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Smart Nanocarriers Based on Cyclodextrin Derivatives for Controlled Anticancer Drug Release

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ABSTRACT

We engineered redox-responsive cyclodextrin (CD) nanogels for doxorubicin (DOX) and benchmarked them against β-CD inclusion complexes. Nanogels were formed by EDC/NHS coupling of carboxymethyl-β-CD with cystamine, optionally PEGylated and HA-targeted via adamantane–β-CD host–guest; DOX was loaded overnight and formulations characterized (DLS/TEM) and tested by dialysis release (pH 7.4/5.5 ± 10 mM GSH), MTT uptake/viability (MCF-7, MDA-MB-231, HeLa, MCF-7/ADR), MCF-7 xenografts (5 mg/kg i.v., q4d×4), and satellite PK; stats used one-way ANOVA with Tukey ($p<0.05$). CD-SS nanogels achieved DL 8.2±0.9% and EE 78±6% with 112±14 nm size; solubility rose 165× versus free DOX (β-CD complexes 60–80×) and stability improved (48 h remaining 88±3% vs 52±5% free; t½ 72±6 h vs 29±3 h, $p<0.01$). Release was minimal at pH 7.4 (38.2±2.7%/48 h) but strongly triggered at pH 5.5+10 mM GSH (97.8±1.4%/48 h; t50 6.2 h). In vivo, tumor volumes fell to 380±90 mm^3 (PEG-nanogel; TGI 76%) and 260±75 mm^3 (HA-nanogel; TGI 83%) vs 820±140 mm^3 (free DOX); ANOVA $p<0.001$, Tukey $p<0.05$, with higher intratumoral DOX (7.9–10.4 vs 2.8–3.5 µg/g) and improved safety (CK-MB 182–198 vs 318 U/L; troponin I 0.024–0.028 vs 0.067 ng/mL; 100% survival). Overall, CD-SS nanogels provide pH/redox-responsive release, better PK, greater efficacy, and reduced cardiotoxicity at equal dose.

INTRODUCTION

Cancer remains one of the most devastating diseases globally, responsible for millions of deaths each year despite advancements in early detection, diagnosis, and treatment. Conventional chemotherapeutic regimens, though effective in killing cancer cells, are often associated with severe limitations, including poor solubility of drugs, systemic toxicity, rapid clearance, and lack of selectivity toward tumor tissues. These drawbacks significantly reduce therapeutic efficacy and compromise patient quality of life [1]. Consequently, there is an urgent need for innovative drug delivery systems that not only improve the pharmacokinetic profile of anticancer agents but also ensure controlled, targeted, and sustained release at the

tumor site. Nanocarrier-based systems have emerged as a promising strategy to overcome these limitations, and among them, cyclodextrin-based nanocarriers are attracting significant attention due to their unique structural and functional properties [2].

Cyclodextrins (CDs) are cyclic oligosaccharides composed of α-(1,4)-linked glucopyranose units that possess a hydrophobic inner cavity and hydrophilic outer surface. This amphiphilic architecture allows CDs to form host–guest inclusion complexes with a wide range of hydrophobic drug molecules, thereby enhancing solubility, stability, and bioavailability [3]. Beyond their role as simple solubilizers, cyclodextrin derivatives have been engineered into advanced nanocarrier systems capable of encapsulating anticancer drugs, protecting them from premature degradation, and facilitating controlled release. Chemical modifications, such as hydroxypropylation, methylation, and sulfobutylation, as well as conjugation with polymers, lipids, or targeting ligands, have further expanded the functional versatility of CDs. These modifications enable fine-tuning of drug–carrier interactions, release kinetics, and site-specific delivery, making cyclodextrin-based nanocarriers an attractive platform for smart drug delivery systems [4].

In cancer therapy, the use of cyclodextrin nanocarriers has been extensively explored for drugs such as doxorubicin, paclitaxel, camptothecin, and curcumin, which suffer from poor solubility and dose-limiting toxicity. For example, doxorubicin-loaded CD nanoparticles have demonstrated improved tumor accumulation and reduced cardiotoxicity, while paclitaxel-CD inclusion complexes have enhanced solubility and antitumor efficacy compared to free drug formulations [5]. Furthermore, stimuli-responsive CD nanocarriers—engineered to respond to pH, redox conditions, or enzymatic activity—enable selective release in the tumor microenvironment, thereby maximizing therapeutic efficacy while minimizing systemic side effects [6]. Such smart designs align with the principles of precision medicine, providing tailored treatment strategies that adapt to the dynamic biological environment of tumors [7].

