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GSH-Responsive Co-Delivery Micelles: A Convergent Platform of Prodrug Chemistry, Microfluidics and Combination Cancer Therapy

1Bhaskar Jyoti Sharma*, 2Sunirmal Bhattacharjee, 3Nabanita Bijoy Das, 4Pralay Mallik, 5Abu Saif Mustaque, 6Sudipta Sarkar

1,3,4,5,6Assistant Professor, Bharat Pharmaceutical Technology, Agartala-799130, India

2Associate Professor, Bharat Pharmaceutical Technology, Agartala-799130, India

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ABSTRACT:

The advancement of smart drug delivery systems represents a significant paradigm shift in oncological therapy, addressing the limitations of conventional chemotherapy. Glutathione (GSH)-responsive polymeric micelles have emerged as a promising platform for the controlled and targeted delivery of anticancer agents. These systems exploit the pronounced redox potential gradient between the extracellular and intracellular environments of tumor cells, where GSH concentration is markedly elevated.

This review provides a comprehensive overview of the recent advancements in GSH-sensitive micellar systems designed for delivering various therapeutic agents. The intricate chemistry of prodrug design has been meticulously examined, with particular emphasis on the covalent conjugation of chemotherapeutic agents to polymeric backbones via disulfide linkages, which function as redox-sensitive devices. The significance of microfluidic technology in facilitating the creation of monodisperse co-delivery micelles and ensuring precise, reproducible, and scalable fabrication with high drug loading and enhanced stability has been thoroughly explored. Furthermore, we elucidated the mechanisms underlying the synergistic effect of an effective spatiotemporal release of drug combinations to enhance apoptosis, circumvent multidrug resistance, and demonstrate potent antitumor activity in various in vitro and in vivo cancer models.

Existing translational challenges and future opportunities are also discussed, considering the potential of integrated systems to redefine the targeted cancer therapies. GSH-responsive co-delivery micelles represent a disruptive technology in oncological nanomedicine through the convergence of rational molecular design, precision nanoengineering, and advanced combination therapy.

1. Introduction

Malignancies remain one of the most challenging issues in modern medicine and are further highlighted by a strong increase in the rates of occurrence and mortality worldwide[1]. Despite the fact that conventional chemotherapy has been a cornerstone of therapeutic modalities in the past, it has ample clinical limitations, including non-selective cytotoxicity in normal tissues, insufficient solubility of many chemotherapeutic agents, unreliable pharmacokinetics making dosing regimens less predictable, and the alarming development of multiple drug resistance. These limitations often lead to suboptimal treatment results and severe side effects, which underline the need for more specific and effective drug delivery systems[2].

With the advent of nanomedicine, the therapeutic environment in the oncology sector has been radically transformed by the ability to selectively deliver drugs to diseased tissues[3]. Polymeric micelles have attracted considerable interest because of their unique core-shell structure, which significantly improves the solubility, stability, and circulation of drugs in the systemic area. This architecture utilizes the Enhanced Permeability and Retention (EPR) effect, which allows passive targeting of tumors without compromising exposure to non-malignant tissue; hence, off-target toxicity is reduced[1].

The improvement of these advances has led to the creation of stimuli-responsive or smart drug delivery systems, which have provided an unprecedented level of precision in cancer therapy. These complex structures are

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designed to respond to certain stimuli specific to the tumor microenvironment, including changes in pH, enzymes, and redox potential[4]. Specifically, glutathione (GSH) -responsive platforms have proven particularly promising because of their ability to mediate the regulated release of drugs into the intracellular milieu via thiol-disulfide exchange reactions. This process not only enhances the specificity of the therapy, but also reduces systemic toxicity because it provides a more precise therapeutic approach[5].

Further advancements in this field have been achieved through the incorporation of co-delivery and prodrug strategies. These methods allow the sequential and regulated release of several therapeutic agents in optimal synergistic proportions, which is not easily achieved with traditional formulations. This complex approach improves the efficacy of therapy and, at the same time, provides the possibility of avoiding developed resistance mechanisms, thus improving patient outcomes[6].

The synthesis of these complex nanocarriers must be reproducible and clinically applicable; thus, high-facility manufacturing procedures are required for their synthesis. Microfluidic fabrication methods have become a powerful solution for controlling important parameters, such as particle size, structural stability, and drug loading efficiency. Such an accuracy solves the problem of reproducibility, which is a common concern in traditional manufacturing[7].

2. Objectives

This review aims to combine progressive ideas, such as GSH-responsive prodrug design, co-delivery systems, and microfluidic fabrication, into a logical structure for next-generation cancer nanomedicine. It offers a critical review of molecular design approaches, technology, therapeutic results, and translational considerations. It also aims to provide holistic insight into the possibility of employing intelligent nanocarriers to overcome the inherent drawbacks of traditional chemotherapy, which would eventually lead to the development of safer and more resilient oncologic therapeutic methods.

3. Molecular Design of GSH-responsive Polymeric Prodrugs

3.1 Fundamental Chemistry of GSH-Responsive Linkages

The inclusion of reduction-sensitive chemical linkages in glutathione (GSH)-responsive micellar systems is essential, as they are maintained intact in circulation in the body but are cleaved at a rapid rate upon entry into tumor cells[8]. The most comprehensively used and well-characterized redox-responsive functionality in nanomedicine is the disulfide bond (–S–S–). The high biochemical applicability of disulfide bonds is explained by their unique physicochemical characteristics, which are very stable under physiological conditions in the extracellular space (oxidative milieu) and are cleaved rapidly when there is an increased concentration of thiol-containing compounds, especially reduced glutathione (GSH), which has a strong thiol group[9]. The cleavage event mainly occurs through thiol–disulfide exchange reactions, with the thiolate anion (GS −) acting as a nucleophilic partner of the disulfide bond to form a mixed disulfide and a free thiol. This is followed by the attack of a second thiolate anion, which causes total reduction of the disulfide bond, resulting in the release of the conjugated drug in its active form. Molecular design can be used to precisely modulate the kinetics of cleavage. For example, steric hindrance of the disulfide bond, such as tertiary or quaternary carbon substituents on atoms adjacent to the sulfur atoms, can be incorporated to significantly slow the rate of cleavage, thus allowing extended drug release profiles[10]. However, electronically activated disulfide bonds may be developed to cleave faster in cases where rapid drug release is required. The redox sensitivity of such systems can be quantitatively determined by the reduction potential of the disulfide bond, which is used to determine the vulnerability of the bond to thiol attacks. Investigators can tune the responsiveness of prodrugs to the redox gradient between the extracellular and intracellular compartments by strategically modulating the reduction potential. This precise control of the trigger threshold helps to reduce the premature release of the drug during the circulatory process and retains a quick release when cells absorb the drug[11]. **Figure 1.** illustrates a schematic representation of GSH-responsive polymeric micelles showing intracellular reduction of disulfide linkages in a high-GSH tumor microenvironment, leading to redox-triggered drug release and targeted cytotoxicity.

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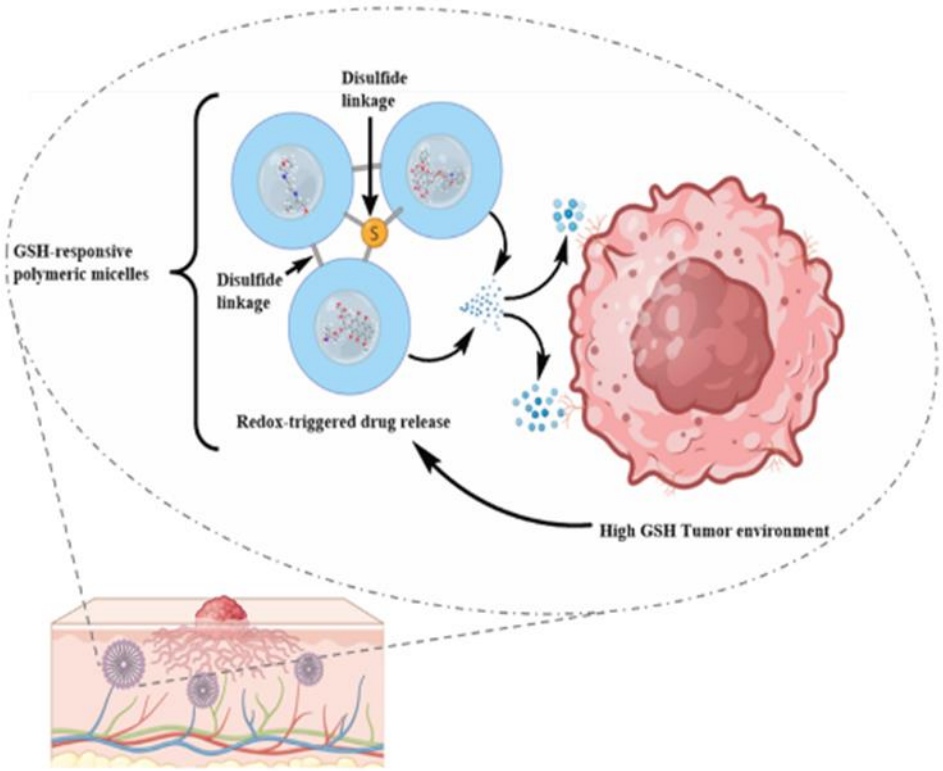

Figure 1: Schematic representation of GSH-responsive polymeric micelles showing intracellular reduction of disulfide linkages.

3.2 Selection and Functionalization of Polymeric Backbones.

The polymer backbone is a key factor that determines the functionality of glutathione (GSH)-responsive prodrug systems, dictating biocompatibility, biodegradability, self-assembly potential, drug-loading capacity, and pharmacokinetics. The design of these advanced nanocarriers has been successfully modified to include both natural and synthetic polymers, each with specific benefits and limitations[12].Natural polysaccharides, most notably, hyaluronic acid (HA) and its derivatives, have been increasingly of interest in the context of being core components of cancer-targeted nanomedicine. HA is a naturally occurring glycosaminoglycan that accumulates repetitive units of disaccharides made up of N-acetyl-D-glucosamine and D-glucuronic acid. This molecule is characterized by high biocompatibility, biodegradability, non-immunogenicity, and strong mucoadhesiveness[13].

Notably, HA is a receptor-specific ligand of the CD44 glycoprotein, which is highly expressed in most malignant cell types, including breast, ovarian, colon, and pancreatic carcinomas. The HA -CD44 interaction provides active targeting potential to HA-based nanocarriers, allowing cellular uptake by enhancing receptor-mediated endocytosis. In addition, the high density of carboxylic acid and hydroxyl groups on the HA backbone makes it easy to chemically modify and enables covalent conjugation of therapeutic agents using redox-responsive linkers[14].

Synthetic polymers also possess additional benefits such as the ability to specifically control the molecular weight, molecular structure, and physicochemical properties. PEG-PCL and PEG-PLGA block copolymers are widely used because of their safety and regulatory approval. In such systems, disulfide bonds can be strategically placed at various loci to achieve different types of drug release mechanisms. When a hydrophobic block or linker is between the drug and the polymer chain, disulfide cleavage allows drug release in a relatively intact micellar structure[15,16]. In contrast, in cases where the disulfide bond is at the end or between the hydrophilic

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PEG and hydrophobic segments, such as PEG-ss-PCL copolymers, GSH-mediated cleavage activates the dissociation of the PEG corona chain, resulting in the instantaneous disassembly of the micelles and uniform drug release[17].

Recent advances have enabled the synthesis of new polymer systems, including polyphosphoesters, in which biodegradable phosphoester bonds are incorporated into the backbone and pendant groups to facilitate convenient drug conjugation. Synthetic methodologies also allow the fabrication of polymers with degradation rates, stimulus responsiveness, and mechanical strength that suit the individual therapeutic needs[18,19].

