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Dual pH/GSH-Responsive ZnO/SiO_2 Hybrid Nanoparticles for Targeted Doxorubicin Delivery in Breast Cancer Therapy :

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(Abstract)

Breast cancer remains one of the most prevalent malignancies among women worldwide, with chemotherapy continuing to play a major role in its clinical management. Despite its potent antitumor activity, the clinical application of doxorubicin (DOX) is limited by several challenges, including poor tumor selectivity, systemic toxicity, and dose-dependent cardiotoxicity. These limitations highlight the need for advanced drug delivery strategies that can improve therapeutic efficacy while minimizing adverse effects.

This study proposes a dual-responsive hybrid nanoplatform composed of zinc oxide (ZnO) and mesoporous silica (SiO_2) nanoparticles for the targeted delivery of doxorubicin to breast cancer cells. The proposed system is designed to exploit two characteristic features of the tumor microenvironment: acidic pH and elevated intracellular glutathione (GSH) levels. The platform combines the complementary properties of its two components, whereby mesoporous silica provides high drug-loading capacity, structural stability, and versatile surface functionalization, while zinc oxide contributes pH-responsive degradation and the generation of reactive oxygen species (ROS), potentially enhancing anticancer activity.

The anticipated findings suggest that integrating pH- and GSH-responsive mechanisms within a single nanoplatform may improve the controlled release of doxorubicin, minimize premature drug leakage during systemic circulation, and enhance intracellular drug delivery to breast cancer cells. Furthermore, the synergistic integration of ZnO and SiO_2 may provide complementary therapeutic benefits by combining efficient drug encapsulation with the intrinsic anticancer properties of zinc oxide. The discussion also highlights the potential therapeutic advantages of this hybrid system, alongside important challenges related to nanoparticle stability biodistribution, long-term biocompatibility, and large-scale manufacturing.

In conclusion, dual pH/GSH-responsive ZnO/SiO_2 hybrid nanoparticles represent a promising strategy for the development of targeted drug delivery systems for breast cancer treatment. Nevertheless, their therapeutic efficacy, biological safety, and clinical applicability require further validation through comprehensive in vitro and in vivo investigations before clinical translation can be considered.

Keywords: Breast cancer; Doxorubicin; Hybrid nanoparticles; Zinc oxide; Silica nanoparticles; pH-sensitive drug delivery; Glutathione-responsive release; Targeted chemotherapy.

Introduction

Breast cancer is one of the most frequently diagnosed malignancies and remains one of the leading causes of cancer-related deaths among women worldwide. Despite significant advances in early diagnosis and therapeutic strategies, chemotherapy continues to represent a fundamental component of breast cancer treatment [1,2].

Doxorubicin (DOX) is widely used due to its potent antitumor activity. However, its clinical application is limited by its poor selectivity toward cancer cells, systemic toxicity, dose-dependent cardiotoxicity, and the development of multidrug resistance (MDR). These challenges highlight the urgent need to develop more efficient and targeted drug delivery systems.

Nanotechnology has revolutionized cancer treatment by enabling the development of nanoscale drug delivery systems that improve drug solubility, prolong circulation time, and enhance drug accumulation within tumors through the enhanced permeability and retention (EPR) effect. Furthermore, these systems may reduce drug-induced toxicity in non-target tissues [3].

Among the various nanocarriers investigated, hybrid nanoparticles have attracted increasing attention because of their ability to combine the distinctive properties of multiple materials within a single functional platform, potentially overcoming the limitations associated with the use of each component individually.

Research Gap

Despite remarkable progress in nanotechnology-based drug delivery systems, significant research gaps remain in the development of effective and clinically applicable hybrid carriers for breast cancer treatment. Most studies have focused on nanoparticles responsive to a single stimulus or based on individual materials, whereas the integration of multiple response mechanisms such as pH and glutathione (GSH) within a ZnO/SiO_2 hybrid platform remains relatively limited.