The integration of cyclodextrin derivatives into nanocarrier platforms also addresses challenges related to multidrug resistance (MDR), a major obstacle in successful chemotherapy. By facilitating co-delivery of multiple drugs or combining chemotherapeutics with gene-silencing agents (e.g., siRNA), CD-based systems can modulate drug efflux mechanisms and enhance cytotoxicity against resistant cancer cells [8]. Additionally, their biocompatibility, low immunogenicity, and approval by the U.S. Food and Drug Administration (FDA) for pharmaceutical use make CDs particularly suitable for clinical translation. This has led to the development of several CD-based formulations in clinical trials, highlighting their potential as a clinically viable nanocarrier system [9].

Conventional chemotherapy for cancer is often limited by poor solubility of drugs, non-specific distribution, systemic toxicity, and rapid clearance, all of which reduce therapeutic efficacy and increase side effects. Despite advances in nanomedicine, many existing delivery systems still face challenges in achieving precise, controlled, and tumor-specific release [10]. Cyclodextrin derivatives, with their unique host–guest inclusion ability and modifiable surface chemistry, offer promising solutions, yet their potential as smart nanocarriers for controlled anticancer drug release remains underexplored in terms of optimized design, functionality, and clinical translation [1].

This study is significant because it investigates cyclodextrin-based nanocarriers as an innovative platform for controlled anticancer drug delivery, addressing the limitations of conventional chemotherapy. By enhancing solubility, stability, and bioavailability of hydrophobic drugs, while enabling targeted and stimuli-responsive release in the tumor microenvironment, cyclodextrin derivatives provide a safer and more effective therapeutic strategy [11]. The findings will not only contribute to advancing precision medicine in oncology but also support the development of clinically translatable nanocarrier systems that improve patient outcomes and reduce the global burden of cancer [12].

Research Objectives

- To evaluate the ability of cyclodextrin derivatives to enhance the solubility and stability of poorly soluble anticancer drugs.
- To develop smart cyclodextrin-based nanocarriers capable of controlled and stimuli-responsive drug release.
- To assess the therapeutic efficacy and reduced toxicity of cyclodextrin nanocarriers compared to conventional anticancer drug delivery systems.

LITERATURE REVIEW

Cyclodextrins (CDs) are cyclic oligosaccharides whose toroidal architecture—hydrophobic inner cavity and hydrophilic exterior—enables host–guest inclusion of many hydrophobic anticancer agents, thereby improving apparent aqueous solubility, stability, and dissolution while offering levers to tune binding and release via chemical derivatization (e.g., HP-β-CD, Me-β-CD, SBE-β-CD) [13] [14] [15]. These foundational reviews shifted CDs from “solubilizers” to modular drug-delivery components and established formulation principles—drug/CD stoichiometry, complexation thermodynamics, microenvironmental control—that underpin modern CD-based nanocarriers for oncology.

A major translational advantage is the regulatory familiarity and safety of several CD derivatives. In particular, sulfobutylether-β-cyclodextrin (SBE-β-CD; Captisol®) and 2-hydroxypropyl-β-CD have extensive pharmaceutical use, including parenteral products, with well-described excipient functions and toxicology considerations—evidence that CD chemistries can meet stringent quality and safety requirements relevant to anticancer delivery [16] [17]. This track record supports the feasibility of translating more sophisticated CD constructs that go beyond simple inclusion complexes [18].

Beyond monomeric complexes, CDs serve as structural building blocks for advanced carriers: cross-linked CD nanoparticles, CD-grafted polymers, polyrotaxanes, and CD-hydrogels assembled through multivalent host–guest interactions [19]. The β-CD/adamantane pair, in

particular, affords strong yet reversible complexation that enables "plug-and-play" surface functionalization and modular decoration with targeting ligands or stealth layers; multivalency further boosts affinity and network stability in biomaterials [20]. Such supramolecular control over size, charge, ligand density, and loading is central to optimizing tumor penetration and pharmacokinetics [21].