3.3 Advanced Strategies for Prodrug Conjugation

The chemistry used to conjugate therapeutic agents to the polymer backbone is a vital part of prodrug design that directly impacts drug loading, kinetics of release, and pharmacological activity. The strategy adopted for conjugation should ensure that the drug is conjugated to a functional group that does not participate in the cytotoxic activity of the drug, thereby maintaining the functional capacity of the drug after conjugation[20]. Carbodiimide-mediated coupling reactions are the most common method for forming amide or ester bonds between polymers based on carboxylic acid and amine or hydroxyl-based drugs using reagents such as 1-ethyl-3-dimethylaminopropyl carbodiimide (EDC) in combination with N-hydroxysuccinimide (NHS). Commonly used crosslinkers are heterobifunctional crosslinkers, such as N-succinimidyl 3 (2 pyridyldithio) propionate (SPDP), which possesses an NHS-ester functional group capable of being attached effectively to amine functional groups on the polymer backbone, and a pyridyl disulfide functional group capable of reacting with thiolated drug analogs to form a disulfide bond[21]. In some cases, synthetic modification is necessary when drugs lack naturally occurring functional groups that can be conjugated. For example, a chemotherapeutic agent such as doxorubicin (DOX) can be derivatized to add a thiol group to create a disulfide bond, without any pharmacological effects after release. Drug conjugation can be accurately localized to the polymer chain of the reaction to maximize the ratio between drug loading and the self-assembly properties of the resulting amphiphilic prodrug[22].

3.4 Novel Prodrug Delivery Systems

Studies on glutathione (GSH)-responsive prodrug design have been developed, compared to traditional polymer drug conjugates, to include a wider variety of advanced architectures that exhibit enhanced functionality and therapeutic efficacy. This development indicates a growing focus on adapting prodrug systems to optimally function under complex biological conditions[23].

One of the notable achievements in this field is the introduction of two-responsive platforms which are responsive to various stimuli of tumor microenvironment, consequently building a logic of the "AND-gate logic that further increases target specificity. A good example of this is the conjugation of a GSH-responsive disulfide bond with a pH-sensitive bond, such as hydrazone, acetal, or benzoic imine, to create constructs that are stable under physiological conditions (pH = 7.4). These constructs are destabilized in the acidic endosomal compartment (pH 5.5 -6.0) and liberated only after complete cleavage by high intracellular GSH concentrations. This multistage activation strategy significantly decreases off-target release and maximizes the bioavailability of drugs in the intracellular space[24,25].

Other examples of innovation include the use of self-immolative linkers that aid in the release of native drug molecules, leaving no linker fragments. These systems usually include a disulfide bond attached to the therapeutic agent through a self-immolative spacer, such as p-aminobenzyloxycarbonyl. This spacer spontaneously rearranges electronically upon disulfide reduction, thereby releasing the intact drugs. Consequently, the active pharmaceutical ingredient is reinstated to the initial chemical structure and form, which benefits pharmacological performance and countermeasures against the possible changes that would result from structural changes[26]. Moreover, advanced combinatorial models have been developed to improve the therapeutic outcomes. For example, an amphiphilic polymeric block that includes doxorubicin (DOX) and a hydrophobic photosensitizer, chlorin e 6 (Ce6), has been engineered to allow both chemotherapy and photodynamic therapy. The GSH-responsive release of DOX works in synergy with the photodynamic activity of Ce6 to achieve a significant anticancer effect in in vitro and in vivo experiments in this system[27].

4 Prodrug system characterization and validation

Thorough characterization of Z-glutathione (GSH)-sensitive prodrug systems is crucial for determining their

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structural integrity, redox sensitivity, and drug release profiles. These complex systems have been systematically assessed using advanced analytical methods.

Nuclear Magnetic Resonance (NMR) spectroscopy provides comprehensive information about polymeric structures, drug conjugation efficiency, and disulfide bond integrity in conjugates. Fourier-transform infrared spectroscopy (FTIR) supports the establishment of covalent bonding during conjugation. Gel permeation chromatography determines changes in the distribution of molecular weights and the successful production of prodrugs[28].

The critical redox-responsive behavior is typically investigated through in vitro drug release studies in the presence or absence of GSH. These experiments indicated that there was negligible drug release under physiological conditions (without GSH), and the release increased significantly when GSH concentrations were similar to those in the intracellular environment of malignant cells were used[29,30].

Polymeric backbone degradation caused by GSH was followed by gel permeation chromatography, which showed migration toward lower molecular weight species, indicating the cleavage of disulfide bonds[10,31].

Biochemical validation was also enhanced by confocal microscopy, which observed intracellular drug release through fluorescence after cellular uptake, and flow cytometric analysis, which measured the kinetics and extent of drug dispersal within the cancer cell lines[29,32].

Table 1 provides a graphical overview of the characterization methods for GSH-responsive polymeric prodrugs. Collectively, these analytical approaches verify the successful design and workability of GSH-responsive prodrug systems, providing a basis for continued investigation of their therapeutic prospects in oncological therapy.

Table 1:GSH-Responsive Polymeric Prodrug Characterization Techniques

Characterization Method	**Information Obtained**	**Significance for Prodrug Development**	**References**
1H1H NMR Spectroscopy	Chemical structure, drug conjugation efficiency, disulfide bond integrity	Confirms successful synthesis and quantitative assessment of drug loading	33–36
FTIR Spectroscopy	Functional groups, chemical bonds formed during conjugation	Verifies formation of specific linkages between polymer and drug	36–39
Gel Permeation Chromatography	Molecular weight and distribution, polymer degradation upon GSH exposure	Monitors prodrug synthesis and validates redox-responsive degradation	16,40,41
In Vitro Drug Release Studies	Drug release kinetics under varying GSH concentrations	Demonstrates redox-responsive behavior and guides therapeutic dosing	16,41,42
Confocal Microscopy	Intracellular drug release and localization	Visualizes spatial and temporal drug release in cellular environments	30,43–45
Flow Cytometry	Quantitative analysis of cellular uptake and drug release	Provides kinetic parameters for drug release in relevant biological systems	8,14,41,46,47

4. Microfabrication of co-delivery micellar systems

4.1 Limitations of Conventional Nanofabrication Methods

Conversion of molecularly designed prodrugs into functional nanocarriers is a critical manufacturing procedure that has an extreme effect on the physicochemical, biological, and therapeutic potential of the end product[20]. Traditional nanofabrication methods,

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such as dialysis, solvent evaporation, emulsion solvent evaporation, and nanoprecipitation, have been widely used to prepare polymeric micelles. However, these methodologies are characterized by several inherent constraints that hinder their effectiveness in developing sophisticated co-delivery models[48]. These processes are mainly batch processes, not standardized, and multistage, resulting in low reproducibility and large batch-to-batch variability in the final product. Poor control of mixing kinetics results in non-homogenous nanoparticle populations with broad size distributions (i.e., high polydispersity index, PDI), which adversely affects pharmacokinetics and biodistribution in vivo[49]. In addition, suboptimal loading of novel therapeutic agents and failure to maintain important synergistic dosages by inefficient encapsulation of a wide range of therapeutic agents, particularly those with different physicochemical properties, are encountered[50]. The lack of strict regulation of the self-assembly process often results in the creation of metastable micellar systems that can readily dissociate upon dilution, release off-target drugs, and potentially cause toxicity[51,52]. Among these production issues, high-tech glutathione-responsive co-delivery systems are especially prone to manufacturing issues, as drug stoichiometry, core-shell structure, and surface properties are extremely critical for achieving the desired therapeutic effects[53]. Consequently, the shortcomings of traditional approaches have proven to be significant obstacles to the clinical use of the most promising nanomedicines, highlighting the need to develop superior fabrication technologies.

4.2 Major Principles of Microfluidic Technology

Microfluidic technology has become a revolutionary manufacturing system that alleviates the major limitations of traditional nanofabrication techniques, owing to its ability to manipulate fluids with precision at the microscale[54]. Microfluidic devices usually consist of 10-100 micrometers (μm) sized networks of channels made of polymers such as polydimethylsiloxane (PDMS), glass, and thermoplastic materials. Microfluidic systems operate on unique fluid dynamics principles that provide unprecedented control over nanoparticle formation[55,56]. Unlike macroscopic configurations, which are characterized by turbulent flow, microfluidic configurations have laminar flow, where fluid parcels move in parallel layers without transverse dispersion, except for molecular diffusion. This flow regime supports predictable and reproducible behaviors[57]. In microfluidics, the Reynolds number (Re) is a key dimensionless quantity used to provide information about the ratio of inertial forces to viscous forces. At the microscale, Re is usually quite small (0 to less than 1), signifying that the viscous forces are predominant, and the flow is laminar. The highly developed ratio between the surface area and volume of the microchannels facilitates the transfer of heat and mass, resulting in rapid and homogeneous diffusion[57]. The coordination of the self-assembly of polymeric micelles, which are known to be highly sensitive to the kinetics of solvent displacement, requires a controlled mixing environment. Microfluidic systems can control the nucleation and growth of nanoparticles to generate highly homogeneous and customized products[58].

4.3 Microfluidic Device Designs for Micelle Fabrication

The designs of microfluidic devices are highly varied, and strive to maximize the output of polymeric micelles, which are essential in numerous applications, particularly in drug delivery systems. These devices are defined by their unique geometrical designs, each possessing different benefits according to specific usage requirements[3,59]. Flow-focusing devices, T-junction devices, and co-flow systems are the three most common types of geometries in microfluidic systems[59–61].

Flow-focusing methods are highly advanced, in which the dispersed phase (usually a solution of polymer and drug dissolved in an organic solvent) is hydrodynamically focused with two counterflow streams of the continuous phase (usually aqueous). This arrangement leads to the creation of a fine filament, which then breaks into minute droplets at the intersection of the flow. The high uniformity of the droplets formed in the flow-focusing apparatus can also be explained by the small channel size and equal forces acting on the dispersed phase, resulting in a high level of monodispersity. Thus, flow focusing is a good option when monodispersity in droplet size is required[60,62,63].

In contrast, T-junction devices are considered to be fundamental geometries in microfluidics. In these designs, the ratio between the dispersed and continuous phases is created at a right-angled junction of the channel. As the continuous phase approaches the junction, it virtually purges the droplets from the dispersed-phase stream. The size of the generated droplets is determined by several factors, such as the channel size, flow rates of both phases, and inherent properties of the fluids used. T-junction devices might

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not be as efficient as flow-focusing devices in the production of very fine droplets; however, owing to their simplicity of construction and operation, they have been extensively used in different applications[62,64].

Co-flow systems use a concentric capillary design in which the dispersed phase is transported by the inner capillary and the continuous phase is transported by the outer capillary. Shear forces applied by the continuous phase form droplets as the inner capillary is drained of liquid. This setup enables the flow rates of the inner and outer streams to be controlled independently, which is especially beneficial in the formation of core-shell structures, where separate layers of the used material need to provide the necessary properties to the final micelles[65–67].

New designs such as staggered herringbone mixers (SHM) have been used to support advanced applications. These mixers enhance chaotic advection, leading to improved mixing and uniformity of droplet formation. Moreover, parallelized designs have the potential to support greater production throughput without compromising the properties of the droplets produced[68,69]. **Figure 2.** represents microfluidic device geometries for micelle fabrication: (A) T-junction, (B) flow-focusing, and (C) co-flow designs, enabling precise control over nanoparticle formation, size, and monodispersity.

