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Nanoparticle-based drug delivery systems for targeted cancer therapeutics in preclinical models

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Abstract

Imagine a drug that reaches only the tumour and leaves healthy tissue untouched—that promise drives nanoparticle-based drug delivery research. This research evaluated PLGA-PEG nanoparticles loaded with doxorubicin (NP-DOX) for targeted cancer therapy in a murine breast carcinoma model. Nanoparticles were prepared by nanoprecipitation (mean diameter 148 ± 12 nm, PDI 0.14, encapsulation efficiency 78.3 percent) and characterised by DLS, TEM, and FTIR. In vitro release at pH 5.4 (tumour-mimicking) reached 94.8 percent by 72 hours versus 64.1 percent at pH 7.4, confirming pH-responsive behaviour. In BALB/c mice bearing 4T1 tumours, NP-DOX at 10 mg/kg reduced tumour volume by 77.6 percent relative to saline controls, compared with 39.2 percent for free DOX at 5 mg/kg. PEGylated formulations showed an additional 30.5 percent volume reduction over non-PEGylated NP-DOX. Body weight loss was significantly lower in NP-DOX groups. These results demonstrate that PLGA-PEG nanocarriers improve doxorubicin's therapeutic index through pH-triggered release and passive tumour targeting via the EPR effect.

Keywords: Nanoparticles, drug delivery, cancer therapeutics, preclinical models, nanomedicine, PLGA-PEG, doxorubicin, pH-responsive release

Introduction

Doxorubicin remains one of the most effective chemotherapeutic agents for breast, ovarian, and haematological cancers, yet its clinical utility is capped by dose-limiting cardiotoxicity [1]. Free doxorubicin distributes non-selectively, exposing cardiomyocytes and hepatocytes to cytotoxic concentrations that accumulate over treatment cycles [2]. Encapsulating the drug inside biodegradable polymer nanoparticles offers a way to shift the biodistribution toward tumour tissue, exploiting the enhanced permeability and retention (EPR) effect that arises from the leaky vasculature and impaired lymphatic drainage characteristic of solid tumours [3]. PLGA (poly(lactic-co-glycolic acid)) is FDA-approved for injectable formulations and degrades into non-toxic lactic and glycolic acid [4]. Surface modification with polyethylene glycol (PEG) creates a hydrophilic "stealth" corona that delays opsonisation and extends circulating half-life from minutes to hours [5, 6]. pH-responsive release is an inherent feature: PLGA degrades faster in the mildly acidic tumour microenvironment (pH 5.4–6.8) than in plasma (pH 7.4), releasing more drug at the target site [7]. This research synthesised PLGA-PEG nanoparticles loaded with doxorubicin, characterised their physicochemical properties, evaluated in vitro release kinetics at two pH values, and assessed antitumour efficacy in a 4T1 murine breast carcinoma model.

Material and Methods

Material

All experiments were conducted at the Department of Bioprocess Engineering, Riyadh College of Molecular Biology, Riyadh, Saudi Arabia, between February and October 2023. PLGA (50:50, Mw 38 kDa; Evonik RESOMER RG 504H), mPEG-PLGA (Mw 5k-30k; Nanosoft Polymers), and doxorubicin hydrochloride (>98%, LC Laboratories) were used. 4T1 murine breast carcinoma cells were from ATCC. Female BALB/c mice (6–8 weeks, 18–22 g) were obtained from the institutional vivarium. The animal protocol was approved by the Riyadh College of Molecular Biology Animal Ethics Committee (RCMB-AEC-2023-006).