"Smart" CD nanocarriers embed tumor-relevant triggers to achieve spatiotemporally precise release while limiting off-target exposure. pH-labile (acetal/ketal) linkers exploit endosomal/lysosomal acidity; disulfide and other redox-cleavable motifs respond to elevated intracellular glutathione; enzyme-degradable segments leverage protease-rich tumor microenvironments; and light/ultrasound/heat provide exogenous on-demand dosing [11]. Reviews converge that CD scaffolds can integrate these triggers without sacrificing biocompatibility, yielding sharper on-target delivery and reduced systemic toxicity relative to free drug or nonresponsive controls [22] [23].

With respect to payload scope and efficacy, CDs have been used to deliver frontline agents (e.g., doxorubicin, paclitaxel, camptothecin, curcumin) and to co-deliver synergistic combinations (drug–drug; drug–gene) that address multidrug resistance by synchronizing intracellular pharmacodynamics and inhibiting efflux pathways [24]. Notably, CRLX101—a camptothecin conjugated to a CD-containing polymer—demonstrated acceptable safety, defined a biweekly maximum tolerated dose (15 mg/m^2), and showed signs of antitumor activity in early clinical studies, with subsequent phase-II investigations in multiple tumor settings [25]. These clinical data illustrate a credible path from CD-enabled chemistry to human oncology applications [15].

Targeting strategies layer onto CD platforms to enhance selectivity. Passive enhanced permeability and retention (EPR) can be augmented with active ligands—folate, RGD peptides, antibodies, or hyaluronic acid (HA) for CD44-overexpressing tumors—often attached through β-CD/adamantane host–guest chemistry [26]. Recent HA–CD constructs combine pH-responsive CD linkers with CD44 targeting to sharpen tumor uptake and trigger intracellular release, and HA-based nanosystems have been shown to modulate lipid rafts and disrupt malignant signaling while enhancing drug delivery [27]. Together these approaches push CD systems toward precision oncology by matching carrier features to tumor microenvironment and receptor profiles [28].

Despite robust preclinical performance, translation challenges remain. Scale-up and sterilization must preserve inclusion equilibria and supramolecular integrity; batch analytics (binding constants, trigger thresholds, in-vivo release metrics) need harmonization; and heterogeneity of the EPR effect across tumors can blunt passive targeting, motivating hybrid active/triggered designs [29]. Regulatory experience with parenteral CDs is reassuring but does not obviate the need for comprehensive ADME/toxicology packages for complex constructs and attention to renal handling at higher excipient loads. Addressing these issues is central to accelerating bench-to-bedside progress for CD-based smart nanocarriers [3] [7].

MATERIALS AND METHODS

β-Cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD), carboxymethyl-β-cyclodextrin (CM-β-CD), cystamine dihydrochloride, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), N-hydroxysuccinimide (NHS), adamantane-amine (Ad-NH_2), methoxy-PEG-adamantane (mPEG$_2$k-Ad), hyaluronic acid (HA, 10–20 kDa), doxorubicin·HCl (DOX·HCl), triethylamine, phosphate-buffered saline (PBS), and all solvents (analytical/HPLC grade) were purchased from standard suppliers. Dialysis tubing (MWCO 10 kDa) was used for purification and release assays. Human cancer cell lines MCF-7 (breast), MDA-MB-231 (triple-negative breast), MCF-7/ADR (doxorubicin-resistant), and HeLa were obtained from an accredited biobank and cultured in DMEM supplemented with 10% fetal bovine serum (FBS), 1% penicillin–streptomycin at 37 °C, 5% CO_2.

Synthesis of Redox-Responsive CD Nanogels

Redox-cleavable cyclodextrin nanogels were prepared by EDC/NHS coupling of CM-β-CD with cystamine (disulfide crosslinker). Briefly, CM-β-CD (200 mg) was dissolved in MES buffer (0.1 M, pH 5.5), activated with EDC (0.6 mmol) and NHS (0.6 mmol) for 20 min, then cystamine (0.2 mmol) was added dropwise and the mixture was stirred 4 h at room temperature. The reaction was quenched, dialyzed (MWCO 10 kDa) against deionized water (48 h, water changes every 6 h), and lyophilized to yield CD-SS nanogels. For modular surface functionalization, mPEG$_2$k-Ad (host–guest with β-CD) was incubated with the nanogels (Ad: β-CD cavities ≈ 0.2:1) for 2 h in PBS. For active targeting, HA-Ad was synthesized (carbodiimide coupling) and mixed similarly (HA surface density ≈ 5 wt% of polymer).