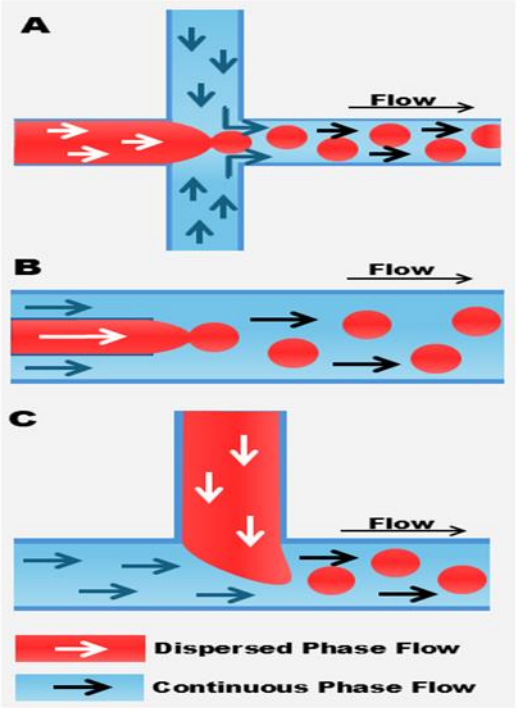

Figure 2: Microfluidic device geometries for micelle fabrication

4.4 Benefits of Microfluidic Fabrication for Co-delivery Systems

Microfluidic technologies provide considerable benefits in the production of glutathione-reactive co-delivery micelles over traditional methods, directly responding to the key quality characteristics required to induce therapeutic efficacy. A key advantage is the ability to produce highly monodisperse nanoparticles with a low polydispersity index (PDI)[70]. Laminar flow represents a naturally stable microchannel regime in which micelles can be assembled under uniform nucleation and growth conditions, producing particle populations with identical size distributions. This homogeneity is essential to explain the behavior in vivo because the size of

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nanoparticles has a direct effect on biodistribution, tumor penetration depth, and cellular uptake processes[71].

The stoichiometry and loading capacity of co-delivered agents can be controlled within a narrow range using microfluidic systems. High-velocity mixing removes the kinetic obstacles to drug encapsulation and enhances the effective loading of conjugated prodrugs and spatially isolated secondary therapeutics. Furthermore, such a clear control maintains optimal synergistic ratios among the combination drugs, which is critical for achieving the highest therapeutic output with minimal resistance to therapy[72]. The microfluidic fabrication pathway typically produces micelles with high kinetic stability for dissociation. Compared to the structures formed by other methods, thermodynamically robust micelles have lower critical micelle concentrations (CMCs) when fewer and tightly controlled mixing conditions are employed. This higher stability allows micelles to survive in systemic circulation, thereby reducing off-target drug release[8,73]. There are also significant benefits in terms of the reproducibility and scalability of microfluidic platforms. Although individual devices feature a modest level of production, the procedure can be scaled up by simultaneously running several identical devices, a technique referred to as number-up, without compromising the high level of control afforded by microfluidics. This can be scaled to production volumes that are clinically and commercially viable in the future. The use of constant operation modes also provides real-time monitoring and quality control in microfluidic systems, which eventually improves the product consistency[74].

4.5 Synthesis Approaches and Parameters Optimization

Polymeric micelles can be synthesized in response to GSH using microfluidic techniques, which involve careful adjustment of various parameters to achieve the required properties of the generated nanoparticles. The most common mechanism used here is solvent displacement, where the polymer and drugs are dissolved in a water-soluble organic solvent such as tetrahydrofuran, acetone, or dimethylformamide, which is the dispersed phase, and the continuous phase is an aqueous solution[75]. One of the parameters of nanoparticle size is the flow rate ratio of the continuous and dispersed phases, which determines nanoparticle size. Increased flow rates in the continuous phase usually lead to small nanoparticles owing to the expansion of the shear forces and mixing. The total flow rate influences the mixing efficiency and hence the homogeneity of the resulting nanoparticles[71]. The polymer concentration and drug-to-polymer ratio should be optimized to achieve high drug loading without affecting micellar structure and stability. The solvent type, pH, and ionic strength are also dependent on the chemical composition of the fluids used, as they influence nanoparticle properties. For example, co-solvents can be used to vary the kinetics of polymer aggregation during the formation of micelles. Moreover, microchannel geometry and surface properties can be optimized to reduce fouling and provide reliable operation over longer periods[76,77]. **Table 2** lists the important parameters for the microfluidic fabrication of GSH-responsive micelles. Recent developments have focused on the application of real-time monitoring methods, including inline dynamic light scattering and ultraviolet-visible spectroscopy, to provide real-time feedback on nanoparticle size and drug loading during fabrication. This feature enables adaptive control, thus guaranteeing consistency in the product quality during the manufacturing process[78].

Table 2: Important parameters in the microfluidic production of GSH responsive Micelle

Parameter Category	Specific Parameters	Impact on Micelle Properties	References
Fluid Dynamics	Flow rate ratio (aqueous: organic), total flow rate, Reynolds number	Determines nanoparticle size, size distribution, and morphology	78–81
Chemical Composition	Polymer concentration, drug-to-polymer ratio, solvent selection, pH, ionic strength	Influences drug loading efficiency, encapsulation	82–85

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Device Design	Channel geometry, mixing elements, surface chemistry, material composition	Affects mixing efficiency, production yield, and operational stability	61,83,86–88
Process Conditions	Temperature, pressure, collection method, purification approach	Impacts final product characteristics, sterility, and scalability	89–93

4.5 Scale-up Strategies and Manufacturing Considerations

To scale up microfluidic fabrication for the clinical applications of microscale devices, suitable scale-up principles must be applied. Individual microfluidic chips usually produce nanoparticles in milligram- to gram-scale amounts daily, but clinical applications require volumes of approximately kilograms to tens of kilograms[94,95]. Parallelization is an easy scaling method because it involves running several microfluidic devices in parallel, where the operation of the multiple devices is coordinated. This method maintains the exact control characteristics of microfluidics and increases the total production capacity. Parallelization should be carefully designed to provide consistent fluid flow in all devices and concurrently collect products[95,96]. In continuous manufacturing strategies, the formation of microfluidic nanoparticles is combined with further purification, concentration, and sterilization processes on a continuous production line. This combined system minimizes operations, eliminates the risk of contamination, and increases the efficiency of the entire process[97–99].

Another important aspect of scale-up is the choice of materials used to manufacture the devices. Although polydimethylsiloxane (PDMS) is commonly used in laboratory prototyping because of its simple fabrication and optical transparency, it may not be suitable for large-scale manufacturing owing to its solvent incompatibility and insufficient mechanical characteristics[100–102]. Thermoplastic polymers, such as poly (methyl methacrylate) (PMMA), cyclic olefin copolymer (COC), and polycarbonate (PC), are chemically more resistant and possess higher mechanical strength, making them the best choice for high-volume production[103].

With the continued development of microfluidic manufacturing for clinical applications, compliance with Good Manufacturing Practice (GMP) regulations is essential. This involves the introduction of strict quality control measures, standard operating procedures, validation of cleaning and sterilization orders, and careful documentation of the entire manufacturing process of the product. These steps are necessary to translate microfluidically engineered glutathione-responsive co-delivery platforms from research facilities to clinical applications[104,105].

5. Therapeutic Use and Efficacy Evaluation

5.1 Applications in mono-chemotherapy

GSH-reactive polymeric micelles are promising vehicles for the delivery of single chemotherapeutic agents, which could reduce the limitations of traditional chemotherapy and enhance the treatment effect.

The redox-regulated drug delivery system ensures minimal untimely leakage into the systemic circulation, thereby reducing off-target toxicity and facilitating prompt and full drug release when the drug is internalized into the reductive intracellular space. The best example of this is doxorubicin (DOX), a chemotherapeutic agent that has been widely studied in GSH-responsive micellar structures. DOX conjugation to polymeric backbones via disulfide linkages significantly reduces systemic toxicity compared to free DOX without affecting antitumor effects[106–108]. There is also in vivo evidence of tumor growth and improved survival rates in cohort models with murine tumors when micellar DOX is administered to tumors compared to those cohorts receiving equimolar free DOX. A salient benefit of targeted delivery platforms is the attenuation of cardiotoxicity, a dose-limiting adverse effect of conventional DOX delivery[109,110].

Paclitaxel (PTX), a highly potent hydrophobic chemotherapeutic agent, has been effectively conjugated to GSH-responsive micellar systems. The use of a prodrug approach significantly enhances the aqueous solubility and systemic circulation half-life of PTX without impairing its cytotoxic effect on intracellular release[111]. GSH-responsive PTX-laden micelles performed better in suppressing tumor growth in orthotopic breast cancer models than traditional PTX preparations (e.g., Taxol 2) and other non-responsive micellar controls[109]. Histopathological tests have shown

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that in micelle-treated samples, there is a severe case of apoptosis and necrosis of tumor cells, with minimal damage to the surrounding normal tissues[112,113].

These mono-chemotherapeutic approaches exert therapeutic effects through synergistic processes, including passive targeting via the increased permeability and retention (EPR) effect, active targeting via surface functionalization (such as hyaluronic acid to mediate uptake by the CD44 receptor), and intracellular targeting through the GSH-mediated drug delivery system. These hierarchical targeting systems optimize intratumoral drug delivery and reduce the exposure to normal tissues, thereby increasing the therapeutic index[114].

5.2 Paradigms of Combination Therapy

GSH-responsive polymeric micelles have co-delivery properties that can be used to implement advanced combination therapy. Such methods allow the concurrent administration of multiple drugs directed at various pathogenic pathways, thereby avoiding the limitations of single-target chemotherapy. These systems are designed to maintain optimal ratios of therapeutic agents between administration and cellular delivery, to maximize therapeutic synergy and avoid drug resistance[4,115,116].

Combination chemotherapy is a basic example of a co-delivery mechanism. These include combinations of drugs with complementary effects (e.g., DNA-damaging agents such as DOX) and microtubule stabilizers (e.g., PTX), which have been found to be more effective than treatment with single agents or combinations of free drugs. The ideal level of synergy is maintained in the delivery process to ensure that cancer cells are not exposed to non-therapeutic drug ratios that could encourage the development of resistance. In addition, the coordinated intracellular release results in the two agents working together in coordination, thus defeating the cellular defense mechanisms to generate a synergistic cytotoxic effect on their molecular targets[117–119].

Combination chemo-photodynamic therapy (PTD) is a relatively new treatment that combines chemotherapy with light-activated therapy. A prime example is the use of an amphiphilic block polymer-DOX prodrug to encapsulate chlorin e6 (Ce6), a hydrophobic photosensitizer. When GSH is internalized into cancer cells, the GSH-mediated release of DOX reacts with the photodynamic effect of Ce6 to produce cytotoxic reactive oxygen species (ROS) under laser irradiation. This combination therapy exhibited significantly improved cytotoxicity in cancer cells compared to either treatment alone, both in vitro and in murine tumor models. The system demonstrated a significant tumor growth inhibitory rate of 58.53 per cent, which was higher than that of monotherapy treatment methods. It is important to note that GSH application in drug delivery can also play a crucial role in making PDT more effective by decreasing the antioxidant abilities of cancerous cells; therefore, it has an amplifying therapeutic effect[120,121].

Combination chemo-immunotherapy is a new area of cancer therapy that takes advantage of the potential of nanocarriers to simultaneously deliver immunomodulatory reagents with traditional chemotherapeutics. For example, the synergistic interaction between a chemotherapeutic agent and an inhibitor of programmed death-ligand 1 (PD-L1) may cause cancer cell death and reverse immunosuppression in the tumor microenvironment[122]. Immunogenic cell death (ICD) can be induced by chemotherapy, which releases tumor antigens and danger signals that stimulate dendritic cell activation and T-cell priming. Simultaneously, the immunotherapy component prevents checkpoint-mediated silencing of T-cells and promotes strong antitumor immunity. This combined approach has demonstrated the potential to convert immunologically cold tumors into hot tumors, which are susceptible to immune attack[123]. **Figure 3.** represents a schematic overview of GSH-responsive micelle-mediated combination therapy, showing intracellular GSH-triggered drug release, reactive oxygen species (ROS) generation in photodynamic therapy, and immune activation for synergistic tumor eradication.