ZnO nanoparticles, although exhibiting anticancer activity and pH-responsive behavior, may suffer from uncontrolled degradation and potential toxicity, necessitating further optimization. Similarly silica nanoparticles provide excellent drug-loading capacity and biocompatibility yet their therapeutic effect relies primarily on drug delivery rather than intrinsic anticancer activity. Rationally combining ZnO and SiO_2 could overcome these limitations by offering synergistic therapeutic effects.

Moreover, few studies have comprehensively addressed drug release mechanisms, biodistribution, long-term safety, and biological interactions of ZnO/SiO_2 hybrid nanoparticles, particularly in the context of dual pH- and GSH-responsive delivery of doxorubicin for breast cancer. Therefore, extensive in vitro and in vivo investigations are required to evaluate their efficacy, toxicity profile, and clinical potential.

The tumor microenvironment plays a critical role in cancer progression and therapeutic response. It consists of cancer cells, immune cells, fibroblasts, blood vessels, and the extracellular matrix. [4]. This environment is characterized by relatively low acidity and elevated intracellular glutathione (GSH) levels compared to normal tissues, resulting from metabolic dysregulation in cancer cells. These physiological features have been exploited to design smart drug delivery systems responsive to both pH and GSH, enabling selective drug release inside cancer cells while minimizing toxicity to healthy tissues. Therefore, the tumor microenvironment represents an ideal biological target for the development of dual-responsive ZnO/SiO_2 hybrid nanoparticles for doxorubicin [5.6]. delivery in breast cancer treatment .

Doxorubicin in Breast Cancer

Doxorubicin (DOX) is one of the most effective chemotherapeutic agents used in breast cancer treatment. Its anticancer activity is mediated through DNA intercalation, inhibition of topoisomerase II, and generation of reactive oxygen species (ROS), ultimately leading to cancer cell death.. However, its clinical application is restricted due to severe cardiotoxicity, systemic side effects, and the emergence of drug resistance .To overcome these limitations, nanoparticle-based drug delivery systems have been developed to improve tumor targeting, enhance controlled drug release, and reduce toxicity to healthy tissues . Among these systems,. dual pH- and GSH-responsive ZnO/SiO_2 hybrid nanoparticles represent a promising platform for targeted doxorubicin delivery in breast cancer[2] therapy .

Properties of Zinc Oxide (ZnO) Nanoparticles

ZnO nanoparticles are characterized by a high surface area, good biocompatibility, and pH-sensitive behavior. In addition, they possess anticancer activity through the generation of reactive oxygen species (ROS) which induce oxidative stress and cancer cell death. .These properties make them an effective component in smart nanosystems, especially when combined with other carriers such as SiO_2. [8.9].

Properties of Mesoporous Silica (SiO_2) Nanoparticles

Mesoporous silica nanoparticles are distinguished by their large surface area, tunable pore size, and excellent structural stability. They provide a high drug-loading capacity with the possibility of functional surface modification to incorporate pH- or GSH-sensitive linkers, thereby enabling selective drug release within the tumor microenvironment. When combined with ZnO, they form a hybrid platform that integrates therapeutic efficacy with controlled drug release. [10.11.12]

Dual pH/GSH-Responsive Drug Delivery Systems

Stimuli-responsive drug delivery systems have emerged as an advanced strategy to improve the selectivity and efficacy of anticancer agents. Among the various endogenous triggers, acidic pH and elevated intracellular glutathione (GSH) levels are the most exploited for designing smart nanocarriers. Since the tumor microenvironment is characterized by low pH and significantly higher GSH concentrations compared to normal tissues, these physiological differences provide an opportunity for site-specific and controlled drug release.

- **pH-Responsive Systems:** Designed to remain stable under physiological conditions (pH 7.4), while releasing their therapeutic payload in the acidic tumor microenvironment or within endosomes and lysosomes (pH 5.0–6.5). This controlled release reduces premature drug leakage and enhances drug accumulation at the tumor site.
- **GSH-Responsive Systems:** Exploit the high intracellular glutathione concentration in cancer cells by incorporating redox-sensitive linkers such as disulfide bonds into the nanoparticle structure. Once internalized by cancer cells, these linkers are cleaved by GSH, leading to nanoparticle disassembly and intracellular drug release. [13.14]
- **Dual pH/GSH-Responsive Systems:** Integrate both mechanisms into a single platform, providing enhanced spatial and temporal control over drug release. This dual strategy improves targeted delivery, increases intracellular drug accumulation, reduces systemic toxicity, and may help overcome multidrug resistance. Consequently, dual-responsive nanocarriers have attracted significant attention as promising platforms for breast cancer therapy and other oncological applications .

