J Nanostruct 14(1): 204-213, Winter 2024

RESEARCH PAPER

Targeted Cancer Therapy: Leveraging Dual pH-Sensitive Polymers Nanoparticles for Doxorubicin Delivery and Tumor Suppression: A Review

Zhanar Rakhimberdiyeva [1]*, Mirzaliev Tolibjon Ganievich [2], Murat Nurushev [3], Ganikhanova Madina Baxretdinovna [4], Aziz Rashidov [5], Ayupov Timur Rustamovich [5], Boboyev Bakhromjon Kenjaevich [6], Daminova Kamola Maratovna [7], Nabieva Dilfuza Utkurovna [8], Rakhmatova Markhabo Rasulovna [9], Abitov Ilnur Ildusovich [10], Ergasheva Zumrad Abduqayumovna [11], Panjiev Normakhmat [12]

[1] *Shymkent university, Mukhtar Auezov South Kazakhstan University, Shymkent, Republic of Kazakhstan*

[2] *Faculty of Uzbek and Russian Philology, Kokand State Pedagogical Institute, Uzbekistan*

[3] *Astana International University, Astana, Kazakhsta*

[4] *Tashkent State Technical University, Uzbekistan*

[5] *Department of Theory of the Russian Language and Literature, Kokand State Pedagogical Institute, Uzbekistan*

[6] *Faculty of Agriculture, Fergana State University, Uzbekistan*

[7] *Department of therapeutic subjects, Tashkent State Dental Institute, Uzbekistan*

[8] *Department of Oncology, Center for the Development of Professional Qualifications of Medical Workers, Tashkent, Uzbekistan*

[9] *Department Clinic Pharmacology, Bukhara State Medical Institute, Uzbekistan*

[10] *Department of Agronomy, Navoi State Mining and Technological University, Navoi, Uzbekistan*

[11] *Andijan State medical institute, Uzbekistan*

[12] *Termez State University, Termez, 190111, Uzbekistan*

ARTICLE INFO

Article History:
Received 08 October 2023
Accepted 19 December 2023
Published 01 January 2024

Keywords:
Cancer
DOX
Polymeric Nanomaterials
Targeted therapies

ABSTRACT

The global burden of cancer continues to strengthen, using the want for innovative treatment methods that beautify efficacy while minimizing adverse effects. traditional chemotherapies, including the extensively used doxorubicin, face considerable demanding situations consisting of off-target toxicity, poor selectivity, and multidrug resistance (MDR). targeted drug shipping systems have emerged as a progressive solution, with dual pH-touchy polymer nanoparticles gaining significant attention. those structures exploit the acidic tumor microenvironment (TME) to enable selective and managed drug launch, improving healing consequences and lowering systemic toxicity. This overview examines the design, synthesis, and capability of dual pH-sensitive polymer systems, their mechanisms of motion, and preclinical validation. moreover, the potential of those nanoparticles to deal with the limitations of DOX remedy is highlighted, paving the way for their integration into clinical practice.

How to cite this article
Rakhimberdiyeva Z., Ganievich M., Targeted M. Cancer Therapy: Leveraging Dual pH-Sensitive Polymers Nanoparticles for Doxorubicin Delivery and Tumor Suppression: A Review. J Nanostruct, 2024; 14(1):204-213. DOI: 10.22052/JNS.2024.01.021

* *Corresponding Author Email: zhanarrakhimberdiyeva@hotmail.com*

INTRODUCTION

Cancer remains one of the maximum pressing worldwide fitness challenges, accounting for about 10 million deaths yearly (WHO, 2022). Traditional therapeutic techniques including surgical procedure, radiation, and chemotherapy, while powerful in unique eventualities, are regularly restrained by way of loss of specificity, systemic aspect outcomes, and disorder recurrence [1]. amongst these, chemotherapy plays a pivotal role in systemic malignancies. In spite of its efficacy, its reliance on cytotoxic agents frequently results in enormous damage to healthy tissues, undermining patient effects[2].

Doxorubicin (DOX) is a cornerstone chemotherapeutic agent widely used inside the treatment of numerous cancers, together with breast cancer, leukemia, and sarcomas [3]. however, its medical application is hampered by giant challenges, inclusive of systemic toxicity, multidrug resistance (MDR), and poor tumor selectivity [4]. These barriers underscore the urgent want for superior drug shipping structures which can improve the therapeutic index of DOX while minimizing its destructive consequences [5]. In current decades, advancements in nanotechnology have opened new avenues for cancer treatment, with a focus on improving the specificity and protection profiles of healing agents. targeted drug transport systems are at the forefront of these improvements, providing the potential to revolutionize most cancers therapy by addressing key challenges together with poor drug bioavailability and nonspecific toxicity [6]. The concept of targeted drug transport aims to selectively shipping therapeutic retailers to the tumor site while sparing healthful tissues [7]. This method is based at the wonderful biological and physicochemical traits of tumors, including enhanced vascular permeability, terrible lymphatic drainage, and precise microenvironmental features like hypoxia and acidity [8]. Nanocarriers designed for targeted drug delivery provide more than one benefits, together with improved tumor accumulation, decreased systemic toxicity, and improved pharmacokinetics. one of the maximum promising techniques for targeted delivery includes using stimuli-responsive materials, especially pH-sensitive polymers [9]. The tumor microenvironment (TME) is characterised by means of a barely acidic extracellular pH (6.5–7. zero), which contrasts with the physiological pH of everyday tissues (7.4) [10]. Moreover, intracellular compartments which includes endosomes and lysosomes show off even lower pH degrees (4.5–5.5). pH-touchy polymers take advantage of these pH gradients to acquire managed drug launch, enhancing therapeutic efficacy at the same time

