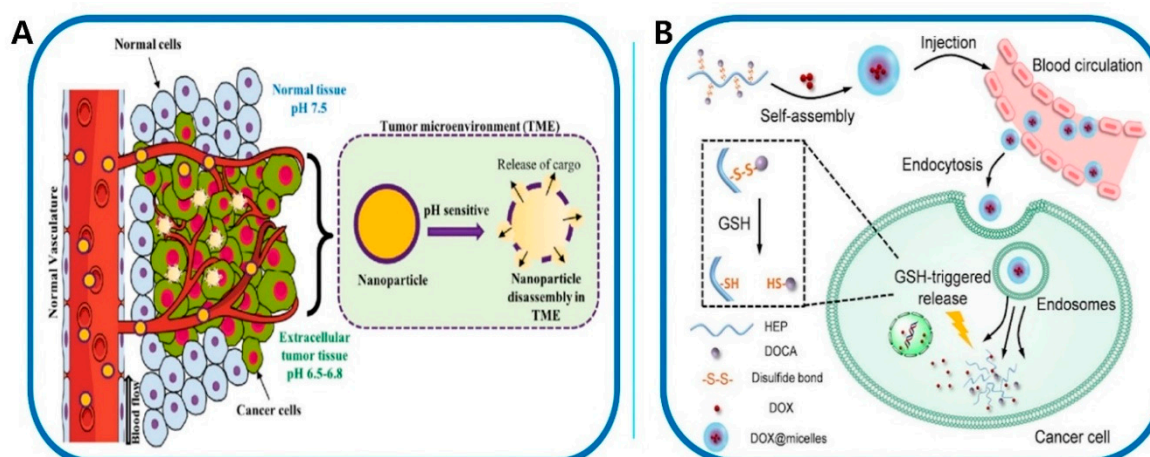
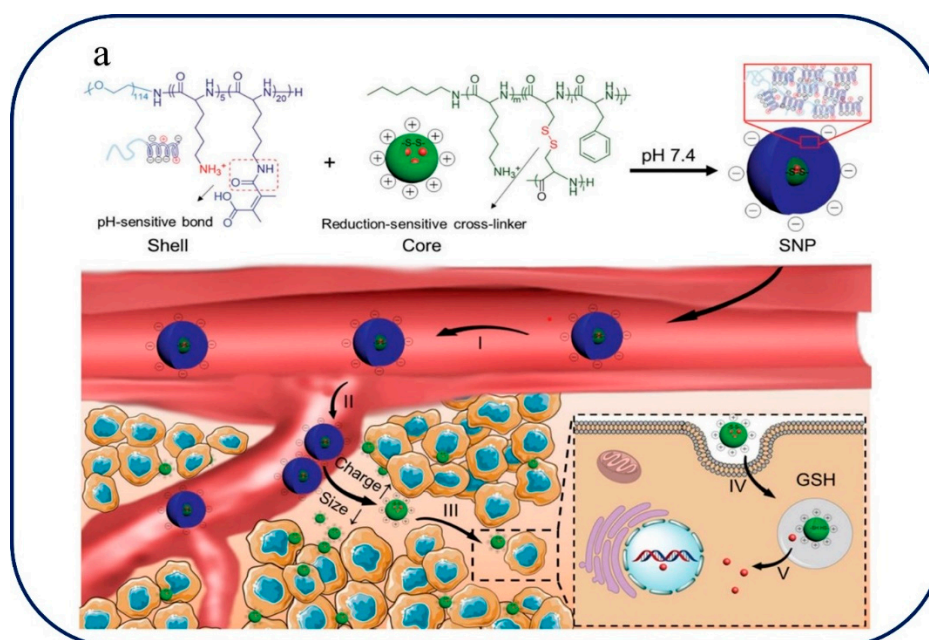


Figure 5. Mechanism of Micelle Self-Assembly and pH activation. A. Diagram showing how micelles come together on their own, releasing DOX in response to GSH. And B. Schematic view of pH activation of nanoparticles by tumor microenvironment [80].