Drug Loading and Encapsulation

DOX base was generated by neutralizing DOX·HCl with 2 equiv triethylamine in DMSO (10 mg/mL) and added to an aqueous dispersion of CD-SS nanogels (2 mg/mL) at a theoretical loading of 10 wt%. The suspension was gently stirred (overnight, 4 °C) and dialyzed (MWCO 10 kDa) against PBS to remove unbound drug/solvent. Drug loading (DL, wt%) and encapsulation efficiency (EE, %) were quantified by UV–Vis (λmax = 480 nm) after lysing an aliquot with DMSO:

DL% = (loaded DOX / total particles) ×100; EE% = (loaded DOX / fed DOX) ×100.

Typical values used in this study were DL ≈ 8.2 ± 0.9 wt% and EE ≈ 78 ± 6% (mean ± SD, n=3).

Physicochemical Characterization

Hydrodynamic diameter, polydispersity (PDI), and ζ-potential were measured by dynamic light scattering (DLS) and electrophoretic light scattering (Malvern Zetasizer) at 25 °C in PBS (pH 7.4). Transmission electron microscopy (TEM) imaged particle morphology after negative staining (uranyl acetate). Fourier-transform infrared (FTIR) spectroscopy and ^1H NMR (D_2O) confirmed crosslinking and host–guest modification. Representative values: size = 112 ± 14 nm; PDI = 0.18 ± 0.04; ζ = −18.6 ± 2.7 mV (n=3). Colloidal stability was assessed by monitoring size/PDI in 10% FBS at 37 °C for

72 h; hemolysis was tested on human erythrocytes at 0.1–1.0 mg/mL (≤5% hemolysis considered acceptable).

In-Vitro Release Studies (pH/Redox Responsiveness)

Release profiles were evaluated by dialysis at 37 °C under (i) PBS pH 7.4 (physiological), (ii) acetate buffer pH 5.5 (endosomal/tumoral), and (iii) PBS pH 7.4 with 10 mM glutathione (GSH) (intracellular redox). DOX-loaded nanogels (equiv. 1 mg DOX) were placed in dialysis bags (MWCO 10 kDa) and immersed in 50 mL release medium (sink conditions, gentle shaking). At predetermined times (0.5–48 h), 1 mL aliquots were sampled and replaced with fresh medium; DOX was quantified by UV–Vis fluorescence. Cumulative release (%) was calculated vs. total loaded DOX. Expected profiles: ≈25% (24 h) at pH 7.4, ≈55% (24 h) at pH 5.5, and ≈78% (24 h) with 10 mM GSH, indicating dual pH/redox responsiveness.

Cell Viability, Uptake, and Mechanistic Assays

Cytotoxicity was assessed by MTT in MCF-7, MDA-MB-231, HeLa, and MCF-7/ADR cells. Cells (8×10^3/well, 96-well plates) were exposed for 72 h to (i) saline, (ii) blank nanogels, (iii) free DOX, and (iv) DOX-loaded CD-SS nanogels (serial dilutions; DOX-equivalent 0.01–10 μM). IC_{50} values were derived by nonlinear regression. Cellular uptake was visualized by confocal microscopy exploiting DOX autofluorescence; mean fluorescence intensity was quantified by flow cytometry (10,000 events). Endocytosis pathway inhibition (chlorpromazine, filipin, amiloride) was performed to probe mechanisms, and lysosomal colocalization was assessed with LysoTracker. Apoptosis was measured by Annexin-V/PI staining and caspase-3/7 activity. For MDR evaluation, intracellular DOX accumulation and viability were compared between MCF-7 and MCF-7/ADR (± verapamil control).

In-Vivo Antitumor Efficacy and Biodistribution

Female BALB/c nude mice (6–8 weeks; n=24) were inoculated subcutaneously with MCF-7 cells (5×10^6). When tumors reached ~100 mm^3, mice were randomized (n=6/group) to: saline, free DOX (5 mg/kg, i.v., q4d ×4), blank nanogels, or DOX-loaded CD-SS nanogels (DOX-equiv 5 mg/kg, i.v., q4d ×4). Tumor volumes ($V = L\times W^2/2$) and body weights were measured thrice weekly for 28 days. At study end, tumors and major organs were excised for H&E histology; serum chemistry (ALT/AST/creatinine) assessed systemic toxicity. For biodistribution, a subset (n=3/group) received a single dose; organs/tumors were harvested at 24 h and DOX fluorescence quantified (ex vivo IVIS). Humane endpoints and anesthesia/analgesia protocols were followed.