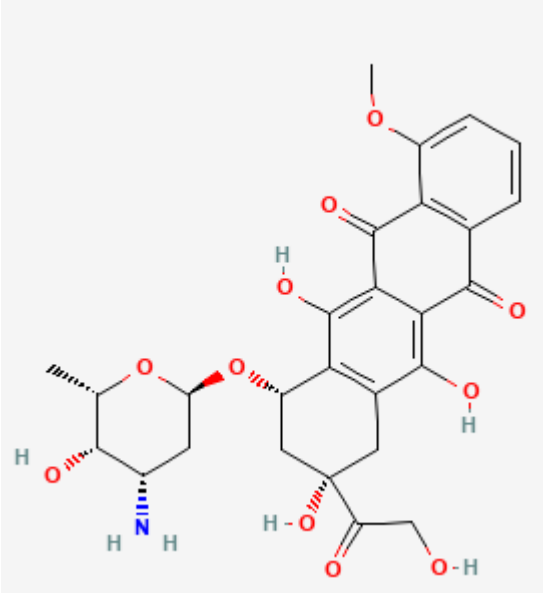

Fig. 1. Chemical structure of DOX

as lowering systemic toxicity [11].

These polymers go through conformational changes, solubility shifts, or chemical bond cleavage in response to acidic situations. dual pH-sensitive systems, which integrate multiple pH-responsive mechanisms, provide more suitable precision and flexibility in drug transport packages, making them especially appropriate for complicated chemotherapeutic regimens [12]. The incorporation of DOX into dual pH-senstive polymer nanoparticles pursuits to maximise the drug's therapeutic results while minimizing its systemic aspect consequences, imparting a unique method to overcoming the restrictions of traditional chemotherapy [13].

The aim of this study is showing the potential of integration of DOX and Ph-senstive polymer in cancer treatment.

This evaluation will explore the mechanisms of movement, design, and synthesis of dual pH-sensitive polymers for DOX delivery, and their capacity packages in focused cancer therapy.

MECHANISMS AND CHALLENGES OF DOXORUBICIN

Mechanism of Action

Doxorubicin, by C_{27} H_{29} NO_{11} chemical formula (Fig. 1 showed chemical structure of it) is a cornerstone chemotherapeutic agent widely used inside the treatment of numerous cancers, including breast cancers, leukemia, and sarcomas [14]. It is efficacy stems from its multifaceted mechanisms of action, which consist of DNA Intercalation, Topoisomerase II Inhibition, and ROS generation [15].

DOX intercalates among DNA base pairs, disrupting the double helix structure and inhibiting DNA replication and transcription. This intercalation efficiently halts the progression of the enzyme DNA polymerase along the DNA strand, for this reason preventing the duplication and transcription of genetic fabric essential for cell division and survival. additionally, the intercalation distorts the helical shape of DNA, interfering with the binding of crucial transcription factors and regulatory proteins, thereby impairing important cell techniques [16].

DOX stabilizes the DNA-topoisomerase II complicated, stopping the re-ligation of DNA strands, leading to double-strand breaks. these breaks are irreparable with the aid of the cellular's equipment, triggering apoptosis [17]. Topoisomerase II is important for assuaging the torsional stress during DNA replication and transcription, and its inhibition ends in deadly DNA damage [18]. This interruption in the regular characteristic of topoisomerase II results inside the accumulation of DNA harm signals, prompting cellular cycle arrest and initiation of apoptotic pathways [19].

DOX induces oxidative stress by producing reactive oxygen species (ROS), which harm cell additives, consisting of lipids, proteins, and DNA. This oxidative strain contributes to cell dying through the induction of apoptosis [20]. The generation of ROS additionally disrupts mitochondrial feature, similarly improving the apoptotic cascade. The immoderate ROS manufacturing effects in lipid peroxidation, leading to membrane harm, lack of membrane integrity, and the eventual launch of seasoned-apoptotic elements from mitochondria, amplifying the cytotoxic effect of DOX [21].

Challenges in Current Delivery Methods

Despite its potent anticancer activity, DOX therapy is associated with significant limitations such as Systemic Toxicity, Multidrug Resistance (MDR), and Poor Tumor Selectivity [22]. DOX accumulates in non-target tissues, in particular the heart, leading to dose-dependent cardiotoxicity. chronic administration frequently results in irreversible cardiac damage, including congestive heart failure [23]. The cardiotoxic effects are more often than not because of the era of ROS and next oxidative harm to cardiac myocytes [24]. This oxidative strain impairs mitochondrial feature in heart cells, inflicting cellular electricity depletion and triggering cardiomyocyte apoptosis. additionally, DOX interferes with calcium homeostasis in cardiomyocytes, exacerbating cardiac disorder [25].

Tumor cells regularly increase resistance to DOX through mechanisms such as overexpression of efflux transporters (e.g., P-glycoprotein), reducing intracellular drug concentrations. MDR substantially reduces the efficacy of DOX, necessitating better doses that growth the hazard of systemic toxicity [26]. Moreover, alterations in drug target molecules and more suitable DNA repair mechanisms contribute to MDR. Tumor cells adapt by using upregulating detoxifying enzymes and efflux pumps, which actively delivery DOX out of cells, lowering its intracellular accumulation and therapeutic efficacy. this adaptability of most

cancers cells poses a prime hurdle in attaining sustained responses to DOX remedy [27].