2.3. pH-Redox Tumor Micro-Environment

TME obtained with combined pH and redox dual-stimuli response (1) for tumor extracellular environment can depend on their size, surface properties, and morphology (response to endosomal pH); thus, credit the barriers like tumor accumulation, tumor penetration, blood circulation, and cellular level uptake (2) the intracellular environment response to pH, GSH level, and ROS cleavable moiety in tumor vasculature, induce the rapid drug-release inside tumor cell. However, especially polymeric nano composites have been developed to overcome both extracellular and intracellular barriers to enhance maximum antitumor effect. In this context, (3) internal stimuli-responsive micelle nanomaterials induced by pathophysiological properties between normal and cancer cells, while undergoing dynamical changes with various factors in vivo. So, it shows difficulties to control nanomaterials with respect to precision and speed of response in TME. (4) As for external stimuli the key objectives are supposed to focusing upon how to achieve high-level deeper penetration without harming normal tissues with maximized specificity, efficacy, and selectivity [98–102]. As above discussed, the stimuli response combination, the intracellular environments are characterized by different pH values, meanwhile pH maintained nearly 7.4 in the normal extracellular compartment. Once being surface internalization or enter through endocytosed, the polymeric drug carriers will firstly encounter the early endosome with nearly 6.2 pH, then entering late endosome within about 5.5 pH, thus tumor cell maintains with lower pH environment due to generated ROS (reactive oxygen species) and free radicals ($-\text{OH}$, H_2O_2 , O_2) present in TME. while ROS level will be sharply increased 3 times more than normal cells. These high reactive molecules construct the combined dual-sensitive pH-redox polymer prodrug and NPs, which addressing the stability dilemma, reduced size, surface charge reversal to enhance triggered drug release in tumor cells. As one instance, such “titratable” groups like carboxylic acids, amine groups have been introduced into prodrug inducing improved extracellular stability led by prolonged circulation, stealth surface, improved tumor accumulation drug (usually cytotoxic drugs). After entering cancer cell ROS triggers initial drug release and protonation formulated with carboxylic group. In addition, di-sulfide have been employed to ROS which associate the core-crosslink polymeric micelles for preventing the drug leakage while carrying out blood circulation. Followed by therapeutic drugs were loaded into NPs materials either covalent binds or non-covalent binds leads to development of polymeric drugs carriers in GSH reduction conditions, thereby enhance the surrounding hydrophilicity and swelling of micellar shell and di-sulfide bond will be cleaved when exposed to abundance of GSH, thereby causing the cellular disassembly of the polymeric micelles structure. Thus, core shell micelles furnished the better DOX drug release in TME by pH-triggered swelling and GSH-triggered disassembly.

Chen et al. reported pH/redox responsive NPs to regulate tumor hypoxia. Here NPs bearing DMMA-modification this usually obtained by tumor acidity (pH) and GSH responsive shell- stacked NPs. The DMMA undergoes surface charge reversal induced the negative charge thick shell and positive charge disulfide-cross-linked core. The NPs entering tumor with negativesurface charge and reach prolonged blood circulation under acidic conditions with large size of NPs about ~145 nm. on other side, addressing the stability dilemma, surface charge reversal and size reduction (~40 nm) to enhancing deeper penetration and cellular uptake. Thereby, drug carriers after entering cancer cells induces cytoplasmic GSH rapid DOX release bears de- cross-linking with polypeptide core. The core shell showed DOX release in tumor cell under pH-triggered and GSH-triggered disassembly resulting into antitumor affect [103]. In the **Figure 6** they explain the pH-redox Tumor-Microenvironment-mediated Cascade and Polypeptide Core Self-Assembly for Targeted Drug Delivery. The pH-redox tumor microenvironment-mediated cascade, which is essential for improving drug delivery, is depicted in Figure 6a. A disulfide-cross-linked polypeptide core and a PEGylated shell are involved in this cascade. PEGylated shells help stabilize nanoparticles and prolong bloodstream circulation, which helps to precisely target tumors. Controlled drug release is made possible by the disulfide-cross-linked polypeptide core, which responds to the redox environment of the tumor.