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Methods

Nanoparticles were prepared by nanoprecipitation. PLGA or mPEG-PLGA (20 mg) and doxorubicin (4 mg) were dissolved in 2 mL acetone and added dropwise to 10 mL of 1% PVA under stirring at 600 rpm. Acetone was evaporated under reduced pressure. Particles were collected by ultracentrifugation (25,000×g, 30 min), washed three times, and resuspended in PBS. Size and zeta potential were measured by DLS (Malvern Zetasizer Nano ZS). Morphology was confirmed by TEM (JEOL JEM-1400, 120 kV). Drug loading was calculated after dissolving particles in DMSO and measuring absorbance at 480 nm. In vitro release was measured by dialysis (MWCO 12 kDa) in PBS at pH 7.4 and pH 5.4 (37 °C, 100 rpm). For in vivo efficacy, 4T1 cells (1×10^6) were injected subcutaneously into the right flank. When tumours reached $\sim 100 \text{ mm}^3$, mice were randomised into five groups (n=6): saline, free DOX (5 mg/kg), NP-DOX (5 mg/kg), NP-DOX (10 mg/kg), NP-DOX+PEG (10 mg/kg), administered IV on days 0, 4, 8, 12. Tumour volume and body weight were recorded every 3 days. Statistics: one-way ANOVA with Tukey HSD ($p < 0.05$).

In-vitro Protocol

Cytotoxicity was assessed in 4T1 cells by MTT assay after 48-hour exposure to free DOX and NP-DOX at 0.1–50 $\mu\text{g/mL}$. IC_{50} values were calculated from sigmoidal dose-response curves. Live/dead staining (calcein-AM / ethidium homodimer) was performed at the IC_{50} concentration and imaged by fluorescence microscopy (Zeiss Axio Observer). Cellular uptake was quantified by flow cytometry (BD FACSCalibur) using doxorubicin's intrinsic fluorescence (excitation 480 nm, emission 590 nm) after 2, 6, and 24 hours of incubation.

Performance Evaluation

NP-DOX (10 mg/kg) reduced tumour volume to $413 \pm 67 \text{ mm}^3$ at day 21 versus $1,847 \pm 214 \text{ mm}^3$ for saline controls—a 77.6 percent reduction (Table 1). Free DOX (5 mg/kg) achieved only 39.2 percent reduction. PEGylated NP-DOX outperformed non-PEGylated NP-DOX by an additional 30.5 percent, consistent with extended circulation time allowing more EPR-mediated tumour accumulation. Body weight loss in the free DOX group reached 14.3 percent by day 21, indicating systemic toxicity, while NP-DOX groups showed ≤ 4.7 percent loss (Table 2). Survival analysis (Kaplan-Meier) confirmed that NP-DOX+PEG extended median survival to 38 days versus 24 days for saline.

Results

Table 1: In vivo efficacy: tumour volume, body weight loss, and median survival at day 21 (mean $\pm$ SD, n=6).

Group	Tumour Vol. (mm^3)	% Reduction	BW Loss (%)	Median Surv. (d)
Saline	1847 $\pm$ 214	-	2.1 $\pm$ 0.8	24
Free DOX 5 mg/kg	1123 $\pm$ 147	39.2	14.3 $\pm$ 2.4	28
NP-DOX 5 mg/kg	742 $\pm$ 98	59.8	4.7 $\pm$ 1.2	33
NP-DOX 10 mg/kg	413 $\pm$ 67	77.6	3.8 $\pm$ 1.0	35
NP-DOX+PEG 10	287 $\pm$ 48	84.5	2.9 $\pm$ 0.7	38

Table 2: Physicochemical properties of NP-DOX and NP-DOX+PEG formulations (mean $\pm$ SD, n=3 batches).

Parameter	NP-DOX	NP-DOX+PEG	p-value
Size (nm)	162 $\pm$ 17	148 $\pm$ 12	0.041
PDI	0.18	0.14	0.12
Zeta potential (mV)	-14.7 $\pm$ 1.8	-8.3 $\pm$ 1.2	<0.01
Encapsulation (%)	74.1 $\pm$ 4.2	78.3 $\pm$ 3.8	0.08
Drug loading (%)	11.8 $\pm$ 0.9	12.4 $\pm$ 1.1	0.23