The nonspecific distribution of DOX limits its therapeutic efficacy, necessitating high doses that exacerbate side outcomes. DOX's lack of ability to differentiate among healthy and cancerous cells leads to enormous collateral damage, resulting in excessive facet outcomes along with myelosuppression, mucositis, and nephrotoxicity [28]. The non-selective nature of DOX's cytotoxicity impacts hastily dividing ordinary cells, along with those within the bone marrow, gastrointestinal tract, and hair follicles, leading to debilitating unfavourable outcomes that considerably impact the excellent of life of patients undergoing treatment [29]. These challenges underscore the urgent need for superior drug transport systems which can enhance the healing index of DOX while minimizing its adverse consequences. progressive methods inclusive of dual pH-senstive polymeric nanoparticles keep promise in addressing these obstacles by improving the selective transport of DOX to tumor cells, as a consequence improving its efficacy and reducing systemic toxicity [30]. These nanoparticles can be engineered to respond to the acidic tumor microenvironment, ensuring that DOX is released primarily at the tumor site, thereby sparing healthful tissues and lowering systemic aspect effects. moreover, using concentrated on ligands on the surface of nanoparticles can further enhance the specificity and uptake of DOX by cancer cells, overcoming MDR and enhancing therapeutic outcomes [31].

DUAL pH-SENSITIVE POLYMERS

Overview of pH-Sensitive Polymers

pH-sensitive polymers are engineered materials designed to respond dynamically to pH modifications in their surroundings. these polymers usually consist of acid-labile bonds or ionizable functional agencies that enable structural adjustments, solubility alterations, or degradation in reaction to acidic conditions determined in pathological sites consisting of tumors [32].

Key characteristics of pH-sensitive polymers include stability at Physiological pH (7.4), Degradation in Acidic Environments (pH 6.5–5.0), and Biocompatibility and Biodegradability [33].

To prevent premature drug release, these polymers are engineered to remain stable within the neutral pH of systemic move. This balance guarantees that the therapeutic agents they carry reach the target site intact [34].

The polymers degrade or go through considerable structural transformations in the mildly acidic extracellular matrix of tumors (pH ~6.5) and even more acidic intracellular compartments (pH ~four.5-5.5) such as endosomes and lysosomes. This degradation triggers the release of the encapsulated drug directly on the site of interest, enhancing therapeutic efficacy and decreasing systemic side results [35].

For scientific applications, it is crucial that these polymers are biocompatible to avoid immune reactions and biodegradable to prevent accumulation in the body, thereby reducing long-term toxicity [36].

Design and Synthesis of Dual pH-Sensitive Polymers

Dual pH-sensitive structures are advanced constructs that combine two distinct pH-responsive mechanisms, providing a hierarchical and specific drug launch profile. these systems make certain that the drug release is finely tuned to the particular pH landscapes encountered in the tumor microenvironment and intracellular organelles [37]. Design features included Outer Layer and inner core.

Outer Layer is attentive to the mildly acidic extracellular pH (~6.5–7.0) of the tumor microenvironment. This initial responsiveness targets the drug-loaded nanoparticles to the tumor site, initiating the drug release method [38].

Inner core is responsive to the relatively acidic intracellular pH (~4.5–5.5) within endosomes or lysosomes. This secondary response ensures that the drug is released inside the cancer cells, enhancing the therapeutic impact [39].

Synthetic methods included some types like Polymer blending, Covalent Bonding, and surface Functionalization [40]. Polymer blending technique involves combining or more polymers with different pH sensitivities to obtain a dual-response profile. as an instance, mixing a polymer that degrades at pH 6.5 with another that degrades at pH 5.0 can offer a step-smart drug release mechanism [41]. Covalent Bonding incorporating acid-labile linkages along with hydrazone, imine, or orthoester bonds within the polymer backbone is a common approach. These bonds are stable at neutral pH but hydrolyze in acidic situations, leading to polymer degradation and subsequent drug release [42].

Surface Functionalization of nanoparticles

may be functionalized with concentrated on ligands, including antibodies or peptides, precise to tumor markers. This not only enhances the targeting performance however also facilitates receptor-mediated endocytosis, thereby enhancing intracellular drug delivery [43]. Latest studies have established the efficacy of dual pH-sensitive polymer systems in improving the pharmacokinetics and pharmacodynamics of anticancer drugs like doxorubicin [44]. Advances in fabrication strategies consisting of emulsion polymerization, self-meeting, and click on chemistry have enabled the suitable manipulate of polymer structure and functionalization [45]. As an instance, emulsion polymerization permits for the manufacturing of uniform nanoparticles with controlled size and surface properties, improving their balance and bioavailability [46]. Self-assembly approaches enable the creation of complicated nanostructures which could encapsulate multiple therapeutic agents, presenting a multifaceted technique to cancer treatment [47]. Click chemistry offers a relatively specific and efficient method for introducing functional groups into polymers, enhancing their focused on and release characteristics [48]. These advancements in the design and synthesis of dual pH-sensitive polymers hold remarkable promise for the future of targeted cancer therapy, potentially overcoming the limitations of traditional chemotherapeutic tactics with the aid of providing a greater precise, and more secure drug delivery system [49]. By leveraging the particular pH gradients in the tumor microenvironment and intracellular compartments, these innovative systems can considerably enhance the healing index of medication like doxorubicin, providing a effective tool in the fight against cancer [50].

MECHANISMS OF ACTION

pH-Responsive Drug Release

The mechanism of drug release in dual pH-sensitive systems entails a precisely controlled, multi-step process that ensures maximal therapeutic efficacy while minimizing systemic toxicity [51].