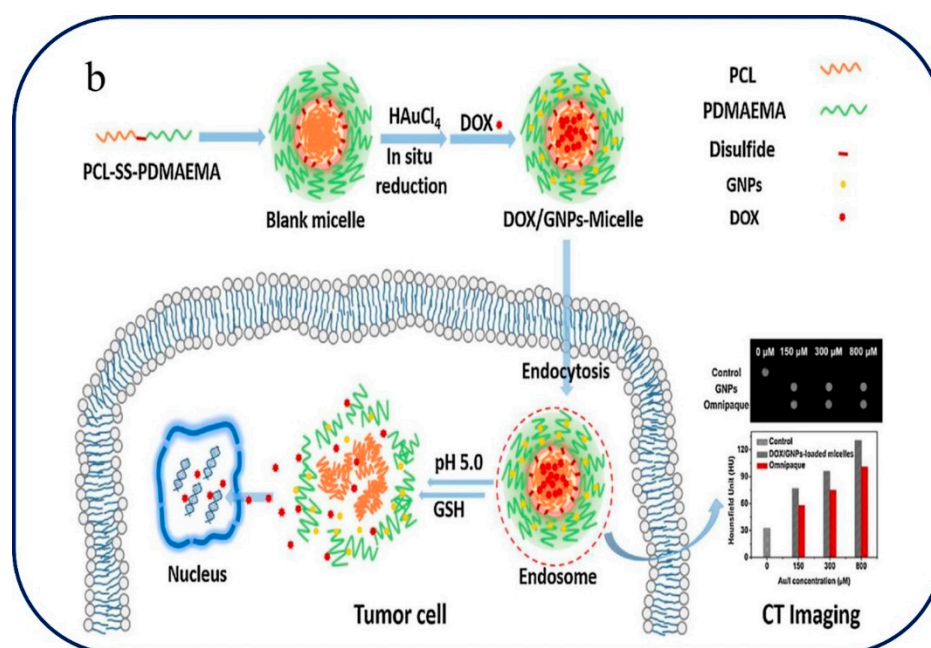


Figure 6. pH-redox Tumor-Microenvironment-mediated Cascade and Polypeptide Core Self-Assembly for Targeted Drug Delivery. (a)pH-redox Tumor-Microenvironment-Mediated Cascade for Optimized Drug Delivery with PEGylated Shell and Disulfide-Cross-Linked Polypeptide Core [103]. (b) polymer PCL-SS-PDMAEMA self-assembly, GNPs and DOX loading and release for cancer chemotherapy and CT imaging [104].

Xiong et al. Have demonstrated the synthesis of pH and redox sensitive micelles for better delivery of DOX and GNPs (gold nano particles). The polymeric micelles consist of amphiphilic copolymer of (PCL-SS-PDMAEMA). The Conjugate PDMAEMA will get protonated and utilizing the acidic conditions, thereby intensifying the hydrophilicity, followed by micellar shell will leads to swelling and di-sulfide bond yield cleavage when exposed to GSH, here cause the disassembly in cellular or sub-cellular compartment. The conjugates NPs loaded with DOX@PCL-SS-PDMAEMA @GNPs, thereby core-shell micelles provide better drug deliveries in tumor cell by pH-trigger swelling and GSH-trigger disassembly in the intercellular region in tumor cells [104]. The self-assembly of PCL-SS-PDMAEMA, the polymer at the center of our drug delivery system, is explored in detail in Figure 6b. This core plays a key role in encapsulating therapeutic components that are necessary for cancer treatment and computed tomography (CT) imaging, such as gold nanoparticles and the anticancer medication DOX [104]. Similarly, shi et al. reported four-arm PCL-PEG copolymer providedwith PCL as hydrophobic which is conjugate with hydrophilic PEG via di-sulfide bond, this disulfide bond gets degraded in response or when exposed to high level GSH in tumor, resulting rapid DOX release [105]. On drug delivery strategies these conjugated di-sulphide bond reduced upon biological milieu due to unique reversible nature of covalent bond present in the cellular compartment and possess-controlled cleavage drug release provides intracellular-redox potential drug delivery tool.[106]. John et al. reported the synthesis Polymeric micelles like p(His)_n-SS-PU-SS-p(His)_n triblock induced by carrying out the polymerization, thereby polyurethane nano daisies triggered drug release in tumor cell [107]. A thorough summary of pH and redox-responsive polymeric nanoparticles and their uses in drug administration is provided in **Table 1**. The numerous polymeric nanoparticles, their loaded cargo/drugs, the targeted drug release, or delivery methods they use, the intended therapeutic or application, the biological evaluation context, and the relevant references are all compiled in this table.

Figure 7. (a) Design and Synthesis of pH-Responsive p(L-histidine) n-SS-polyurethane-SS-p(L-histidine) n Triblock Copolymers (n = 25, 35, 50, and 75) for Intracellular Drug Release. (b) Insights view of Self-Assembled Polyurethane Nano daisies Triggered by pH-Responsive p(His) Blocks and Disulfide Bond Cleavage in Response to GSH [107].

Table 1. The different pH/redox responsive polymeric nanoparticles, drug delivery strategies and their mechanisms.