ZnO/SiO_2 Hybrid Nanoparticles

Hybrid nanoparticles composed of zinc oxide (ZnO) and silica (SiO_2) have attracted considerable attention as advanced carriers for targeted drug delivery, owing to the complementary properties of zinc oxide and mesoporous silica.

The proposed integration of these two components into a single platform combines the high drug-loading capacity, structural stability, and excellent biocompatibility of silica with the pH-responsive degradability and intrinsic anticancer activity of zinc oxide.

This synergistic combination may improve the overall performance of nanocarriers for cancer treatment. Within the hybrid system, mesoporous silica acts as a drug reservoir, enabling the efficient encapsulation of chemotherapeutic agents such as doxorubicin (DOX).

In contrast, zinc oxide nanoparticles are proposed to provide pH-responsive behavior through their gradual degradation under acidic conditions, both in the tumor microenvironment and within endosomes and lysosomes. This degradation may facilitate controlled drug release.

Furthermore, the degradation of zinc oxide results in the release of zinc ions, which may promote the generation of reactive oxygen species (ROS) and enhance cancer cell death, potentially providing an additional therapeutic effect.

Proposed Hybrid System

The integration of ZnO nanoparticles with SiO_2 into a dual-responsive (pH/GSH) nanoplatform represents an innovative strategy for the selective delivery of doxorubicin inside cancer cells. ZnO undergoes degradation in the acidic tumor microenvironment, releasing reactive oxygen species (ROS) to enhance therapeutic efficacy, while SiO_2 provides high drug-loading capacity, structural stability, and the possibility of surface modification with GSH-sensitive linkers [15]. This synergistic combination enables targeted drug release and reduces systemic toxicity.

Mechanism of Drug Delivery

- The ZnO/SiO_2 hybrid nanoparticles release doxorubicin (DOX) through a dual pH/GSH-responsive mechanism [6]. After intravenous injection, the particles remain stable under physiological conditions (pH 7.4), thereby minimizing premature drug release during circulation [7]. Their nanoscale size facilitates passive accumulation at the tumor site via the enhanced permeability and retention (EPR) effect .
- Upon entering breast cancer cells through endocytosis, the nanoparticles encounter the acidic environment of endosomes and lysosomes (pH 5.0–6.5), along with elevated intracellular glutathione (GSH) levels. Low pH accelerates ZnO degradation, while high GSH concentrations cleave disulfide bonds on the nanoparticle surface These dual triggers destabilize the hybrid carrier, resulting in controlled intracellular release of doxorubicin.
- The released doxorubicin diffuses into the nucleus, where it intercalates with DNA and inhibits topoisomerase II, leading to DNA damage, induction of apoptosis, and suppression of cancer cell proliferation .
- Overall, this dual-responsive strategy enhances drug accumulation at the tumor site, improves therapeutic efficacy, reduces off-target toxicity, and mitigates the risk of multidrug resistance compared to conventional chemotherapy.

Potential Applications

Dual pH/GSH-responsive ZnO/SiO_2 hybrid nanoparticles hold significant promise as advanced drug delivery systems for breast cancer therapy. By enabling controlled and localized release of doxorubicin, this smart carrier is expected to enhance therapeutic efficacy while reducing systemic toxicity and minimizing damage to healthy tissues.

Beyond doxorubicin delivery, the proposed hybrid platform can be adapted to load a wide range of anticancer agents, including chemotherapeutics, nucleic acids, proteins, and combination therapies. Surface modification with targeting ligands such as folic acid, peptides, or antibodies may further improve tumor-specific uptake and therapeutic efficiency.

In addition, ZnO/SiO_2 hybrid nanoparticles can serve as multifunctional platforms for **theranostic applications**, integrating both therapeutic and diagnostic functions into a single system. Their flexible design also makes them promising candidates for personalized cancer therapy and combination treatments aimed at overcoming multidrug resistance .