1.Extracellular Triggering, the mildly acidic tumor microenvironment (TME) with a pH range of 6.5–7.0 initiates the destabilization of the outer layer of the nanoparticle. This outer layer is often composed of materials which includes poly (ethylene glycol) (PEG) that can shield the inner core in the neutral pH of systemic stream however turn out to be destabilized under mildly acidic conditions [52]. The improved permeability and retention (EPR) effect, a phenomenon in which nanoparticles preferentially collect in tumor tissues due to the leaky vasculature, similarly aids in targeting the nanoparticles to the tumor site. This preliminary destabilization exposes the inner core of the nanoparticle, which is designed to respond to even extra acidic conditions within the tumor cells [53].

2.Intracellular Activation that Upon internalization through cancer cells via mechanisms including endocytosis, the nanoparticles are transported to the endosomes and lysosomes, wherein the pH is markedly acidic (4.5–5.5) [54]. This acidic environment triggers the degradation of acid-labile bonds, such as hydrazone or imine linkages, or induces the ionization of polymer organizations in the inner core [55]. The rapid degradation or swelling of the inner core facilitates the release of the encapsulated drug, doxorubicin (DOX), directly into the cytoplasm of cancer cells. This targeted release maximizes the concentration of DOX on the site of action, improving its cytotoxic effects on the tumor cells whilst minimizing exposure to healthy tissues [56].

The hierarchical pH-responsive mechanism ensures minimal drug leakage during systemic circulation, thereby improving specificity and therapeutic efficacy. This controlled release profile is pivotal in enhancing the pharmacokinetics and pharmacodynamics of DOX, taking into consideration extra effective cancer treatment with decreased side effects [57].

Targeting Tumor Microenvironment

The tumor microenvironment (TME) is characterized by means of numerous wonderful features that contribute to cancer development and resistance to remedy, which include hypoxia, acidic pH, and a dense extracellular matrix. dual pH-senstive nanoparticles are uniquely prepared to exploit those features for effective drug delivery [58].

1. Exploiting Acidic conditions, The acidic extracellular pH in the TME turns on the drug launch mechanism of the nanoparticles, ensuring that the therapeutic agents are released preferentially on the tumor site online. This selective activation spares everyday tissues from exposure to high drug concentrations, as a result

reducing systemic toxicity and side outcomes. via leveraging the pH gradients, those nanoparticles can attain higher local drug concentrations within the tumor, improving therapeutic efficacy [59].

2. Improving Penetration, Nanoparticles with optimized sizes, typically less than 100 nm, and surface modifications, such as PEGylation or focused on ligands, can penetrate deep into tumor tissues. this is critical for bypassing the physical barriers posed via the dense extracellular matrix, which frequently impedes the transport of traditional drugs. more suitable tumor penetration ensures that the drug reaches all areas of the tumor, including hypoxic areas that are typically resistant to therapy [60]. Hypoxia in the TME is a major contributor to chemoresistance, because it induces the expression of diverse survival pathways in cancer cells. via localizing drug release to the TME, dual pH-sensitive structures can mitigate the outcomes of hypoxia. The elevated concentration of DOX in hypoxic areas can overcome resistance mechanisms and induce apoptosis in those otherwise resilient cancer cells [61]. Additionally, the capability to hold effective drug levels within the TME enables to disrupt the supportive interactions among cancer cells and their microenvironment, in addition enhancing the healing outcome [62]. Dual pH-sensitive structures can also be engineered to carry multiple therapeutic dealers, allowing mixture treatments that target multiple pathways simultaneously. As an example, co-delivery of DOX with different chemotherapeutic agents, immune modulators, or gene therapy vectors within the same nanoparticle can provide a complete attack at the tumor, addressing both the cancer cells and the supportive TME [63]. The development and alertness of dual pH-sensitive polymer nanoparticles constitute a promising frontier in targeted most cancers remedy, supplying a strategic benefit in the precise and effective delivery of chemotherapeutics like doxorubicin. persevered studies and scientific validation are crucial to completely realize their capability and integrate these advanced structures into standard oncological practices.

PRECLINICAL AND CLINICAL STUDIES

Jin-Shi Du et al [64], designed dual pH-sensitive polymer–drug conjugate nanoparticulate device to triumph over the challenges. The nanoparticle is able to reversing its surface charge from negative to wonderful at tumor extracellular pH (∼6.8) to facilitate cell internalization. subsequently, the substantially increased acidity in subcellular compartments such as the endosome (∼5.0) similarly promotes doxorubicin release from the endocytosed drug vendors. This dual pH-sensitive nanoparticle has showed enhanced cytotoxicity in drug-resistant cancer stem cells, indicating its amazing capability for cancer therapy.

Wanxian Luo et al [65], investigated the capacity of a dual-targeted pH-sensitive doxorubicin prodrug-microbubble complicated (DPMC) in ultrasound (US)-assisted antitumor therapy. The doxorubicin prodrug (DP) includes a succinylated-heparin carrier conjugated with doxorubicin (DOX) thru hydrazone linkage and decorated with dual targeting ligands, folate and cRGD peptide. mixture of microbubble (MB) and DP, generated through avidin-biotin binding, promoted intracellular accumulation and progressed therapeutic efficiency assisted via US cavitation and sonoporation. Aggregates of prepared DP have been found with an inhomogeneous size distribution (common diameters: 149.6±29.8 nm and 1036.2±38.eight nm, PDI: 1.0) whilst DPMC exhibited a uniform distribution (average diameter: five.804±2.1 μm), facilitating its utilization for drug delivery. notably, upon US exposure, DPMC was disrupted and aggregated DP dispersed into homogeneous small-sized nanoparticles (average diameter: 128.6±42.3 nm, PDI: 0.21). DPMC could target to angiogenic endothelial cells in tumor location thru αvβ3-mediated recognition and eventually facilitate its specific binding to tumor cells mediated through popularity of folate receptor (FR) after US exposure. In vitro experiments showed higher tumor specificity and killing capability of DPMC with US than loose DOX and DP for breast most cancers MCF-7 cells. furthermore, significant accumulation and specificity for tumor tissues of DPMC with US were detected using in vivo fluorescence and ultrasound molecular imaging, indicating its capability to integrate tumor imaging and therapy. in particular, via inducing apoptosis, inhibiting cell proliferation and antagonizing angiogenesis, DPMC with US produced better tumor inhibition rates than DOX or DPMC with out US in MCF-7 xenograft tumor-bearing mice while inducing no obvious body weight loss. this strategy provides an effective platform for the delivery of large-sized or aggregated particles to tumor sites,

thereby extending their therapeutic applications in vivo.