Polymeric nano particles	Cargo/drug	Drug release / targeting	Therapy	Biological evolution	Reference
poly (β -amino esters)	CD44	Controlled drug release	Breast cancer, lung metastasis	In vitro	85
Conjugated (C-dots-HBA-dox) and (C-dots-S-S-dox)	Doxorubicin	Controlled drug release	Cancer chemotherapy	In vitro	86
PEG-PAA(SH)-PDEA	FITC-BSA/CC	Controlled drug release	Cancer therapy	In vitro	87
PCL-b-P(OEGMA-co-MAEBA)	Camptothecin or Doxorubicin	Accelerated drug release	Cancer chemotherapy	In vitro	88
acrylic acid (AAc) and 2-methacryloyl ethyl acrylate (MEA)	Doxorubicin	Rapid drug release	Anti-cancer treatment	In vitro	89
PMAA nanohydrogels	Doxorubicin	Controlled drug release	Anti-cancer treatment	In vitro	90
(PDPA) capsules	Rhodamine B isothiocyanate-labeled OVA	Cargo release	--	In vitro	91
Poly (2-(pyridin-2-yl)disulfanyl) ethyl acrylate)	RPDSG/DOX	Controlled drug release	Cancer therapy	In vitro	92
cross-linked polyphosphazene	Curcumin and Ce6	Controlled drug release	Cancer therapy	In vivo and In vitro	93
DEXssPEGCOOH	Doxorubicin	Targeted release	Cancer therapy	In vitro	94
RPAE-PEG	Doxorubicin	Controlled drug release	Cancer therapy	In vitro	95
MSNs (DOX@PRMSNs)	Doxorubicin	targeting ligands	Cancer therapy	In vitro	96
DOX@Dex-SS nanogel	Doxorubicin	Cumulative amount drug release	Cancer chemotherapy	In vitro	97

3. Design Principles and Fabrication Methods

This section delves into the design principles behind pH and redox-responsive polymer-nanocomposites. It explores how these materials respond to change in pH and redox conditions typically found in tumor microenvironments. Various fabrication methods, including nanoprecipitation, emulsion polymerization, and layer-by-layer assembly, are discussed in detail, highlighting their advantages and limitations in creating drug-loaded polymer-nanocomposites with specific responsive properties.

3.1. Design Principles of pH and Redox-Responsive Polymer-Nanocomposites

The design of pH-responsive polymer-nanocomposites is centered on exploiting the acidic nature of the tumor microenvironment. The extracellular pH of solid tumors is generally lower (around 6.5-7.2) than that of healthy tissues (approximately 7.4) [12]. To achieve pH responsiveness,

researchers incorporate pH-sensitive moieties into the polymer matrix. Common pH-sensitive groups include weakly acidic functional groups, such as carboxylic acids (-COOH) and sulfonic acids (-SO₃H), which undergo ionization in response to pH changes [59,61]. As the pH drops in the tumor microenvironment, these acidic groups become ionized, leading to a charge repulsion effect and subsequent swelling or disintegration of the polymer-nanocomposite, triggering drug release. Redox responsiveness relies on the altered redox potential in cancer cells due to elevated levels of reducing agents, such as glutathione (GSH) [108]. Cancer cells maintain a higher concentration of GSH, which serves as a reducing agent in intracellular redox reactions. Researchers design redox-responsive polymer-nanocomposites by incorporating disulfide (-SS-) linkages or other redox-sensitive motifs. In the reducing environment of cancer cells, the disulfide bonds are cleaved, causing the polymer-nanocomposite to destabilize and release the drug payload [59]. To achieve dual responsiveness, both pH and redox-sensitive elements are combined in the polymer-nanocomposite. This design enables fine-tuning of drug release based on the combined effect of pH and redox conditions in the tumor microenvironment. By strategically incorporating pH-sensitive and redox-sensitive functionalities, the polymer-nanocomposite can respond to two different stimuli, enhancing the precision and control of drug release.

3.2. Fabrication Methods

Nanoprecipitation is a commonly employed technique for fabricating polymer-nanocomposites with high drug loading capacity. Using this technique, a drug and polymer solution are made independently, with the polymer including groups that are sensitive to pH and/or redox. Following the combination of these solutions usually with strong shear or sonication the organic solvent rapidly diffuses into the aqueous phase, causing the spontaneous production of nanoparticles. Numerous medication delivery applications can benefit from the exact control over particle size and drug loading that the nanoprecipitation technique offers. This method's simplicity and scalability allow for the precise control over the release profile and the encapsulation of both hydrophilic and hydrophobic medicines. There are a few restrictions to consider, though. Possible medication instability brought on by contact with organic solvents during manufacture. Restricted ability to regulate the nanoparticles' surface properties and difficulties in attaining consistent drug dispersion [109].