5.3 Preclinical Validation Models and Methods

Strict preclinical testing is necessary to determine the therapeutic potential of glutathione-responsive co-delivery systems and to support further clinical translation. These tests lie on a continuum of modalities, from the analysis of device complexity to in vitro cellular testing and in vivo animal experiments. Primary screening for antitumor effects and possible synergistic effects is typically conducted using standard cytotoxicity assays, such as MTT, sulforhodamine B (SRB), and CCK-8 assays[124]. Drug interactions were quantitatively determined using combination indices (CI), which were computed using the Chou-Talalay method: $CI < 1$ indicates synergy, $CI = 1$ indicates additivity, and $CI > 1$ indicates antagonism[125–127]. In GSH-responsive systems, a comparative analysis of the therapeutic effects on

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different cancer cell lines with varying intracellular GSH levels provides important information regarding redox-dependent activity[127]. Flow cytometry and confocal microscopy were used to visualize and quantify the internalization of fluorescently labelled micelles and subsequent drug release via cellular uptake and intracellular trafficking[8,78,128]. These experiments usually show increased uptake of target-functionalized micelles (e.g., hyaluronic acid-functionalized micelles) compared to non-targeted formulations and intracellular drug release by the detection of fluorescence produced by disulfide cleavage. Further insights into subcellular trafficking kinetics and release dynamics have been presented in studies that used organelle-specific markers for co-localization studies[129]. Mechanistic studies have examined the cellular pathways that mediate cell death. Western blotting can be used to verify changes in proteins involved in apoptosis (caspases, PARP, and Bcl -2 family members), cell cycle control, and proteins involved in DNA damage response, whereas flow cytometric annexin V/propidium iodide staining measures the fractions of apoptotic and necrotic cells. Such studies have repeatedly shown that co-delivery systems induce a superior level of apoptosis compared to single agents or previous combination strategies[130].

In vivo efficacy is used to test the antitumor effect of tumors in murine models to determine their effects in a physiologically relevant model. An early efficacy test is usually conducted using subcutaneous xenografts that are created by surgically implanting human cancer cells into immunodeficient mice. More advanced orthotopic models, in which tumor cells are reintroduced into their tissue of origin, provide greater physiological relevance and allow the investigation of metastatic behaviors[131]. Patient-derived xenograft (PDX) models, which are formed as a result of subcutaneous implantation of human tumor fragments into mice, are considered a better surrogate of inter-tumor heterogeneity and treatment response. The efficacy of therapies in these models is traditionally measured by serial changes in tumor dimensions to determine tumor volume, where the percentage tumor growth inhibition (TGI) is the most important parameter[132]. Other clinically relevant endpoints include overall survival and metastatic incidence. Morphological associations of treatment reactions, including necrosis, apoptosis, and slowed proliferation, were determined through histopathological examination of excised tumors[133]. Pharmacokinetic and biodistribution analyses, including fluorescence imaging, liquid scintillation counting, and LC-MS/MS, help to understand the spatiotemporal distribution of drug carriers and released drugs[134]. The intratumoral concentration of micellar formulations is always higher than that of free drugs owing to the improved permeability and retention (EPR) effect and targeting ability. Minimal deposition in sensitive normal tissues (e.g., the heart and kidney) highlights a safety profile that is currently being optimized by introducing targeted nanocarriers[135].

5.4 Safety and Toxicity Assessment

The safety assessment phase is a key element in the preclinical development of glutathione (GSH)-sensitive co-delivery systems for cancer therapy. Acute toxicity tests assess changes in body weight, clinical signs, and mortality after a single or short-term repeated doses. Repeated-dose toxicity tests determine the cumulative toxicity of a substance during prolonged periods of exposure, along with clinical pathology tests such as hematology, clinical chemistry, and histopathological analyses of the target organs[136,137].

To measure cardiotoxicity related to anthracycline-based formulations, the cardiotoxic effects of doxorubicin (DOX) are specifically measured using echocardiography, cardiac biomarker measurements (e.g., troponin), and histopathological examination of myocardial tissue. The significantly decreased cardiotoxicity of DOX with the use of GSH-responsive micelles is a key benefit compared with conventional formulations[110,138,139].

Hemocompatibility tests evaluate the possible undesirable effects on blood constituents, such as the hemolysis, platelet activation, and complement activation. These assays are especially applicable when nanocarriers are administered intravenously because in such cases, the nanocarrier undergoes a vast amount of blood contact[25,115,140].

GSH-responsive systems exhibit improved safety profiles compared to traditional chemotherapy, demonstrating decreased rates and degrees of typical chemotherapy-associated toxicities, including myelosuppression, gastrointestinal harm, and cardiotoxicity. This increased safety profile allows for the use of increased or extended effective doses, which may result in better therapeutic efficacy[137].

6. Regulatory and manufacturing considerations

6.1 Technology Transfer and Scale-up Issues

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Translating laboratory-scale synthesis to the industrial level is a very important issue in the evolution of glutathione-responsive polymeric micelles. Although there are notable benefits associated with microfluidic technology in terms of product quality and reproducibility, any system that has been scaled to a commercially viable production level should be evaluated against a set of factors[1,141].

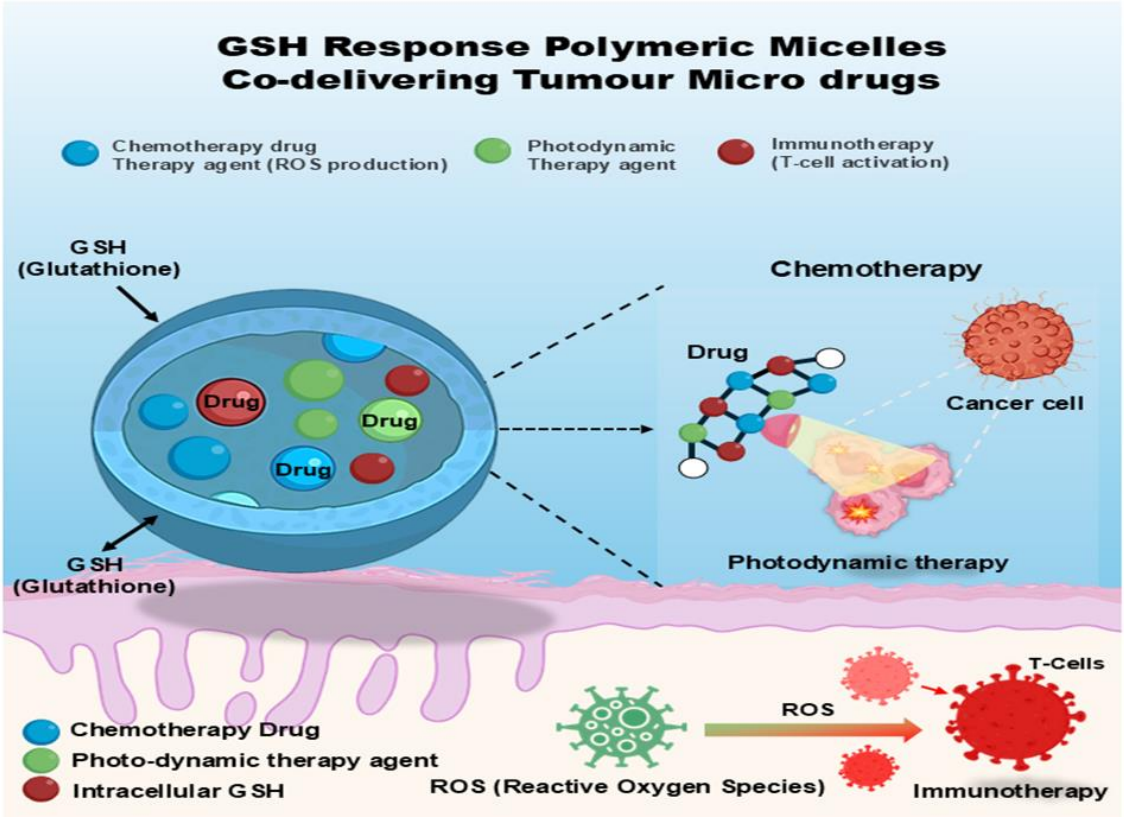

Figure 3: Schematic overview of GSH-responsive micelle-mediated combination therapy

The parallelization approach, which involves the simultaneous functioning of several microfluidic devices, faces engineering issues related to fluid distribution, pressure equilibration, and product collection. The necessity of standard operation of all units implies the manufacture of high-quality microfluidic chips and implementation of sophisticated fluid-handling systems with a high level of accuracy. As a second alternative, cascaded systems with built-in distribution networks can be developed to ensure a smooth flow throughout all units operating in parallel[142,143].

As opposed to traditional batch manufacturing, current manufacturing platforms that combine the formation of microfluidic nanoparticles and downstream manufacturing, such as solvent removal, purification, concentration, and sterilization, are more efficient, reproducible, and provide greater control over quality. However, these integrated systems require significant engineering investments and process streamlining. To maintain the consistency of product quality during the continuous manufacturing process, real-time monitoring of critical quality attributes (CQA) based on the use of Process Analytical Technology (PAT) tools is needed[144–146].

The issue of transferring technology established in academic research laboratories to industrial manufacturing settings creates further problems regarding knowledge management, process validation and quality system implementation. Initial cooperation with manufacturing professionals and regulatory staff may help to detect possible scale-up problems at the initial level of development[147].

6.2 Regulatory Requirements and Quality Control

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In accordance with regulatory requirements, it is crucial to determine and manage critical quality attributes (CQAs) during the manufacturing process. The parameters generally assessed when using glutathione (GSH)-responsive micellar systems include particle size and distribution, drug loading and encapsulation efficiency, redox-responsive profile of drug release, sterility, endotoxin, and micellar stability during storage. One of the issues related to the concept of complex nanopharmaceuticals is that comparability should be demonstrated following changes in the manufacturing processes, which require extensive analysis and characterization, and possibly further biological testing[148,149].

Polymeric prodrug systems exhibit complex chemical and structural characteristics, requiring complex analytical methods for thorough characterization. Orthogonal analytical methods are required to assess drug conjugation efficiency, molecular weight distribution, and disulfide bond integrity. To clarify how redox-responsive behaviour is achieved, it is important to conduct in vitro studies on drug release under physiologically relevant conditions. Stability tests must evaluate not only the chemical stability of the prodrug conjugate but also the physical stability of the micellar assembly under different storage conditions. One of the most important factors to be observed is the possible leakage of the drug during storage and any change in the size or shape of the micellar microstructure over time. Setting the right specifications and acceptance criteria for release and stability testing should be scientifically grounded and statistically tested in several production batches[41,42,150].

6.3 Safety Evaluation and Regulatory Toxicology

The safety assessment of GSH-responsive polymeric micelles requires the use of standard regulatory toxicology and nanomaterial-specific studies. In addition to drug release measurements, extensive pharmacokinetic and tissue distribution studies of the polymer carrier and its degradation products are required to establish a proper safety profile. The possibility of accelerated blood clearance (ABC) after repeated administration, which is often attributed to PEGylated nanocarriers, necessitates an in-depth study[75,151,152].

The pathways of biodegradation and elimination of polymeric constituents are also important safety factors. In particular, for disulfide-containing polymers, it is crucial to explain the degradation of thiol-terminated fragments and to define their metabolic and excretion pathways. Naturally occurring polymers, including hyaluronic acid (HA), should be strictly assessed using proper in vitro and in vivo models. These substances may possess potential genotoxic and carcinogenic properties and should be evaluated according to regulatory requirements, with special consideration given to any new degradation products of disulfide cleavage[153–155].

Cardiotoxicity is a primary issue to consider in formulations that include anthracyclines, although the risk presented by this particular delivery system is lower than that of traditional formulations. The five-step safety assessment must be based on the ideas of Quality by Design (QbD), which in turn allows recognition of the most important material characteristics and process parameters that determine the level of product safety. This would allow active risk management during the product lifecycle[1,115,134]

7. Future Projections

7.1 New Developments and Research Prospects.

GSH-responsive polymeric micelles are undergoing dynamic development, and several new technologies are likely to enhance their therapeutic potential. A more specific response is obtained when GSH sensitivity is combined with other tumor microenvironmental signals, such as pH, enzyme activity, and reactive oxygen species, in a combinatorial manner in multi-stimuli-responsive systems. These systems have progressively complex molecular structures but offer better spatial and temporal control of drug release[8,108].