Advantages

Dual pH/GSH-responsive ZnO/SiO_2 hybrid nanoparticles offer several advantages compared to conventional chemotherapy and single-component carriers:

- **Combined Properties:** They integrate the high drug-loading capacity and excellent biocompatibility of mesoporous silica with the pH-responsive degradation and intrinsic anticancer activity of ZnO

- **Controlled and Localized Release:** Enable precise drug release within the tumor microenvironment, reducing premature leakage during systemic circulation
- **Enhanced Intracellular Delivery:** The dual responsiveness improves doxorubicin transport into breast cancer cells by responding to both elevated acidity and high intracellular glutathione levels
- **Improved Therapeutic Outcomes:** Expected to increase treatment efficacy, reduce systemic toxicity, and minimize side effects on healthy tissues
- **Surface Functionalization:** The hybrid surface allows further modification with targeting ligands or imaging agents, making them promising candidates for advanced targeted delivery and theranostic applications

Current Clinical Progress and Translational Challenges

Although nanotechnology-based drug delivery systems have shown promising results in preclinical studies, the clinical translation of ZnO/SiO_2 hybrid nanoparticles remains at an early stage. Several nanomedicine formulations have already entered clinical trials or received regulatory approval for cancer treatment; however, most ZnO/silica-based hybrid carriers are still under investigation due to challenges related to safety reproducibility, and large-scale production.

Preclinical studies have demonstrated that ZnO/SiO_2 hybrid nanoparticles can provide efficient drug loading, controlled release, improved tumor targeting, and enhanced therapeutic outcomes. Nevertheless, translating these advantages into clinical applications requires comprehensive evaluation of pharmacokinetics, biodistribution, biodegradation behavior, immune responses, and long-term toxicity. Potential accumulation of nanoparticles in non-target organs and unpredictable biological interactions remain important concerns.

In addition, manufacturing challenges including precise control of particle size, surface properties, stability, and batch-to-batch consistency must be addressed to ensure reliable clinical performance. Regulatory approval also requires standardized protocols for nanoparticle characterization and extensive safety assessments.

Future efforts should focus on optimizing the design of ZnO/SiO_2 hybrid nanoparticles, strengthening tumor-specific targeting strategies, and conducting robust in vivo studies followed by well-designed clinical trials. Advances in biomaterials engineering and nanomedicine are expected to facilitate the transition of these smart carriers from laboratory research to practical applications in personalized breast cancer therapy.

Limitations and Future Perspectives

Despite significant progress, several challenges hinder the clinical translation of these systems, such as:

- Difficulty in large-scale production while maintaining structural uniformity.
- The need for extensive clinical studies to validate safety and efficacy.
- Regulatory hurdles associated with drug approval processes

Future research should emphasize improving hybrid nanoparticle design to enhance targeting efficiency, increase drug-loading capacity, and achieve precise release control. Surface modification with tumor-specific ligands and integration of imaging agents may further strengthen therapeutic performance and enable theranostic applications. Moreover, comprehensive in vitro and in vivo studies, followed by well-structured clinical trials, are essential to confirm efficacy and safety. Continuous advancements in nanotechnology and biomaterials science are expected to accelerate the development of smart drug delivery systems for more effective and personalized breast cancer treatment.

Conclusion

The development of dual pH/GSH-responsive ZnO/SiO_2 hybrid nanoparticles represents a promising step toward improving the efficacy of breast cancer chemotherapy. This system combines the high drug-loading capacity and controlled release properties of SiO_2 with the anticancer activity of ZnO through reactive oxygen species generation. Such a dual strategy enables targeted doxorubicin release within the tumor microenvironment, thereby reducing systemic toxicity and enhancing therapeutic outcomes.

Although clinical translation faces challenges—including large-scale production difficulties and the need for extensive clinical validation—ongoing progress in nanotechnology and personalized medicine opens promising avenues for future adoption of these systems in medical practice The integration of scientific innovation with clinical support may establish these hybrid platforms as a cornerstone of next-generation targeted cancer therapies.

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