Another flexible technique for creating pH and redox-responsive polymer nanocomposites is emulsion polymerization. This procedure creates a stable emulsion by dispersing monomers, a medication, and an emulsifying agent in an aqueous phase. After that, the emulsion is polymerized using appropriate polymerization techniques or by introducing free radicals. As a result, the polymer-nanocomposites that are produced are usually composed of core-shell structures, where the drug payload is contained within the core. The ability to encapsulate a broad variety of medications and the method's good control over drug loading, surface properties, and particle size are among its benefits. The use of emulsifying chemicals that may affect biocompatibility, the requirement for strict purification procedures, and the possibility of drug degradation during polymerization are limitations. Layer-by-layer assembly is a versatile technique that involves the sequential deposition of alternating layers of oppositely charged polymers or polyelectrolytes onto a substrate. By incorporating pH and redox-sensitive polymers in the multilayer assembly, researchers can design polymer-nanocomposites with tunable responsiveness. Drug molecules can be loaded within the interlayer spaces or encapsulated within one of the layers. Advantages like its precise control over film thickness and drug loading, ability to tailor responsiveness through layer selection, and compatibility with a variety of drugs [29].

Limitations are time-consuming process, may result in relatively thick films, and potential challenges in maintaining film stability in vivo. This design principles and fabrication methods of pH and redox-responsive polymer-nanocomposites play a pivotal role in their application as site-specific drug delivery systems in cancer therapy [110]. By ingeniously engineering these biomaterials to respond to the unique microenvironment of tumors, researchers can enhance therapeutic efficacy while minimizing off-target effects. Nanoprecipitation, emulsion polymerization, and layer-by-layer

assembly are promising techniques to create drug-loaded polymer-nanocomposites with specific responsive properties, and ongoing research in this field is expected to lead to the development of more sophisticated and effective dual-stimuli responsive biomaterials for personalized cancer treatment [29].

4. Biocompatibility and Safety

Biocompatibility and safety are critical aspects in the development and clinical translation of biomaterials, especially for applications in drug delivery systems. In this context, pH and redox-responsive polymer-nanocomposites have gained significant interest due to their potential to respond to specific physiological conditions, making them suitable candidates for targeted drug delivery. However, before these materials can be safely used in clinical settings, thorough examination and evaluation of their biocompatibility and potential long-term effects on healthy tissues are essential.

The Biocompatibility refers to the ability of a material to interact favorably with biological systems without causing adverse reactions or toxicity. In the case of pH and redox-responsive polymer-nanocomposites, their interaction with the surrounding biological environment is of utmost importance. pH is a crucial parameter that varies in different tissues and cellular compartments. Target sites can be precisely controlled for drug release thanks to the conformational changes that pH-responsive polymers in nanocomposites can undergo in response to local pH levels. In vitro tests employing cell cultures are carried out to evaluate biocompatibility by monitoring cell survival, growth, and any possible cytotoxicity brought on by these materials [87]. In vivo studies are also performed using animal models to evaluate the tissue response and systemic effects after administration of these polymer-nano-composites. Redox-responsive biomaterials can respond to changes in the cellular redox state, which is often altered in disease states [93]. These materials can be designed to release drugs in response to specific intracellular redox conditions. Biocompatibility evaluations for redox-responsive polymer-nanocomposites involve similar in vitro and in vivo studies as those for pH-responsiveness [85–93]. The long-term effects of biomaterials on healthy tissues are crucial to assess to ensure patient safety during extended drug delivery applications. These evaluations require long-term in vivo studies using animal models. To assess the biocompatibility of these materials over time, researchers examine tissue responses, possible inflammatory reactions, and systemic impacts over prolonged periods of time. An important factor in determining the safety of pH and redox-responsive polymer-nanocomposites is preclinical toxicology research. To find possible harmful effects, establish safe dosage ranges for therapeutic usage, and ascertain dose-response correlations, these investigations entail extensive testing in animals. Adhering to regulatory criteria for the conduct of these studies is essential to guarantee a thorough evaluation of the safety of the materials prior to human trials. Creating intelligent biodegradable materials is a crucial factor in ensuring safe medication administration. The ability of a substance to decompose into non-toxic metabolites and finally leave the body is known as biodegradability. This feature is especially crucial for long-term uses because it keeps materials from building up in tissues. To verify the safety profile of these materials, biocompatibility assessments should consider the products of their breakdown. A comprehensive assessment of the biocompatibility and safety of pH and redox-responsive polymer-nanocomposites is necessary for their effective clinical translation as drug delivery systems. By means of preclinical toxicity investigations and thorough assessments of their interactions with healthy tissues, scientists can guarantee the creation of secure biomaterials for precise and regulated medication administration across a range of medical uses.