More intensive targeting techniques using two or more ligands or based on stimulus-responsive surface markers allow an enhanced level of specificity for tumor recognition and cellular uptake. To increase tumor penetration and cellular internalization, transformable nanoparticles designed to tune their size, shape, or surface characteristics in response to a given stimulus can be programmed to sequentially cross various biological barriers[156,157].

Another potential area of research is the integration of diagnostic and therapeutic systems to formulate theranostic systems. These systems can also track delivery, release, and therapeutic responses using imaging agents, including fluorescence probes and MRI contrast agents, as well as therapeutic payloads. This method can facilitate personalized treatment planning

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and dose optimization according to the pharmacokinetics and tumor characteristics of individual patients[158–160].

Bioinspired and biomimetic approaches to synthetic nanoparticle coating or structural innovation can increase the biological compatibility and functionality of synthetic nanocarriers by using natural cellular components, such as cell membranes and exosomes, as coating materials. Biomimetic systems have been shown to have better circulation times, lower immunogenicity, and better targeting, because their natural surface properties are preserved[161].

7.2 Clinical Translation Roadmap

The effective transfer of GSH-responsive co-delivery systems from preclinical research to clinical practice requires effective planning and implementation. Lead candidates must be selected based on extensive in vitro and in vivo assays that focus on proven therapeutic advantages over current standards of care and accurately define the target patient population[162,163]. The development of clinically relevant manufacturing processes that can regularly generate materials of definite quality is an important milestone. Pre-IND meetings with regulatory authorities may provide the necessary guidance for the design and implementation of preclinical trials[164,165]. Preliminary evidence-based clinical studies should be directed towards patient groups with a high level of unmet medical requirements and tumors with augmented permeability and retention (EPR) impact[166,167]. Biomarker strategies and sophisticated imaging methods can provide pharmacodynamic information on target engagement and the mechanisms of action in early clinical trials[168]. The possibility of personalized medicine through patient stratification using tumor biology, CD44 expression, GSH levels, and imaging-based treatment selection is encouraging. Clinical outcomes can be significantly improved by the growth of companion diagnostics, which can determine which patients are likely to respond to these nanotherapeutics[169,170].

8. Conclusion

GSH-responsive polymeric micelles have emerged as a transformative platform in modern oncological nanomedicine, bridging the gap between intelligent molecular design and clinically viable therapeutic strategies. By harnessing the elevated redox potential of the tumor microenvironment, these nanocarriers enable site-specific drug release, reduce systemic toxicity, and enhance their therapeutic efficacy. Their integration with advanced prodrug chemistry allows for precise control over drug conjugation and release kinetics, while microfluidic fabrication ensures superior monodispersity, stability, and scalability compared with conventional manufacturing techniques. This synergistic convergence of stimuli responsiveness, co-delivery strategies, and engineering precision has shown significant promise in overcoming multidrug resistance and improving patient outcomes in preclinical studies.

Moreover, the ability to combine multiple therapeutic modalities, such as chemotherapy, photodynamic therapy, and immunotherapy, within a single nanoplatform, underscores their versatility and potential to redefine standard cancer treatment paradigms. Although challenges remain in technology transfer, regulatory compliance, and large-scale production, ongoing advancements in GMP-compatible microfluidics, quality-by-design approaches, and biomimetic surface engineering are rapidly bridging these gaps.

Ultimately, GSH-responsive micellar systems represent a critical step toward precision and personalized cancer therapy. Their continued evolution, combined with rigorous preclinical validation and well-structured clinical translation strategies, could pave the way for next-generation combination therapies that offer higher efficacy, reduced toxicity, and improved quality of life in patients with cancer.

References

1. Wan D, Pan J, Li C. Polymeric Micelles with Reduction-Responsive Function for Targeted Cancer Chemotherapy. ACS Appl Bio Mater. 2020 Jan 21;3(2):1139–1146.
2. Meng W, Huang L, Guo J, Xin Q, Liu J, Hu Y. Innovative Nanomedicine Delivery: Targeting Tumor Microenvironment to Defeat Drug Resistance. Pharmaceutics. 2024 Dec 3;16(12):1549.
3. Luhar M, Viradiya R, Panjabi S, Patel G. Nanotechnology in Ocular Drug Delivery: The Potential of Polymeric Micelles as a Drug Delivery Vehicle. Journal of Ocular Pharmacology and Therapeutics. 2025 Mar 1;41(2):54–64.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 1125-1148 | ISSN:2251-6727

4. Jin Z, Guo S, Al Amili M. Tumor Microenvironment-Responsive Drug Delivery Based on Polymeric Micelles for Precision Cancer Therapy: Strategies and Prospects. Biomedicines. 2024 Feb 11;12(2):417.

5. Palminteri M, Ferraresi A, Trotta F, Dhakar NK, Isidoro C, Caldera F, et al. Cyclodextrin nanosponge for the GSH-mediated delivery of Resveratrol in human cancer cells. Nanotheranostics. 2021 Jan 1;5(2):197–212.

6. Chen D, Lu X, Liu X, Tian J. Nanoparticle drug delivery systems for synergistic delivery of tumor therapy. Front Pharmacol. 2023 Feb 16;14.

7. Rawas-Qalaji M, Cagliani R, Al-Hashimi N, Al-Dabbagh R, Al-Dabbagh A, Hussain Z. Microfluidics in drug delivery: review of methods and applications. Pharmaceutical Development and Technology. 2022 Dec 30;28(1):61–77.

8. Sun C, Qi L, He B, Yang L, Lu J, Zhong Z, et al. Redox-sensitive polymeric micelles with aggregation-induced emission for bioimaging and delivery of anticancer drugs. J Nanobiotechnol. 2021 Jan 7;19(1).

9. Ma W, Wang X, Zhang D, Mu X. Research Progress of Disulfide Bond Based Tumor Microenvironment Targeted Drug Delivery System. IJN. 2024 July 1;19:7547–7566.

10. Lee CG, Kwon T, Kim B, Nam JS, Lee J, Lee C. Dual-Modulated Release of a Cytotoxic Photosensitizer Using Photogenerated Reactive Oxygen Species and Glutathione. Angew Chem Int Ed. 2022 Sept 12;61(42).

11. Liu T, Lu Q, Zuo S, Cheng M, He Z, Zhang H, et al. Hybrid chalcogen bonds in prodrug nanoassemblies provides dual redox-responsivity in the tumor microenvironment. Nat Commun. 2022 Nov 24;13(1).

12. Li J, Xing X, Yu XQ, Gu B, Liu YH, Hu ZE, et al. GSH/pH dual-responsive biodegradable camptothecin polymeric prodrugs combined with doxorubicin for synergistic anticancer efficiency. Biomater Sci. 2019 Jan 1;7(8):3277–3286.

13. Fu CP, Cai XY, Chen SL, Yu HW, Fang Y, Feng XC, et al. Hyaluronic Acid-Based Nanocarriers for Anticancer Drug Delivery. Polymers. 2023 May 16;15(10):2317.

14. Simhadri A, Sana J, Dommeti M. A Comprehensive Review on the Nanotechnology-based Intranasal Drug Delivery Systems for Brain Targeting. JOPIR. 2024 Aug 4;2(4):015–023.

15. Bonacucina G, Mencarelli G, Cespi M, Palmieri GF, Giorgioni G. Thermosensitive Self-Assembling Block Copolymers as Drug Delivery Systems. Polymers. 2011 Apr 19;3(2):779–811.

16. Ferrentino N, Behroozi Kohlan T, Mehrtashfar S, Finne-Wistrand A, Pappalardo D. Dual-Responsive Nanoparticles for Smart Drug Delivery: A NIR Light-Sensitive and Redox-Reactive PEG-PCL-Based System. Biomacromolecules. 2024 Nov 11;25(12):7660–7673.

17. Jiang J, Niu C, Li J, Wang W, Zhou B, Wu W, et al. Fabrication of Polymer Micelles with Zwitterionic Shell and Biodegradable Core for Reductively Responsive Release of Doxorubicin. Polymers. 2019 June 9;11(6):1019.

18. Ulbrich K, Zbořil R, Bakandritsos A, Tuček J, Holá K, Šubr V. Targeted Drug Delivery with Polymers and Magnetic Nanoparticles: Covalent and Noncovalent Approaches, Release Control, and Clinical Studies. Chem Rev. 2016 Apr 25;116(9):5338–5431.

19. Bagade OM, Doke-Bagade PE, Wankhade KS, Doke SE. Lipid And Polymer Based Nano-Phytotherapeutics. Nanofab. 2023 Dec 20;8.

20. Guerassimoff L, Nicolas J, Bossion A, Ferrere M. Stimuli-sensitive polymer prodrug nanocarriers by reversible-deactivation radical polymerization. Chem Soc Rev. 2024 Jan 1;53(12):6511–6567.

21. Wu R, Zhu JJ, Liu J, Jiang LP. Effects of Small Molecules on DNA Adsorption by Gold Nanoparticles and a Case Study of Tris(2-carboxyethyl)phosphine (TCEP). Langmuir. 2019 Sept 19;35(41):13461–13468.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 1125-1148 | ISSN:2251-6727

22. Yang Y, Wang S, Wang Y, Zhou S, Sun B, Liu H, et al. Trisulfide bond-mediated doxorubicin dimeric prodrug nanoassemblies with high drug loading, high self-assembly stability, and high tumor selectivity. Sci Adv. 2020 Nov 4;6(45).

23. Bai Y, Tian W, Li X, Fan L, Li M, Shang Q, et al. Host-guest interaction-based supramolecular prodrug self-assemblies for GSH-consumption augmented chemotherapy. J Mater Chem B. 2022 Jan 1;10(26):4952–4958.

24. Chen B, Dai W, Zhang Q, He B, Zhang H, Wang Y, et al. Current Multistage Drug Delivery Systems Based on the Tumor Microenvironment. Theranostics. 2017 Jan 1;7(3):538–558.

25. Song J, Tan Y, Yang Z, Wang X, Wang B, Yao H, et al. Schiff-Linked PEGylated Doxorubicin Prodrug Forming pH-Responsive Nanoparticles With High Drug Loading and Effective Anticancer Therapy. Front Oncol. 2021 Mar 25;11.

26. Edupuganti VVSR, Gamble AB, Tyndall JDA. Self-immolative Linkers in Prodrugs and Antibody Drug Conjugates in Cancer Treatment. PRA. 2021 May 8;16(4):479–497.

27. Cheng G, Tao S, Liu S, Wang P, Zhang C, Liu J, et al. Glutathione-Responsive Polymersome with Continuous Glutathione Depletion for Enhanced Photodynamic Therapy and Hypoxia-Activated Chemotherapy. ACS Macro Lett. 2024 Apr 29;13(5):599–606.

28. Loh XJ, Yee BJH, Chia FS. Sustained delivery of paclitaxel using thermogelling poly(PEG/PPG/PCL urethane)s for enhanced toxicity against cancer cells. J Biomedical Materials Res. 2012 May 23;100A(10):2686–2694.

29. Wang SY, Pan YH, Qu YC, Chen XX, Shao N, Niu LY, et al. Activatable theranostic prodrug scaffold with tunable drug release rate for sequential photodynamic and chemotherapy. Smart Molecules. 2024 Feb 20;2(1).

30. Chen H, Wang Z, Xu S, Zong S, Chen P, Wu L, et al. SERS-fluorescence monitored drug release of a redox-responsive nanocarrier based on graphene oxide in tumor cells. ACS Appl Mater Interfaces. 2014 Oct 13;6(20):17526–17533.

31. Bej R, Ghosh S. Glutathione Triggered Cascade Degradation of an Amphiphilic Poly(disulfide)-Drug Conjugate and Targeted Release. Bioconjugate Chem. 2018 Dec 17;30(1):101–110.

32. Wei X, Liao J, Davoudi Z, Zheng H, Chen J, Li D, et al. Folate Receptor-Targeted and GSH-Responsive Carboxymethyl Chitosan Nanoparticles Containing Covalently Entrapped 6-Mercaptopurine for Enhanced Intracellular Drug Delivery in Leukemia. Marine Drugs. 2018 Nov 8;16(11):439.