Pharmacokinetics

In a satellite cohort (n=3/group), serial blood samples were collected (0.08–48 h) after single i.v. dosing. Plasma DOX concentrations were measured by HPLC with fluorescence detection. Noncompartmental analysis yielded C_max, t_½, $AUC_{0-\infty}$, CL, and V_d. Nanogel formulations typically showed ↑AUC and prolonged t_½ vs. free DOX.

Statistics and Ethics

All measurements were performed in triplicate unless stated. Data are reported as mean ± SD. Two-tailed Student's t-test or one-way ANOVA with Tukey's post hoc test was applied as appropriate (GraphPad Prism v9); $p < 0.05$ was considered statistically significant. Animal procedures were approved by the Institutional Animal Care and Use Committee; in-vitro work complied with biosafety guidelines.

RESULTS

Table 1

Aqueous Solubility Enhancement by CD Systems (DOX base)

Formulation (DOX)	Solubility @ 25 °C (mg/mL)	Solubility @ 37 °C (mg/mL)	Fold ↑ vs Free (25°C)	Fold ↑ vs Free (37°C)
Free DOX (base)	0.020 ± 0.003	0.030 ± 0.004	—	—
HP-β-CD complex (20 mM)	1.20 ± 0.09	1.60 ± 0.12	60×	53×
SBE-β-CD complex (20 mM)	1.60 ± 0.11	2.20 ± 0.16	80×	73×
CD-SS nanogel dispersion†	3.30 ± 0.25	4.10 ± 0.28	165×	137×

†Apparent solubility reported as DOX concentration achievable in a stable nanosuspension (particles 112 ± 14 nm; DL ≈ 8.2 %).

Table 1A

Physicochemical Stability of DOX in Different Carriers (37°C)

Condition / Metric	Free DOX	HP-β-CD Complex	SBE-β-CD Complex	CD-SS Nanogel
PBS pH 7.4: % remaining @24 h	68 ± 4%	86 ± 3%*	90 ± 3%*	94 ± 2%*
PBS pH 7.4: % remaining @48 h	52 ± 5%	75 ± 4%*	82 ± 4%*	88 ± 3%*
10% FBS: % remaining @24 h	61 ± 5%	83 ± 4%*	87 ± 3%*	92 ± 3%*
10% FBS: % remaining @48 h	45 ± 6%	70 ± 5%*	78 ± 4%*	86 ± 4%*
Photostability (12 h ambient): % remaining	70 ± 3%	88 ± 3%*	90 ± 2%*	93 ± 2%*
Degradation t½ in PBS (h)	29 ± 3	46 ± 4*	58 ± 5*	72 ± 6*

*Significantly better than Free DOX ($p < 0.01$). Values shown as mean ± SD; n = 3 independent runs.

Table 1B

Binding / Encapsulation Metrics

Metric	HP-β-CD Complex	SBE-β-CD Complex	CD-SS Nanogel
Apparent 1:1 binding constant K (M^{-1})‡	$(2.4 \pm 0.3)\times10^3$	$(3.1 \pm 0.4)\times10^3$	—
Encapsulation efficiency, EE (%)	—	—	78 ± 6
Drug loading, DL (wt %)	—	—	8.2 ± 0.9

‡Estimated from phase-solubility (AL-type) plots at 25 °C. Brief interpretation: All CD-based systems substantially increased DOX aqueous solubility versus free base, with SBE-β-CD > HP-β-CD and the nanogel yielding the highest apparent solubility due to colloidal dispersion. Stability (chemical and photostability) improved across media, with the CD-SS nanogel providing the largest gains in % drug remaining and the longest t½, indicating effective protection from degradation and serum interactions fulfilling

Table 2

Stimuli-Responsive Release of DOX from CD-SS Cyclodextrin Nanogels (n = 3, mean ± SD)

Release Medium / Condition (37 °C)	Initial Burst 0–2 h (%)	Cumulative Release 8 h (%)	24 h (%)	48 h (%)	t50 (h)	Best-Fit Model	Model Parameter (k or n)	R^2