5. Future Perspectives and Challenges

This section provides an overview of the potential applications of pH and redox-triggered polymer-nanocomposites in cancer therapy as they move closer to clinical trials. It talks about how novel approaches are required to raise drug loading capability, response specificity, and in vivo stability. Additionally, possible synergies with other systems that respond to stimuli and combination therapy are investigated. The ability of pH and redox-responsive polymer-

nanocomposites to load drugs is one of their main problems. To maximize the amount of therapeutic chemicals that may be loaded onto these biomaterials without sacrificing their stability and responsiveness, researchers should concentrate on creating novel techniques. Enhanced drug loading efficiencies can be attained by investigating new methods of drug encapsulation and surface modifications. Even if site-specific medication release is possible with pH and redox-responsive polymer-nanocomposites, obtaining even greater response specificity is essential. Future research should aim to design biomaterials that respond only to the precise tumor microenvironment and avoid premature drug release in non-targeted tissues. This could involve incorporating additional stimuli-responsive elements or utilizing advanced targeting ligands. The stability and longevity of polymer-nanocomposites in the complex in vivo environment are vital for their successful clinical translation. Researchers need to address challenges related to biodegradation, immune responses, and potential clearance from the body. Developing stable, long-lasting polymer-nanocomposites will ensure sustained drug release and optimize therapeutic outcomes. The future of cancer therapy lies in personalized medicine. pH and redox-responsive polymer-nanocomposites can be further customized based on individual patient characteristics and specific tumor types. Tailoring drug payloads, stimuli responsiveness, and targeting ligands to match each patient's unique profile could significantly enhance treatment efficacy and minimize side effects.

Despite promising preclinical results, translating pH and redox-triggered polymer-nanocomposites from the laboratory to clinical practice presents challenges. Rigorous testing in large animal models and addressing potential toxicity concerns are essential steps in the journey towards human trials. Cancer cells exhibit substantial heterogeneity, even within the same tumor. Adapting pH and redox-responsive biomaterials to accommodate this diversity poses a significant challenge. Strategies to tackle intra-tumoral variability and ensure efficient drug delivery to all tumor regions need to be explored. The approval process for novel biomaterials in clinical settings involves stringent regulatory guidelines. Demonstrating the safety, efficacy, and long-term effects of pH and redox-responsive polymer-nanocomposites will be critical for gaining regulatory approval and market acceptance. While combining different stimuli-responsive systems or therapies holds promise for enhanced treatment outcomes, it introduces complexities in terms of drug interactions, dosage optimization, and potential adverse effects. Developing effective combination strategies that maximize synergies while minimizing drawbacks is a considerable challenge. For widespread clinical adoption, pH, and redox-responsive polymer-nanocomposites must be scalable and cost-effective. Identifying suitable, readily available raw materials and streamlining the manufacturing processes will be essential to reduce production costs and ensure affordability for patients.

6. Conclusions

In conclusion, pH, and redox-triggered polymer-nanocomposites hold significant promise as future generation dual-stimuli responsive biomaterials for site-specific drug release in cancer therapy. Their ability to precisely target tumor cells while sparing healthy tissues has the potential to revolutionize cancer treatment, offering improved therapeutic outcomes and enhanced patient quality of life. Nevertheless, further research and clinical investigations are essential to overcome the existing challenges and unlock the full potential of these innovative biomaterials in cancer therapeutics.

The development of pH and redox-responsive polymer-nanocomposites as dual-stimuli responsive biomaterials has shown great promise in revolutionizing cancer therapy. However, to fully harness their potential, researchers must address the challenges of drug loading capacity, response specificity, in vivo stability, and regulatory approval. Collaborative efforts between researchers, clinicians, and industry stakeholders are crucial to overcome these obstacles and pave the way for the successful clinical translation of these innovative biomaterials. As advancements continue, pH and redox-responsive polymer-nanocomposites hold immense potential to improve cancer treatment and ultimately contribute to better patient outcomes.

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