33. Jia H, Chang K, Gu SY. Synthesis and Properties of Reversible Disulfide Bond-based Self-healing Polyurethane with Triple Shape Memory Properties. Chin J Polym Sci. 2019 May 21;37(11):1119–1129.

34. Zhang Q, Zhang M, He J, Ni P. A polyphosphoester-conjugated camptothecin prodrug with disulfide linkage for potent reduction-triggered drug delivery. J Mater Chem B. 2015 Jan 1;3(24):4922–4932.

35. Wen H, Zhou M, Zhang J, Pan Y, Zhang X, Tan Y, et al. Physicochemical Characterization, Antioxidant and Anticancer Activity Evaluation of an Acidic Polysaccharide from Alpinia officinarum Hance. Molecules. 2024 Apr 16;29(8):1810.

36. Emel'Yanov AI, Trofimova OM, Pozdnyakov AS, Bolgova YI. Green Synthesis of Soluble Polysilsesquioxane with Phthalimide Groups. IJMS. 2023 Dec 19;25(1):57.

37. Tao X, Zhao T, Qiu W, Li H. Synthesis of nanosized zirconium carbide from preceramic polymers by the facile one-pot reaction. Polymers for Advanced Techs. 2010 Feb 4;21(4):300–304.

38. Öztürk T, Hazer B, Göktaş M. One-step synthesis of triarm block copolymers via simultaneous reversible-addition fragmentation chain transfer and ring-opening polymerization. J of Applied Polymer Sci. 2010 Mar 29;117(3):1638–1645.

39. Gülel Ş, Güvenilir Y. Lipase catalyzed synthesis of bio-based polyamide 5.6: an alternative route. Journal of Macromolecular Science, Part A. 2023 Dec 18;61(1):69–78.

40. Du K, Feng F, Xia Q, Sun J. Visible Light and Glutathione Dually Responsive Delivery of a Polymer-Conjugated Temozolomide Intermediate for Glioblastoma Chemotherapy. ACS Appl Mater Interfaces. 2021 Nov 17;13(47):55851–55861.

41. Kayal S, Kola P, Pal J, Mandal M, Dhara D. Self-Indicating Polymer Prodrug Nanoparticles for pH-Responsive Drug Delivery in Cancer Cells and Real-Time Monitoring of Drug Release. ACS Appl Bio Mater. 2024 Aug 26;7(9):5810–5822.

42. Li J, Liu P. Facile Synthesis of a Redox-Responsive Hyperbranched Polymer Prodrug as a Unimolecular Micelle for the Tumor-Selective Drug Delivery. Bioconjugate Chem. 2022 Jan 28;33(2):411–417.

43. Drude N, Roller M, Königs H, Winz OH, Möller M, Morgenroth A, et al. Impact of Glutathione Modulation on Stability and Pharmacokinetic Profile of Redox-Sensitive Nanogels. Small. 2018 Feb 19;14(14):1704093.

44. Xu W, Li Q, Deng J, Wu C, Li K, Wang J, et al. Cancer cell membrane-coated nanogels as a redox/pH dual-responsive drug carrier for tumor-targeted therapy. J Mater Chem B. 2021 Jan 1;9(38):8031–8037.

45. Guo WW, Lu YY, Wang TT, Yang QY, Gao J, Han M, et al. Intracellular Restructured Reduced Glutathione-Responsive Peptide Nanofibers for Synergetic Tumor Chemotherapy. Biomacromolecules. 2019 Dec 18;21(2):444–453.

46. Sethuraman V, Kandasamy R, Krishnaswami V, Janakiraman K. Recent Progress in Stimuli-Responsive Intelligent Nano Scale Drug Delivery Systems: A Special Focus Towards pH-Sensitive Systems. CDT. 2021 Jan 28;22(8):947–966.

47. Guo X, Shi C, Cai Z, Yang G, Wang J, Zhou S. Dual-Responsive Polymer Micelles for Target-Cell-Specific Anticancer Drug Delivery. Chem Mater. 2014 July 28;26(15):4405–4418.

48. Shaikh R, Bhattacharya S. Polymeric Micelles in Colorectal Cancer Therapy: A Comprehensive Review of Nano-drug Delivery Strategies, Copolymer Types, Physicochemical Characteristics, and Therapeutic Applications. CMC. 2025 June 1;32(20):4033–4054.

49. Mares AG, Marti JS, Pujals S, Pacassoni G, Albertazzi L. Formulation of tunable size PLGA-PEG nanoparticles for drug delivery using microfluidic technology. PLoS ONE. 2021 June 18;16(6):e0251821.

50. Stefanache A, Lungu II, Anton N, Damir D, Gutu C, Olaru I, et al. Chitosan Nanoparticle-Based Drug Delivery Systems: Advances, Challenges, and Future Perspectives. Polymers. 2025 May 23;17(11):1453.

51. Berillo D, Yeskendir A, Zharkinbekov Z, Raziyeva K, Saparov A. Peptide-Based Drug Delivery Systems. Medicina. 2021 Nov 5;57(11):1209.

52. Wang J, Xing X, Huang F, Zhou C, Lou J, Liang W, et al. Cationic amphiphilic drugs self-assemble to the core–shell interface of PEGylated phospholipid micelles and stabilize micellar structure. Phil Trans R Soc A. 2013 Oct 13;371(2000):20120309.

53. Silindir Gunay M, Yekta Ozer A, Chalon S. Drug Delivery Systems for Imaging and Therapy of Parkinson's Disease. CN. 2016 Apr 8;14(4):376–391.

54. Mehraji S, Devoe DL. Microfluidic synthesis of lipid-based nanoparticles for drug delivery: recent advances and opportunities. Lab Chip. 2024 Jan 1;24(5):1154–1174.

55. Duan C, Wang W, Xie Q. Review article: Fabrication of nanofluidic devices. Biomicrofluidics. 2013 Mar 1;7(2):026501.

56. Vincenti L, Pellegrino P, Cascione M, De Matteis V, Farella I, Quaranta F, et al. Crafting at the nanoscale: A comprehensive review of mechanical Atomic force microscopy-based lithography methods and their evolution. Materials & Design. 2024 May 22;243:113036.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 1125-1148 | ISSN:2251-6727

57. Xia HM, Wu JW, Zhang J, Wang ZP, Zheng JJ. Nonlinear microfluidics: device physics, functions, and applications. Lab Chip. 2021 Jan 1;21(7):1241–1268.

58. Perumal S, Lee W, Atchudan R. A Review of Polymeric Micelles and Their Applications. Polymers. 2022 June 20;14(12):2510.

59. Damiati S, Kodzius R, Damiati SA, Kompella UB. Microfluidic Devices for Drug Delivery Systems and Drug Screening. Genes. 2018 Feb 16;9(2):103.

60. Kumar P, Pathak M, Kumar V. Droplet formation dynamics under perpendicular and head-on dispersed phase configuration in a microfluidic T-junction. Physics of Fluids. 2024 Nov 1;36(11).

61. Luo J, Yang K, Yang Y, Lu W, Fu Q, Liu J, et al. Research Strategies for Precise Manipulation of Micro/Nanoparticle Drug Delivery Systems Using Microfluidic Technology: A Review. Pharmaceutical Fronts. 2024 May 23;06(02):e69–e100.

62. Liu Z, Zhao J, Pang Y, Wang X. Generation of droplets in the T-junction with a constriction microchannel. Microfluid Nanofluid. 2018 Oct 20;22(11).

63. Zeng W, Chang H, Neužil P, Wang B. Quantitative study of droplet generation by pressure-driven microfluidic flows in a flow-focusing microdroplet generator. Physics of Fluids. 2024 Mar 1;36(3).

64. Roshan U, Dai Y, Yadav AS, Hettiarachchi S, Mudugamuwa A, Zhang J, et al. Flexible droplet microfluidic devices for tuneable droplet generation. Sensors and Actuators B: Chemical. 2024 Sept 10;422:136617.

65. Nieves-Remacha MJ, Jensen KF, Kulkarni AA. Hydrodynamics of Liquid–Liquid Dispersion in an Advanced-Flow Reactor. Ind Eng Chem Res. 2012 Dec 4;51(50):16251–16262.

66. Lin Q, Bao J, Li Q, Tan D, Li L, Zheng R, et al. Transport Mechanism and Optimization Design of LBM–LES Coupling-Based Two-Phase Flow in Static Mixers. Processes. 2025 May 26;13(6):1666.

67. Park JE, Kang TG, Jung SY. The impact of thixotropic behavior on microfluidic mixing in a staggered-herringbone mixer. Physics of Fluids. 2024 Apr 1;36(4).

68. Kwak TJ, Najera MA, Nam YG, Chang WJ, Lee SW, Strickler JR. Convex Grooves in Staggered Herringbone Mixer Improve Mixing Efficiency of Laminar Flow in Microchannel. PLoS ONE. 2016 Nov 4;11(11):e0166068.

69. Hwang YH, Shepherd SJ, Kim D, Mukalel AJ, Mitchell MJ, Issadore DA, et al. Robust, Scalable Microfluidic Manufacturing of RNA-Lipid Nanoparticles Using Immobilized Antifouling Lubricant Coating. ACS Nano. 2024 Dec 19;19(1):1090–1102.

70. Maged A, Abdelbaset R, Mahmoud AA, Elkasabgy NA. Merits and advances of microfluidics in the pharmaceutical field: design technologies and future prospects. Drug Delivery. 2022 May 25;29(1):1549–1570.

71. Jaradat E, Weaver E, Meziane A, Lamprou DA. Microfluidic paclitaxel-loaded lipid nanoparticle formulations for chemotherapy. International Journal of Pharmaceutics. 2022 Oct 19;628:122320.

72. Fabozzi A, Borzacchiello A, Pagliuca M, Della Sala F, Solimando N, Longobardo G, et al. Design of functional nanoparticles by microfluidic platforms as advanced drug delivery systems for cancer therapy. Lab Chip. 2023 Jan 1;23(5):1389–1409.

73. Wang J, Li Z, Wang C, Wang X, Qiu H, Li S, et al. Polylactide-Cholesterol Stereocomplex Micelle Encapsulating Chemotherapeutic Agent for Improved Antitumor Efficacy and Safety. j biomed nanotechnol. 2018 Dec 1;14(12):2102–2113.

74. Bauer TA, Rosenauer C, Barz M, Maskos M, Koynov K, Siemer S, et al. Complex Structures Made Simple - Continuous Flow Production of Core Cross-Linked Polymeric Micelles for

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 1125-1148 | ISSN:2251-6727

Paclitaxel Pro-Drug-Delivery. Advanced Materials. 2023 Apr 6;35(21).

75. Ghezzi M, Pescina S, Padula C, Santi P, Del Favero E, Cantù L, et al. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. Journal of Controlled Release. 2021 Feb 27;332:312–336.

76. Wu W, Zhang J, Hao X, Yi P, Cheng Y, Li Z, et al. 4/6-Herto-arm and 4/6-mikto-arm star-shaped block polymeric drug-loaded micelles and their pH-responsive controlled release properties: a dissipative particle dynamics simulation. Phys Chem Chem Phys. 2019 Jan 1;21(27):15222–15232.

77. Iacobazzi RM, Azzariti A, Lopedota AA, Bruno V, Lee BC, Di Fonte R, et al. Microfluidic-Assisted Preparation of Targeted pH-Responsive Polymeric Micelles Improves Gemcitabine Effectiveness in PDAC: In Vitro Insights. Cancers. 2021 Dec 21;14(1):5.

78. Xiao L, Zhang L, Li S, Zhu Y, Yu Q, Liu Z, et al. Visualization and Quantification of Drug Release by GSH-Responsive Multimodal Integrated Micelles. JACS Au. 2024 Mar 5;4(3):1194–1206.

79. Mottaghi S, Nazari M, Fattahi SM, Nazari M, Babamohammadi S. Droplet size prediction in a microfluidic flow focusing device using an adaptive network based fuzzy inference system. Biomed Microdevices. 2020 Sept 1;22(3).