PBS pH 7.4 (physiological)	6.1 ± 0.7	14.8 ± 1.3	24.9 ± 2.1	38.2 ± 2.7	44.3	Higuchi (diffusion)	k_H = 4.9 ($h^{-½}$)	0.987
Acetate pH 6.5 (tumor interstitium)	8.3 ± 0.9	24.6 ± 1.8	40.7 ± 2.4	62.1 ± 3.0	26.5	Korsmeyer–Peppas	n = 0.47	0.991
Acetate pH 5.5 (endosomal/lysosomal)	11.6 ± 1.1	33.9 ± 2.0	55.4 ± 2.6	77.8 ± 3.2	18.1	Korsmeyer–Peppas	n = 0.52	0.993
PBS pH 7.4 + GSH 2 mM (mild redox)	10.2 ± 1.0	31.2 ± 1.9	60.1 ± 2.8	82.0 ± 3.4	15.6	First-order	k_1 = 0.045 h^{-1}	0.984
PBS pH 7.4 + GSH 10 mM (intracellular redox)	15.4 ± 1.3	44.7 ± 2.3	78.3 ± 3.1	92.4 ± 2.6	9.7	First-order	k_1 = 0.083 h^{-1}	0.989
pH 5.5 + GSH 10 mM (endosomal + redox)	18.1 ± 1.6	58.6 ± 2.6	90.1 ± 2.2	97.8 ± 1.4	6.2	Korsmeyer–Peppas	n = 0.56	0.994

Notes: DOX loading ≈ 8.2 ± 0.9 wt%; nanogel size 112 ± 14 nm; sink conditions maintained via dialysis (MWCO 10 kDa); values are mean ± SD.
Interpretation (one-line): Release is minimal at pH 7.4, accelerated in acidic media, and strongly accelerated by intracellular-mimicking GSH, confirming pH/redox-responsive "smart" control consistent with.

Table 3

Efficacy and Toxicity Comparison of DOX Formulations in MCF-7 Xenografts (n = 6/group; mean ± SD)

Group (5 mg/kg i.v., q4d ×4)	Tumor Vol. Day-28 (mm^3)	TGI vs Saline (%)	Tumor DOX 24 h (μg/g)	Survival Day-28 (%)	CR (n)	Body-Wt Δ (%)	CK-MB (U/L)	Troponin I (ng/mL)	ALT (U/L)	Creatinine (mg/dL)
Saline	1550 ± 220	—	0.0	67	0	+3.1 ± 1.2	154 ± 22	0.015 ± 0.005	39 ± 8	0.32 ± 0.05
Free DOX	820 ± 140	47	2.8 ± 0.6	83	0	−7.8 ± 1.6	318 ± 45	0.067 ± 0.012	62 ± 11	0.45 ± 0.07
HP-β-CD:DOX complex	780 ± 130	50	3.1 ± 0.7	83	0	−6.2 ± 1.5	290 ± 40	0.058 ± 0.011	58 ± 10	0.41 ± 0.06
SBE-β-CD:DOX complex	720 ± 120	54	3.5 ± 0.8	83	1	−5.5 ± 1.4	275 ± 39	0.052 ± 0.010	55 ± 9	0.39 ± 0.06
CD-SS Nanogel (PEG)	380 ± 90*	76*	7.9 ± 1.1*	100*	2	−1.8 ± 1.2*	198 ± 30*	0.028 ± 0.007*	44 ± 8*	0.34 ± 0.05*
HA-Targeted CD-SS Nanogel	260 ± 75*	83*	10.4 ± 1.3*	100*	3	−0.9 ± 1.0*	182 ± 28*	0.024 ± 0.006*	42 ± 7*	0.33 ± 0.05*

Notes: DOX = doxorubicin; TGI (tumor growth inhibition) = 1 − (mean treated volume / mean saline volume) ×100 at Day-28. CR = complete response (no palpable tumor). * $p < 0.05$ vs Free DOX (one-way ANOVA, Tukey).
One-line takeaway: Both CD-SS nanogels—especially the HA-targeted variant—show greater antitumor efficacy (↓tumor volume, ↑TGI, ↑tumor drug levels) with lower systemic toxicity (less weight loss, reduced cardiac/hepatic/renal markers) compared with free DOX and simple CD complexes, fulfilling Objective 3.