Wei Xiong et al [66], studied dual temperature/pH-sensitive poly(N-isopropylacrylamide-co-acrylic acid) nanogel (PNA) was prepared and applied as a drug carrier. The anti-cancer drug doxorubicin (DOX) turned into covalent sure to PNA thru an acid-labile hydrazone linkage. DOX–PNA conjugates had a pH-dependent LCST, which changed into 41 °C and 43 °C at pH 5.3 and 6.8 respectively, but higher than 50 °C at pH 7.4. The nanogels which were hydrophilic under LCST and changed to hydrophobic state above LCST possessed dual pH/temperature established cellular uptake and cytotoxicity. With increasing temperature, the cell uptake of DOX–PNA was nearly no distinction at pH 7.4, but enhanced approximately 43% at pH 6.8. So the cytotoxicity of DOX–PNA additionally increased in higher temperature and decrease pH value. It changed into able to distinguish tumor extracellular pH from physiological pH under hyperthermia of 43 °C, suggesting a great ability for anti-cancer therapy.

Lu Zhng et al [67], synthesized a prodrug copolymer mPEG-PAsp(DIP-co-BZA-co-DOX) (PDBD) turned into and assembled into a nanoscale vesicle comprising a PEG corona, a reduction and pH dual-sensitive hydrophobic membrane and an aqueous lumen encapsulating doxorubicin hydrochloride (DOX·HCl) and arsenite (As). The dual stimulation-sensitive design of the vesicle gave rise to rapid release of the physically entrapped DOX·HCl and arsenite inner acidic lysosomes, and chemically conjugated DOX inside the cytosol with excessive glutathione (GSH) attention. in the optimized attention range, arsenite previously identified as a promising anticancer agent from traditional chinese medication can down-regulate the expressions of anti-apoptotic and multidrug resistance proteins to sensitize cancer cells to chemotherapy. therefore, the DOX-As-co-loaded vesicle demonstrated potent anticancer activity. as compared to the most effective DOX-loaded vesicle, the DOX-As-co-loaded one induced more than twice the apoptotic ratio of MCF-7/ADR breast cancer cells at a low As concentration (0.5 μM), due to the synergistic consequences of DOX and As. The drug loading strategy integrating chemical conjugation and physical encapsulation in stimulation-sensitive companies enabled efficient drug loading in the system.

Xiuwen Guan et al [68], Designed a novel pH-touchy rate-conversion protecting system, by using the electrostatic binding of polyethylenimine (PEI)-poly(l-lysine)-poly(l-glutamic acid) (PELG), PEI, and cis-aconityl-doxorubicin (CAD). Doxorubicin (DOX) was modified by means of cis-aconityl linkage to form acid-sensitive CAD, which was then adsorbed via the definitely charged PEI. The PEI/CAD complexes have been subsequently shielded with the pH-responsive fee-conversion PELG. In everyday tissues, the PELG/PEI/CAD complexes had been negatively charged; in acidic tumor tissues, the shielding PELG was definitely charged and detached from the PELG/PEI/CAD complexes. The resulting definitely charged PEI/CAD complexes as a result became uncovered and have been endocytosed. CAD became then cleaved within the acidic intracellular environment of endosomes and lysosomes, and converted again into DOX. The charge reversal of the PELG/PEI/CAD complexes turned into proven by using zeta ability analysis at extraordinary pH values. moreover, DOX release multiplied with decreasing pH. cellular uptake and confocal laser scanning microscopy analyses showed that, at pH 6.8, PELG/PEI/CAD had the very best endocytosis price and greater DOX entered cell nuclei. more importantly, the gadget confirmed great cytotoxicity in opposition to most cancers cells. these consequences revealed that the aggregate of pH-sensitive price-conversion shielding with pH-sensitive drug release is a ability drug shipping system for tumor treatment.

CONCLUSION

The improvement of dual pH-sensitive polymer nanoparticles represents a significant advancement in the discipline of centered most cancers therapy, specially for the delivery of doxorubicin (DOX). these sophisticated delivery systems leverage the particular acidic environments of the tumor microenvironment (TME) and intracellular booths to acquire specific and managed drug launch. The dual pH-responsive mechanism ensures that DOX is released frequently at the tumor site, minimizing systemic toxicity and enhancing therapeutic efficacy. This targeted technique addresses main challenges related to traditional DOX therapy, such as systemic toxicity, multidrug resistance (MDR), and negative tumor selectivity. By exploiting the pH gradients in the TME and intracellular organelles, dual pH-sensitive polymer nanoparticles decorate drug accumulation in tumors, enhance