80. Thorsen T, Arnold FH, Quake SR, Roberts RW. Dynamic pattern formation in a vesicle-generating microfluidic device. Phys Rev Lett. 2001 Apr 30;86(18):4163–4166.

81. Gavali SR, Pawar DPM. Computational analysis of a four-flap valveless micropump (FFVM) for low reynolds number applications in microfluidic systems. Phys Scr. 2024 June 6;99(7):075011.

82. Bilati U, Allémann E, Doelker E. Poly(D,L-lactide-co-glycolide) protein-loaded nanoparticles prepared by the double emulsion method—processing and formulation issues for enhanced entrapment efficiency. Journal of Microencapsulation. 2005 Mar 1;22(2):205–214.

83. Zahariev N, Marudova M, Milenkova S, Uzunova Y, Pilicheva B. Casein Micelles as Nanocarriers for Benzydamine Delivery. Polymers. 2021 Dec 13;13(24):4357.

84. Huanbutta K, Teppitak V, Sangnim T, Klinchuen N, Deebugkum T, Suwanpitak K, et al. Key Fabrications of Chitosan Nanoparticles for Effective Drug Delivery Using Flow Chemistry Reactors. IJN. 2023 Dec 1;18:7889–7900.

85. Xu L, Zhao Z, Zhao C, Li Y, Liu Y, Weng Y, et al. Development of a concentration-controlled sequential nanoprecipitation for making lipid nanoparticles with high drug loading. Aggregate. 2023 June 17;4(6).

86. Zu Y, Jiang R, Zhao X, Sun Z, Zu B, Zhao D, et al. A Novel Preparation Method for Camptothecin (CPT) Loaded Folic Acid Conjugated Dextran Tumor-Targeted Nanoparticles. IJMS. 2011 June 28;12(7):4237–4249.

87. Ashar F, Hani U, Osmani RAM, Kazim SM, Selvamuthukumar S. Preparation and Optimization of Ibrutinib-Loaded Nanoliposomes Using Response Surface Methodology. Polymers. 2022 Sept 17;14(18):3886.

88. Wang Z, Zhang P, Hao N, Yang S, Huang TJ, Rich J, et al. Acoustofluidics for simultaneous nanoparticle-based drug loading and exosome encapsulation. Microsyst Nanoeng. 2022 Apr 28;8(1).

89. Zhang L, Chen Q, Ma Y, Sun J. Microfluidic Methods for Fabrication and Engineering of Nanoparticle Drug Delivery Systems. ACS Appl Bio Mater. 2019 Nov 25;3(1):107–120.

90. Karthikeyan K, Sujatha L. Study of Permissible Flow Rate and Mixing Efficiency of the Micromixer Devices. International Journal of Chemical Reactor Engineering. 2019 Jan 26;17(1).

91. Wang K, Huang K, Wang L, Lin X, Tan M, Su W. Microfluidic Strategies for Encapsulation, Protection, and Controlled Delivery of Probiotics. J Agric Food Chem. 2024 June 26;72(27):15092–15105.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 1125-1148 | ISSN:2251-6727

92. Wu J, Lee D, Yadavali S, Issadore DA, Hwang Y. Micro-Patterning Wettability in Very Large Scale Microfluidic Integrated Chips for Double Emulsion Generation. Adv Funct Materials. 2023 Oct 17;34(3).

93. Abrishamkar A, Nilghaz A, Naeimirad M, Demello AJ, Saadatmand M. Microfluidic-assisted fiber production: Potentials, limitations, and prospects. Biomicrofluidics. 2022 Nov 17;16(6):061504.

94. Jia F, Gao Y, Wang H. Recent Advances in Drug Delivery System Fabricated by Microfluidics for Disease Therapy. Bioengineering. 2022 Oct 29;9(11):625.

95. Lim JM, Bertrand N, Valencia PM, Rhee M, Langer R, Jon S, et al. Parallel microfluidic synthesis of size-tunable polymeric nanoparticles using 3D flow focusing towards in vivo study. Nanomedicine: Nanotechnology, Biology and Medicine. 2013 Aug 20;10(2):401–409.

96. Carvalho BG, Michelon M, Han SW, De La Torre LG, Ceccato BT. Advanced Microfluidic Technologies for Lipid Nano-Microsystems from Synthesis to Biological Application. Pharmaceutics. 2022 Jan 7;14(1):141.

97. Maeki M, Okada Y, Uno S, Sugiura K, Suzuki Y, Okuda K, et al. Mass production system for RNA-loaded lipid nanoparticles using piling up microfluidic devices. Applied Materials Today. 2023 Feb 16;31:101754.

98. Garg S, Heuck G, Ip S, Ramsay E. Microfluidics: a transformational tool for nanomedicine development and production. Journal of Drug Targeting. 2016 Aug 5;24(9):821–835.

99. Santoso A, David MK, Boukany PE, Van Steijn V, Van Ommen JR. Atmospheric pressure atomic layer deposition for in-channel surface modification of PDMS microfluidic chips. Chemical Engineering Journal. 2024 Aug 30;498:155269.

100. Mehta G, Cha W, Tung YC, Lee J, Takayama S, Linderman JJ. Hard Top Soft Bottom Microfluidic Devices for Cell Culture and Chemical Analysis. Anal Chem. 2009 Apr 21;81(10):3714–3722.

101. Schneider S, Loskill P, Schlünder K, Brás EJS, Schneider O. Facile Patterning of Thermoplastic Elastomers and Robust Bonding to Glass and Thermoplastics for Microfluidic Cell Culture and Organ-on-Chip. Micromachines. 2021 May 18;12(5):575.

102. Agha A, Alamoodi N, Abu-Nada E, Alnaimat F, Alazzam A, Mathew B, et al. A Review of Cyclic Olefin Copolymer Applications in Microfluidics and Microdevices. Macro Materials & Eng. 2022 Apr 26;307(8):2200053.

103. Shakeri A, Jarad NA, Khan S, F Didar T. Bio-functionalization of microfluidic platforms made of thermoplastic materials: A review. Analytica Chimica Acta. 2021 Nov 22;1209:339283.

104. Toth MJ, Kim Y, Kim T. Robust manufacturing of lipid-polymer nanoparticles through feedback control of parallelized swirling microvortices. Lab Chip. 2017 Jan 1;17(16):2805–2813.

105. Novoa JJ, Arendzen CH, Grundeken E, Rabelink TJ, Rajaei B, Dijkers PF, et al. Good Manufacturing Practice–compliant human induced pluripotent stem cells: from bench to putative clinical products. Cytotherapy. 2024 Mar 5;26(6):556–566.

106. Hu H, Ao Y, Xu H, Li Y, Yang X, Wan Y, et al. Redox-Sensitive Hydroxyethyl Starch-Doxorubicin Conjugate for Tumor Targeted Drug Delivery. ACS Appl Mater Interfaces. 2016 Nov 7;8(45):30833–30844.

107. Zhuo W, Zhang R, Yi L, Guo A, Zhang X, Gao X, et al. A Targeted and Responsive Nanoprodrug Delivery System for Synergistic Glioma Chemotherapy. Small. 2024 Mar 3;20(30).

108. Darge HF, Addisu KD, Tsai HC, Birhan YS, Hanurry EY, Mekonnen TW, et al. Actively Targeting Redox-Responsive Multifunctional Micelles for Synergistic Chemotherapy of Cancer. ACS Omega. 2024 July 29;9(32):34268–34280.

109. Zhang L, Liu Z, Huang J, Kong C, Qian F, Chen H, et al. Improving Drug Delivery of Micellar Paclitaxel against Non-Small Cell Lung Cancer by Coloading Itraconazole as a Micelle Stabilizer

and a Tumor Vascular Manipulator. Small. 2018 Nov 16;14(51):1802112.

110. He M, Chen X, Yu F, Qin B, Wang H, Lavery L, et al. Enhanced Antitumor Efficacy and Reduced Cardiotoxicity of Ultrasound-Mediated Doxorubicin Delivery by Microbubble-Liposome Complexes. Ultrasound in Medicine & Biology. 2025 Aug 1;51(8):1240–1249.

111. Zhang M, Ying N, Chen J, Wu L, Liu H, Luo S, et al. Engineering a pH-responsive polymeric micelle co-loaded with paclitaxel and triptolide for breast cancer therapy. Cell Proliferation. 2024 Jan 16;57(6).

112. Yuan H, Truchan N, Luan X, Guo H, He M, Burnett J, et al. Albumin Nanoparticle of Paclitaxel (Abraxane) Decreases while Taxol Increases Breast Cancer Stem Cells in Treatment of Triple Negative Breast Cancer. Mol Pharmaceutics. 2020 June 2;17(7):2275–2286.

113. Lang T, Zhang P, Dong X, Huang Y, Li Y, Yin Q, et al. Ly6Chi Monocytes Delivering pH-Sensitive Micelle Loading Paclitaxel Improve Targeting Therapy of Metastatic Breast Cancer. Adv Funct Materials. 2017 May 11;27(26):1701093.

114. Zhou N, Meng L, Yan K, Shao Y, Yu D, Wang D, et al. Acid-Responsive and Biologically Degradable Polyphosphazene Nanodrugs for Efficient Drug Delivery. ACS Biomater Sci Eng. 2020 June 1;6(7):4285–4293.

115. Zhang C, Zhao Y, Zhao Y, Li X, Wang Y, Liu H, et al. Biodegradable Micelles for NIR/GSH-Triggered Chemophototherapy of Cancer. Nanomaterials. 2019 Jan 11;9(1):91.

116. Xiang H, Phua SZF, Tham HP, Liu JG, Zhao Y, Chen H. Cyclometalated Iridium(III)-Complex-Based Micelles for Glutathione-Responsive Targeted Chemotherapy and Photodynamic Therapy. ACS Appl Mater Interfaces. 2017 Aug 9;9(33):27553–27562.

117. Zhu F, Ren F, Tan G, Liu S, Jiang Y, Yu Z, et al. Smart nanoplatform for sequential drug release and enhanced chemo-thermal effect of dual drug loaded gold nanorod vesicles for cancer therapy. J Nanobiotechnol. 2019 Mar 27;17(1).

118. Guo Y, Zhong W, Peng C, Guo L. Topical Delivery of Dual Loaded Nano-Transfersomes Mediated Chemo-Photodynamic Therapy against Melanoma via Inducing Cell Cycle Arrest and Apoptosis. IJMS. 2024 Sept 5;25(17):9611.

119. Bashiru M, Macchi S, Hooshmand N, Griffin RJ, Ishtiaq A, Jalihal A, et al. Doxorubicin-Based Ionic Nanomedicines for Combined Chemo-Phototherapy of Cancer. ACS Appl Nano Mater. 2024 Jan 17;7(2):2176–2189.

120. Sun H, Wang X, Feng M, Chen S, Yin B, Wang R, et al. Near-infrared photothermal liposomal nanoantagonists for amplified cancer photodynamic therapy. J Mater Chem B. 2020 Jan 1;8(32):7149–7159.

121. Chen Y, Chen Y, Wang Z, Yang L, Zhang Y, Zhang Z, et al. Iron-based MOF with Catalase-like activity improves the synergistic therapeutic effect of PDT/ferroptosis/starvation therapy by reversing the tumor hypoxic microenvironment. J Nanobiotechnol. 2024 Nov 14;22(1).

122. Ma B, Ma Y, Deng B, Xiao P, Huang P, Wang D, et al. Tumor microenvironment-responsive spherical nucleic acid nanoparticles for enhanced chemo-immunotherapy. J Nanobiotechnol. 2023 May 26;21(1).

123. Li Y, Tan L, Li Q, Huang X, Zhang H, Wu C, et al. CDK12/13 inhibition induces immunogenic cell death and enhances anti-PD-1 anticancer activity in breast cancer. Cancer Letters. 2020 Sept 15;495:12–21.