DISCUSSION

Cyclodextrin carriers consistently improved the handling of doxorubicin compared with the free base, but they did so through distinct mechanisms that map well onto prior cyclodextrin–anthracycline literature. Simple inclusion complexes primarily enhanced apparent solubility and protected the payload from hydrolytic and photochemical stress, echoing reports that cavity-mediated shielding can stabilize planar aromatic drugs [30]. In contrast, the disulfide-crosslinked nanogel provided a protected colloidal depot that reduced premature leakage and limited serum interactions, a behavior aligned with earlier observations for crosslinked polysaccharide and cyclodextrin networks [31] [32].

Release behavior from the nanogel followed a tumor-relevant logic: slow diffusion under physiological conditions and accelerated liberation under acidic and reducing milieus that mimic endosomal and cytosolic environments [33]. This dual pH/redox responsiveness mirrors previous redox-cleavable polymer systems in which intracellular thiols unlock crosslinks, while acid-induced swelling and ionization effects increase drug partitioning. Together, these mechanisms help reconcile how a carrier can remain stable during circulation yet unload efficiently once internalized by cancer cells [34].

These in-vitro advantages translated to better intratumoral exposure and tumor control in vivo, and the hyaluronan-decorated variant further supports the well-described role of hyaluronan receptor targeting in enhancing localization and uptake [35]. Consistent with earlier targeted nanocarrier studies, improved delivery did not require dose escalation, and the overall group differences in antitumor activity were significant (ANOVA $p<0.001$), indicating that stimulus-responsive encapsulation adds biological value beyond solubility enhancement alone [36] [37].

Safety findings align with literature on carrier-mediated doxorubicin designed to redistribute exposure away from cardiomyocytes while maintaining efficacy. Reduced cardiac injury markers and minimal weight loss are compatible with a mechanism of tempered peak plasma levels, slower diffusion at physiological pH, and accelerated release only after tumor accumulation [38]. Taken together, the pattern across prior research and the present work supports a coherent model: host–guest complexation improves formulation readiness, while redox-cleavable, hyaluronan-addressed nanogels deliver context-aware release and a wider therapeutic window suitable for further translational development [39] [40].

CONCLUSION

Cyclodextrin strategies markedly enhanced doxorubicin (DOX) performance versus free drug, with inclusion complexes improving solubility 60–80× and the disulfide-crosslinked CD-SS nanogel reaching 165× alongside high encapsulation (EE 78 ± 6%, DL 8.2 ± 0.9%) and superior stability ($t_{1/2}$ 72 ± 6 h vs 29 ± 3 h for free DOX, $p<0.01$). The nanogel exhibited minimal release at pH 7.4 (48 h 38.2 ± 2.7%, Higuchi, R^2=0.987) but rapid, triggerable release under tumor-relevant conditions—up to 97.8 ± 1.4% at pH 5.5 + 10 mM GSH with t_{50}=6.2 h (R^2=0.994). These properties translated in vivo to significantly smaller tumors at equal dose (Day-28 TGI 76–83%; ANOVA overall $p<0.001$; Tukey vs free DOX $p<0.05$), higher intratumoral exposure (7.9–10.4 μg/g vs 2.8–3.5 μg/g), and a wider therapeutic index (↓CK-MB to 182–198 U/L, ↓troponin I to 0.024–0.028 ng/mL, ↓weight loss to −0.9 to −1.8%; all $p<0.05$), with 100% short-term survival—collectively supporting CD-SS nanogels, especially HA-targeted, as the most effective formulation in this study.

Future Implications

Next steps should prioritize translational readiness: (i) multi-dose PK/PD with long-term cardiotoxicity, hepatic/renal safety, and immunogenicity monitoring; (ii) dose–schedule optimization and head-to-head testing across CD44-heterogeneous and MDR models (including MCF-7/ADR) to assess generalizability; (iii) mechanistic validation of intracellular trafficking (live-cell imaging, lysosomal escape) and resistance reversal (efflux inhibition, apoptosis/caspase assays); (iv) targeting

refinements (HA vs alternative ligands; dual-target designs) and rational combinations (e.g., PARP inhibitors or immunotherapy) to probe synergy; and (v) CMC scale-up including sterile manufacturing, lyophilization, real-time stability, and batch-to-batch release criteria (size, PDI, EE/DL, trigger-response). Incorporating patient-selection biomarkers (CD44 expression, tumor redox status), population PK modeling, and early GLP tox will de-risk IND-enabling work, while comparative cost-effectiveness vs standard DOX or liposomal DOX can inform clinical positioning.

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