penetration into tumor tissues, and mitigate hypoxia-induced resistance. These advantages translate into advanced remedy consequences, along with increased tumor suppression and decreased side consequences. the integration of biocompatibility and biodegradability within the design of those polymers in addition supports their potential for scientific application. The future of dual pH-sensitive polymer nanoparticles in cancer therapy is promising, with several areas of ongoing studies and improvement, enhanced targeting capabilities, destiny studies will focus on enhancing the specificity of those nanoparticles through incorporating superior concentrated on ligands. These ligands could consist of antibodies, peptides, or small molecules that apprehend and bind to tumor-specific antigens, thereby improving the selective delivery of DOX to cancer cells. Multifunctional Nanoparticles, The development of multifunctional nanoparticles which can simultaneously deliver multiple therapeutic agents or combine therapeutic and diagnostic capabilities (theranostics) is an thrilling location of studies. these multifunctional structures could offer synergistic results, improving the general efficacy of most cancers treatment. Combination therapies, dual pH-sensitive polymer nanoparticles can be used to co-deliver DOX with other chemotherapeutic agents, immune modulators, or gene remedy vectors. This technique has the capacity to overcome resistance mechanisms and provide a comprehensive attack on the tumor. Personalized medicine, Advances in nanotechnology and genomics could permit the customization of dual pH-senstive polymer nanoparticles for character sufferers based on their genetic and molecular profiles. personalized nanoparticles could optimize remedy efficacy and decrease adverse effects, aligning with the principles of precision medicine. In conclusion, dual pH-sensitive polymer nanoparticles hold wonderful promise for revolutionizing cancer remedy by way of improving the delivery and efficacy of doxorubicin. continued studies and scientific validation will be crucial to fully comprehend their capacity and combine these advanced structures into routine cancer treatent, in the end improving affected person outcomes and quality of life.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Review for "Upper Tract Urinary Carcinoma: A Unique Immuno-Molecular Entity and a Clinical Challenge in the Current Therapeutic Scenario". SAGE Publications; 2023.
2. Compton C. Systemic Therapy for Cancer. Cancer: The Enemy from Within: Springer International Publishing; 2020. p. 223-257.
3. Ibrahim AA, Nsairat H, Al-Sulaibi M, El-Tanani M, Jaber AM, Lafi Z, et al. Doxorubicin conjugates: a practical approach for its cardiotoxicity alleviation. Expert Opinion on Drug Delivery. 2024;21(3):399-422.
4. Review for "Recent developments in photodynamic therapy and its application against multidrug resistant cancers". IOP Publishing; 2023.
5. Pradeep Prabhu P, Mohanty B, Lobo CL, Balusamy SR, Shetty A, Perumalsamy H, et al. Harnessing the nutriceutics in early-stage breast cancer: mechanisms, combinational therapy, and drug delivery. Journal of nanobiotechnology. 2024;22(1):574-574.
6. Deshmukh R, Sethi P, Singh B, Shiekmydeen J, Salave S, Patel RJ, et al. Recent Review on Biological Barriers and Host-Material Interfaces in Precision Drug Delivery: Advancement in Biomaterial Engineering for Better Treatment Therapies. Pharmaceutics. 2024;16(8):1076.
7. Hypoxia-Responsive, Polymeric Nanocarriers for Targeted Drug Delivery to Estrogen Receptor-Positive Breast Cancer Cell Spheroids. American Chemical Society (ACS).
8. Chaudhary B, Kumar P, Arya P, Singla D, Kumar V, Kumar D, et al. Recent Developments in the Study of the Microenvironment of Cancer and Drug Delivery. Curr Drug Metab. 2022;23(13):1027-1053.
9. Zhao X, Bai J, Yang W. Stimuli-responsive nanocarriers for therapeutic applications in cancer. Cancer biology & medicine. 2021;18(2):319-335.
10. Peppicelli S, Calorini L, Bianchini F, Papucci L, Magnelli L, Andreucci E. Acidity and hypoxia of tumor microenvironment, a positive interplay in extracellular vesicle release by tumor cells. Cell Oncol. 2024.
11. Justus CR, Dong L, Yang LV. Acidic tumor microenvironment and pH-sensing G protein-coupled receptors. Front Physiol. 2013;4:354-354.
12. Madhu CR, Patel BH. pH-Sensitive Polymers with their Important Applications (A Review). Current Physical Chemistry. 2024;14(2):93-115.
13. Kaushik A, Khan S, Pharasi N, Mani S. Dual pH and ultrasound responsive nanocarriers: A smart approach in cancer theranostics. J Drug Deliv Sci Technol. 2024;95:105560.
14. Lao J, Madani J, Puértolas T, Alvarez M, Hernández A, Pazo-Cid R, et al. Liposomal Doxorubicin in the treatment of breast cancer patients: a review. Journal of drug delivery. 2013;2013:456409-456409.
15. Sharma NK, Bahot A, Sekar G, Bansode M, Khunteta K, Sonar PV, et al. Understanding Cancer's Defense against Topoisomerase-Active Drugs: A Comprehensive Review. Cancers (Basel). 2024;16(4):680.
16. Rivankar S. An overview of doxorubicin formulations in cancer therapy. J Cancer Res Ther. 2014;10(4):853.
17. Sinha BK. Cracking the Code: Understanding Cancer's Defense against Topoisomerase-Active Drugs: A