124. Featherston T, Helem S, Smyth LCD, Hampton MB, Paumann-Page M. Comparing automated cell imaging with conventional methods of measuring cell proliferation and viability. Toxicology Mechanisms and Methods. 2024 June 15;34(8):886–896.

125. Arul M, Roslani AC, Cheah SH. Heterogeneity in cancer cells: variation in drug response in different primary and secondary colorectal cancer cell lines in vitro. In Vitro CellDevBiol-Animal. 2017 Jan 24;53(5):435–447.

126. Parczyk J, Ruhnau J, Piaskowski NN, Eickholt B, Wu H, Schilling M, et al. Dichloroacetate and PX-

478 exhibit strong synergistic effects in a various number of cancer cell lines. BMC Cancer. 2021 Apr 30;21(1).

127. Gökşen Tosun N. Enhancing therapeutic efficacy in breast cancer: a study on the combined cytotoxic effects of doxorubicin and MPC-3100. Naunyn-Schmiedeberg's Arch Pharmacol. 2023 Nov 2;397(5):3249–3259.

128. Sun H, Meng F, Zhong Z, Deng C, Cheng R. Reduction-responsive polymeric micelles and vesicles for triggered intracellular drug release. Antioxidants & Redox Signaling. 2014 Feb 20;21(5):755–767.

129. Abdullah-Al-Nahain A, Park SY, Lee KD, Lee H, Lee YS. Development of Disulfide Core-Crosslinked Pluronic Nanoparticles as an Effective Anticancer-Drug-Delivery System. Macromolecular Bioscience. 2011 June 29;11(9):1264–1271.

130. Sargazi S, Mukhtar M, Rahdar A, Barani M, Pandey S, Díez-Pascual AM. Active Targeted Nanoparticles for Delivery of Poly(ADP-ribose) Polymerase (PARP) Inhibitors: A Preliminary Review. IJMS. 2021 Sept 25;22(19):10319.

131. Singhal SS, Mirzapoiazova T, Garg P, Sharma S, Ramisetty SK, Kulkarni P, et al. Recent Advancement in Breast Cancer Research: Insights from Model Organisms-Mouse Models to Zebrafish. Cancers. 2023 May 29;15(11):2961.

132. Abdolahi S, Ghazvinian Z, Muhammadnejad S, Saleh M, Asadzadeh Aghdaei H, Baghaei K. Patient-derived xenograft (PDX) models, applications and challenges in cancer research. J Transl Med. 2022 May 10;20(1).

133. Sharifi M, Falahati M, Jafari S, Zheng Y, Paray BA, Gong G, et al. Antimetastatic Activity of Lactoferrin-Coated Mesoporous Maghemite Nanoparticles in Breast Cancer Enabled by Combination Therapy. ACS Biomater Sci Eng. 2020 May 13;6(6):3574–3584.

134. Majumder N, G Das N, Das SK. Polymeric micelles for anticancer drug delivery. Ther Deliv. 2020 Sept 15;11(10):613–635.

135. Song M, Aipire A, Dilxat E, Li J, Xia G, Jiang Z, et al. Research Progress of Polysaccharide-Gold Nanocomplexes in Drug Delivery. Pharmaceutics. 2024 Jan 9;16(1):88.

136. Meng X, Shen Y, Zhao H, Lu X, Wang Z, Zhao Y. Redox-manipulating nanocarriers for anticancer drug delivery: a systematic review. J Nanobiotechnol. 2024 Sept 28;22(1).

137. Al Refaai KA, Alsawaftah NA, Abuwatfa W, Husseini GA. Drug Release via Ultrasound-Activated Nanocarriers for Cancer Treatment: A Review. Pharmaceutics. 2024 Oct 27;16(11):1383.

138. Lin Z, Wu C, Song D, Zhu C, Wu B, Wang J, et al. Sarmentosin alleviates doxorubicin-induced cardiotoxicity and ferroptosis via the p62-Keap1-Nrf2 pathway. Redox Report. 2024 Aug 16;29(1).

139. Shen BY, Wang GJ, Shen JJ, Kang D, Li XN, Zhu ZP, et al. Is the combinational administration of doxorubicin and glutathione a reasonable proposal? Acta Pharmacol Sin. 2018 Sept 14;40(5):699–709.

140. Xiong B, Liu P, Huang Y, Lin Y, Liu H, Yi M, et al. A pH/GSH Dual-Responsive, Folic Acid Targeted Drug Delivery System Based on Bovine Serum Albumin Nanoparticles for Cancer Therapy. Part & Part Syst Charact. 2024 Feb 15;41(6).

141. Xu Z, Kang Y, Liu S, Wang M. Glutathione-Responsive Polymeric Micelles Formed by a Biodegradable Amphiphilic Triblock Copolymer for Anticancer Drug Delivery and Controlled Release. ACS Biomater Sci Eng. 2015 June 16;1(7):585–592.

142. Amstad E, Cohen N, Weitz DA, Eggersdorfer M, Ren CL, Kodger TE, et al. Parallelization of microfluidic flow-focusing devices. Phys Rev E. 2017 Apr 14;95(4–1).

143. Butt MA, Imran Akca B, Mateos X. Integrated Photonic Biosensors: Enabling Next-Generation Lab-on-a-Chip Platforms. Nanomaterials. 2025 May 13;15(10):731.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(6), 1125-1148 | ISSN:2251-6727

144. Ko SH, Chandra D, Ouyang W, Han J, Kwon T, Karande P. Nanofluidic device for continuous multiparameter quality assurance of biologics. Nature Nanotech. 2017 May 22;12(8):804–812.

145. Chemmalil L, Li Z, Tan Z, West J, Kuang J, Ehamparanathan V, et al. Online/at-line measurement, analysis and control of product titer and critical product quality attributes (CQAs) during process development. Biotech & Bioengineering. 2020 Aug 24;117(12):3757–3765.

146. Gyorgypal A, Chundawat SPS. Integrated Process Analytical Platform for Automated Monitoring of Monoclonal Antibody N-Linked Glycosylation. Anal Chem. 2022 Apr 6;94(19):6986–6995.

147. Khinvasara T, Ness S, Shankar A. Leveraging AI for Enhanced Quality Assurance in Medical Device Manufacturing. AJRCoS. 2024 Apr 8;17(6):13–35.

148. Malik DJ, Fernandes D, Weichert H, Collin J, Goldschmitt D, Goncalves-Ribeiro H, et al. Advanced Manufacturing, Formulation and Microencapsulation of Therapeutic Phages. Clinical Infectious Diseases. 2023 Nov 2;77(Suppl 5):S370–S383.

149. Sheybanifard M, Metselaar JM, Damen M, Gerich A, De Laporte L, Omidinia-Anarkoli A, et al. Liposome manufacturing under continuous flow conditions: towards a fully integrated set-up with in-line control of critical quality attributes. Lab Chip. 2023 Jan 1;23(1):182–194.

150. Liu X, Hu XY, Shao W, Zhang D, Peng L, Yao C, et al. GSH-Responsive supramolecular nanoparticles constructed by β-d-galactose-modified pillar[5]arene and camptothecin prodrug for targeted anticancer drug delivery. Chem Commun. 2017 Jan 1;53(61):8596–8599.

151. Yu T, Wang Y, Hu J, He H, Li G, Su X, et al. Dual-Responsive Micelles with Aggregation-Induced Emission Feature and Two-Photon Aborsption for Accurate Drug Delivery and Bioimaging. Bioconjugate Chem. 2019 July 1;30(7):2075–2087.

152. Martín Giménez VM, Galante MJ, Manucha W, Zucchi IA, Arya G. Photo-responsive polymeric nanocarriers for target-specific and controlled drug delivery. Soft Matter. 2021 Jan 1;17(38):8577–8584.

153. Menna P, Recalcati S, Minotti G, Cairo G. An introduction to the metabolic determinants of anthracycline cardiotoxicity. Cardiovasc Toxicol. 2007 Apr 25;7(2):80–85.

154. Gaballa S, Naguib Y, Mady F, Khaled K. Polyethylene glycol: Properties, applications, and challenges. Journal of advanced Biomedical and Pharmaceutical Sciences. 2023 Dec 21;0(0):26–36.

155. Raval H, Bhattacharya S. Exploring the Potentials of Hyaluronic Acid-coated Polymeric Nanoparticles in Enhanced Cancer Treatment by Precision Drug Delivery, Tackling Drug Resistance, and Reshaping the Tumour Micro Environment. CMC. 2025 June 1;32(20):3960–3999.

156. Zhu L, Torchilin VP. Stimulus-responsive nanopreparations for tumor targeting. Integrative Biology. 2012 Aug 6;5(1):96–107.

157. Srinivasarao DA, Padhy HP, Famta P, Shah S, Srivastava S, Kumar R, et al. Unravelling the role of tumor microenvironment responsive nanobiomaterials in spatiotemporal controlled drug delivery for lung cancer therapy. Drug Deliv and Transl Res. 2024 July 22;15(2):407–435.

158. Bigaj-Józefowska MJ, Coy E, Załęski K, Zalewski T, Grabowska M, Jaskot K, et al. Biomimetic theranostic nanoparticles for effective anticancer therapy and MRI imaging. Journal of Photochemistry and Photobiology B: Biology. 2023 Nov 8;249:112813.

159. Kelkar SS, Reineke TM. Theranostics: Combining Imaging and Therapy. Bioconjugate Chem. 2011 Aug 29;22(10):1879–1903.

160. Altinbasak I, Alp Y, Sanyal R, Sanyal A. Theranostic nanogels: multifunctional agents for simultaneous therapeutic delivery and diagnostic imaging. Nanoscale. 2024 Jan 1;16(29):14033–14056.

161. Fukuta T, Kogure K. Biomimetic Nanoparticle Drug Delivery Systems to Overcome Biological Barriers for Therapeutic Applications. Chem Pharm Bull. 2022 May 1;70(5):334–340.

162. Lai X, Tan L, Wang S, Geng X, Hu J. A pH-Responsive System Based on Fluorescence Enhanced Gold Nanoparticles for Renal Targeting Drug Delivery and Fibrosis Therapy. IJN. 2020 Aug 1;15(49):5613–5627.

163. Kim M, Choi H, Jang DJ, Kim HJ, Sub Y, Gee HY, et al. Exploring the clinical transition of engineered exosomes designed for intracellular delivery of therapeutic proteins. Stem Cells Translational Medicine. 2024 June 5;13(7):637–647.

164. Bonnet S, Perros F, Guignabert C, Hassoun PM, Humbert M, Rabinovitch M, et al. Translating Research into Improved Patient Care in Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2017 Mar 1;195(5):583–595.

165. Aisen PS, Jimenez-Maggiora GA, Rafii MS, Walter S, Raman R. Early-stage Alzheimer disease: getting trial-ready. Nat Rev Neurol. 2022 Jan 1;18(7):389–399.

166. Li H, Li L, Zhang X, Xu Z, Liu W, Zhao Z, et al. Preclinical evaluation of MRG002, a novel HER2-targeting antibody-drug conjugate with potent antitumor activity against HER2-positive solid tumors. Antibody Therapeutics. 2021 July 19;4(3):175–184.

167. Haider M, Elsherbeny A, Pittalà V, Fallica AN, Alghamdi MA, Greish K. The Potential Role of Sildenafil in Cancer Management through EPR Augmentation. JPM. 2021 June 21;11(6):585.

168. Dasgupta A, Biancacci I, Kiessling F, Lammers T. Imaging-assisted anticancer nanotherapy. Theranostics. 2020 Jan 1;10(3):956–967.

169. Miedema IHC, Huisman MC, Lammers T, Doeleman E, Menke-Van Der Houven Van Oordt CW, Rijcken CJF, et al. PET-CT Imaging of Polymeric Nanoparticle Tumor Accumulation in Patients. Advanced Materials. 2022 Apr 25;34(21):2201043.

170. Cooley MB, Wegierak D, Exner AA. Using imaging modalities to predict nanoparticle distribution and treatment efficacy in solid tumors: The growing role of ultrasound. WIREs Nanomed Nanobiotechnol. 2024 Mar 1;16(2).