Comprehensive Review. MDPI AG; 2023.
18. O'Driscoll M. Diseases associated with defective responses to DNA damage. Cold Spring Harb Perspect Biol. 2012;4(12):a012773.
19. Kciuk M, Gielecińska A, Mujwar S, Kołat D, Kałuzińska-Kołat Ż, Celik I, et al. Doxorubicin-An Agent with Multiple Mechanisms of Anticancer Activity. Cells. 2023;12(4):659.
20. Rawat PS, Jaiswal A, Khurana A, Bhatti JS, Navik U. Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. Biomedicine & Pharmacotherapy. 2021;139:111708.
21. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. The Journal of Immunology. 1997;158(8):3902-3908.
22. Majidinia M, Mirza-Aghazadeh-Attari M, Rahimi M, Mihanfar A, Karimian A, Safa A, et al. Overcoming multidrug resistance in cancer: Recent progress in nanotechnology and new horizons. IUBMB Life. 2020;72(5):855-871.
23. Su X, Zhang X, Liu W, Yang X, An N, Yang F, et al. Advances in the application of nanotechnology in reducing cardiotoxicity induced by cancer chemotherapy. Semin Cancer Biol. 2022;86:929-942.
24. Nagy A, Börzsei D, Hoffmann A, Török S, Veszelka M, Almási N, et al. A Comprehensive Overview on Chemotherapy-Induced Cardiotoxicity: Insights into the Underlying Inflammatory and Oxidative Mechanisms. Cardiovasc Drugs Ther. 2024.
25. Wenningmann N, Knapp M, Ande A, Vaidya TR, Ait-Oudhia S. Insights into Doxorubicin-induced Cardiotoxicity: Molecular Mechanisms, Preventive Strategies, and Early Monitoring. Mol Pharmacol. 2019;96(2):219-232.
26. Micallef I, Baron B. The Mechanistic Roles of ncRNAs in Promoting and Supporting Chemoresistance of Colorectal Cancer. Non-coding RNA. 2021;7(2):24.
27. Khalili-Tanha G, Moghbeli M. Long non-coding RNAs as the critical regulators of doxorubicin resistance in tumor cells. Cell Mol Biol Lett. 2021;26(1):39-39.
28. Lin J, Shigdar S, Fang DZ, Xiang D, Wei MQ, Danks A, et al. Improved efficacy and reduced toxicity of doxorubicin encapsulated in sulfatide-containing nanoliposome in a glioma model. PLoS One. 2014;9(7):e103736-e103736.
29. Ajaykumar C. Overview on the Side Effects of Doxorubicin. Advances in Precision Medicine Oncology: IntechOpen; 2021.
30. Farhoudi L, Hosseinikhah SM, Kazemi-Beydokhti A, Arabi L, Alavizadeh SH, Moosavian SA, et al. pH-sensitive polymeric micelles enhance the co-delivery of doxorubicin and docetaxel: an emerging modality for treating breast cancer. Cancer Nanotechnol. 2024;15(1).
31. Tian H, Zhang T, Qin S, Huang Z, Zhou L, Shi J, et al. Enhancing the therapeutic efficacy of nanoparticles for cancer treatment using versatile targeted strategies. J Hematol Oncol. 2022;15(1):132-132.
32. Gomte SS, Agnihotri TG, Khopade S, Jain A. Exploring the potential of pH-sensitive polymers in targeted drug delivery. J Biomater Sci Polym Ed. 2023;35(2):228-268.
33. Lou H, Fang H, Wang T, Wang D, Han Q, Zhou W, et al. Biodegradable Porous Polymeric Drug with pH-Stimuli-Responsive Delivery Capacity for Combined Cancer Therapy. ACS Applied Polymer Materials. 2021;4(1):714-724.
34. Tao Y, Liu S, Zhang Y, Chi Z, Xu J. A pH-responsive polymer based on dynamic imine bonds as a drug delivery material with pseudo target release behavior. Polymer Chemistry. 2018;9(7):878-884.
35. Binauld S, Stenzel MH. Acid-degradable polymers for drug delivery: a decade of innovation. Chemical Communications. 2013;49(21):2082.
36. Elmowafy EM, Tiboni M, Soliman ME. Biocompatibility, biodegradation and biomedical applications of poly(lactic acid)/poly(lactic-co-glycolic acid) micro and nanoparticles. Journal of Pharmaceutical Investigation. 2019;49(4):347-380.
37. Chen H, Kuang Y, Liu R, Chen Z, Jiang B, Sun Z, et al. Dual-pH-sensitive mesoporous silica nanoparticle-based drug delivery system for tumor-triggered intracellular drug release. Journal of Materials Science. 2018;53(15):10653-10665.
38. Li R, Xie Y. Nanodrug delivery systems for targeting the endogenous tumor microenvironment and simultaneously overcoming multidrug resistance properties. Journal of Controlled Release. 2017;251:49-67.
39. Chen WH, Luo GF, Zhang XZ. Recent Advances in Subcellular Targeted Cancer Therapy Based on Functional Materials. Adv Mater. 2018;31(3).
40. Khulbe KC, Feng C, Matsuura T. The art of surface modification of synthetic polymeric membranes. J Appl Polym Sci. 2009;115(2):855-895.
41. Bhattacharya S, Prajapati BG, Singh S. A critical review on the dissemination of PH and stimuli-responsive polymeric nanoparticular systems to improve drug delivery in cancer therapy. Critical Reviews in Oncology/Hematology. 2023;185:103961.
42. Patra D, Basheer B, Shunmugam R. pH-Responsive Materials: Properties, Design, and Applications. ACS Symposium Series: American Chemical Society; 2023. p. 145-179.
43. Sanità G, Carrese B, Lamberti A. Nanoparticle Surface Functionalization: How to Improve Biocompatibility and Cellular Internalization. Frontiers in molecular biosciences. 2020;7:587012-587012.
44. Singh J, Nayak P. <scp>pH</scp>-responsive polymers for drug delivery: Trends and opportunities. J Polym Sci. 2023;61(22):2828-2850.
45. Moradi R, Aliyev A. Functionalized nanofibers for the realization of superhydrophobic surfaces. Functionalized Nanofibers: Elsevier; 2023. p. 329-367.
46. Generalova AN, Zubov VP. Design of polymer particle dispersions (latexes) in the course of radical heterophase polymerization for biomedical applications. Colloids Surf B Biointerfaces. 2018;166:303-322.
47. Wang J, Li Y, Nie G. Multifunctional biomolecule nanostructures for cancer therapy. Nature reviews Materials. 2021;6(9):766-783.
48. Lallana E, Sousa-Herves A, Fernandez-Trillo F, Riguera R, Fernandez-Megia E. Click Chemistry for Drug Delivery Nanosystems. Pharm Res. 2011;29(1):1-34.
49. Chen Z, Wang X, Zhao N, Chen H, Guo G. Advancements in pH-responsive nanocarriers: enhancing drug delivery for tumor therapy. Expert Opinion on Drug Delivery. 2023;20(11):1623-1642.
50. Liu M, Du H, Zhang W, Zhai G. Internal stimuli-responsive nanocarriers for drug delivery: Design strategies and applications. Materials Science and Engineering: C. 2017;71:1267-1280.

51. Yang T, Wu Z, Wang P, Mu T, Qin H, Zhu Z, et al. A large-inner-diameter multi-walled carbon nanotube-based dual-drug delivery system with pH-sensitive release properties. Journal of Materials Science: Materials in Medicine. 2017;28(7).
52. Kanamala M, Wilson WR, Yang M, Palmer BD, Wu Z. Mechanisms and biomaterials in pH-responsive tumour targeted drug delivery: A review. Biomaterials. 2016;85:152-167.
53. Kalyane D, Raval N, Maheshwari R, Tambe V, Kalia K, Tekade RK. Employment of enhanced permeability and retention effect (EPR): Nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer. Materials Science and Engineering: C. 2019;98:1252-1276.
54. Wang D, Zhou Y, Li X, Qu X, Deng Y, Wang Z, et al. Mechanisms of pH-Sensitivity and Cellular Internalization of PEOz-b-PLA Micelles with Varied Hydrophilic/Hydrophobic Ratios and Intracellular Trafficking Routes and Fate of the Copolymer. ACS Applied Materials and Interfaces. 2017;9(8):6916-6930.
55. Deirram N, Zhang C, Kermaniyan SS, Johnston APR, Such GK. pH-Responsive Polymer Nanoparticles for Drug Delivery. Macromol Rapid Commun. 2019;40(10).
56. Bisht A, Avinash D, Sahu KK, Patel P, Das Gupta G, Kurmi BD. A comprehensive review on doxorubicin: mechanisms, toxicity, clinical trials, combination therapies and nanoformulations in breast cancer. Drug Delivery and Translational Research. 2024.
57. Kalaydina R-V, Bajwa K, Qorri B, Decarlo A, Szewczuk MR. Recent advances in "smart" delivery systems for extended drug release in cancer therapy. International journal of nanomedicine. 2018;13:4727-4745.
58. Efthimiadou EK, Theodosiou M, Toniolo G, Abu-Thabit NY. Stimuli-responsive biopolymer nanocarriers for drug delivery applications. Stimuli Responsive Polymeric Nanocarriers for Drug Delivery Applications, Volume 1: Elsevier; 2018. p. 405-432.
59. Du J, Lane LA, Nie S. Stimuli-responsive nanoparticles for targeting the tumor microenvironment. Journal of controlled release : official journal of the Controlled Release Society. 2015;219:205-214.
60. Suk JS, Xu Q, Kim N, Hanes J, Ensign LM. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. Adv Drug Del Rev. 2016;99(Pt A):28-51.
61. Sa P, Sahoo SK, Dilnawaz F. Responsive Role of Nanomedicine in the Tumor Microenvironment and Cancer Drug Resistance. Curr Med Chem. 2023;30(29):3335-3355.
62. Sun Y. Tumor microenvironment and cancer therapy resistance. Cancer Lett. 2016;380(1):205-215.
63. Zhai L, Luo C, Gao H, Du S, Shi J, Wang F. A Dual pH-Responsive DOX-Encapsulated Liposome Combined with Glucose Administration Enhanced Therapeutic Efficacy of Chemotherapy for Cancer. International journal of nanomedicine. 2021;16:3185-3199.
64. Du J-Z, Du X-J, Mao C-Q, Wang J. Tailor-Made Dual pH-Sensitive Polymer–Doxorubicin Nanoparticles for Efficient Anticancer Drug Delivery. Journal of the American Chemical Society. 2011;133(44):17560-17563.
65. Luo W, Wen G, Yang L, Tang J, Wang J, Wang J, et al. Dual-targeted and pH-sensitive Doxorubicin Prodrug-Microbubble Complex with Ultrasound for Tumor Treatment. Theranostics. 2017;7(2):452-465.
66. Xiong W, Wang W, Wang Y, Zhao Y, Chen H, Xu H, et al. Dual temperature/pH-sensitive drug delivery of poly(N-isopropylacrylamide-co-acrylic acid) nanogels conjugated with doxorubicin for potential application in tumor hyperthermia therapy. Colloids Surf B Biointerfaces. 2011;84(2):447-453.
67. Zhang L, Xiao H, Li J, Cheng D, Shuai X. Co-delivery of doxorubicin and arsenite with reduction and pH dual-sensitive vesicle for synergistic cancer therapy. Nanoscale. 2016;8(25):12608-12617.
68. Guan X, Li Y, Jiao Z, Chen J, Guo Z, Tian H, et al. A pH-sensitive charge-conversion system for doxorubicin delivery. Acta Biomater. 2013;9(8):7672-7678.