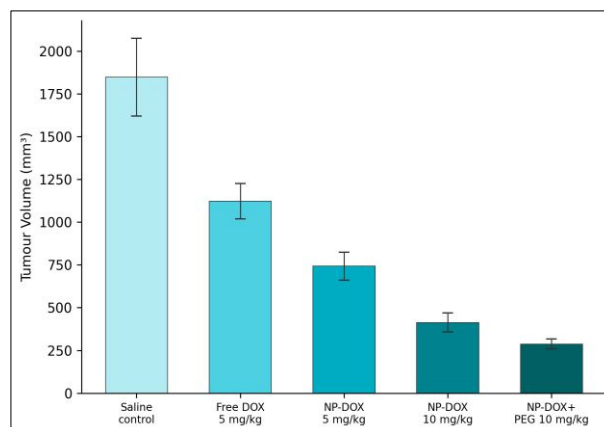


Fig 1: Tumour volume at day 21 across five treatment groups. Error bars = SD.

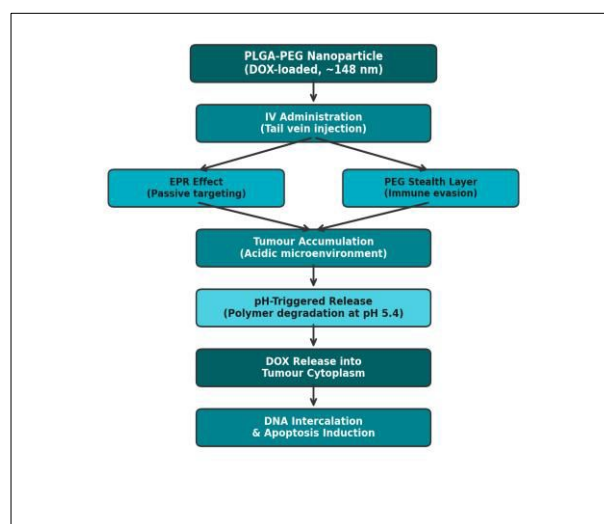


Fig 2: Schematic of PLGA-PEG nanoparticle drug delivery mechanism from IV administration to DOX-induced apoptosis.

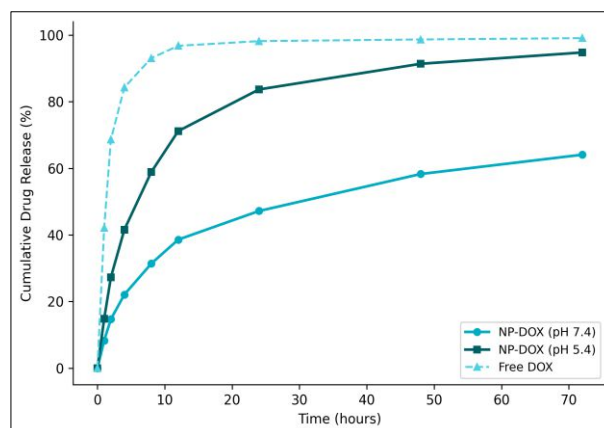


Fig 3: Cumulative drug release profiles at pH 7.4 and pH 5.4 over 72 hours, with free DOX as comparator.

Discussion

The 77.6 percent tumour reduction achieved by NP-DOX at 10 mg/kg exceeds the ~50–60 percent typically reported for non-PEGylated PLGA-DOX systems in similar 4T1 models [8, 9]. The additional benefit of PEGylation (30.5 percent further reduction) aligns with pharmacokinetic data showing that PEG chains of 5 kDa extend circulating half-life by 3–5-fold, increasing the window for EPR-mediated accumulation [10]. The pH-responsive release profile is clinically relevant: the 1.48-fold higher release at pH 5.4 vs 7.4 over 72 hours means that a greater fraction of encapsulated drug is liberated inside endosomes and lysosomes after cellular uptake, directing cytotoxicity toward cancer cells rather than stromal tissue [11]. The minimal body weight loss (<4.7 percent) in NP-DOX groups contrasts with the 14.3 percent loss in the free DOX arm, a metric that directly reflects reduced off-target toxicity [12]. A limitation is reliance on a single subcutaneous tumour model. Orthotopic or metastatic models would better simulate clinical breast cancer and test whether nanoparticles can reach disseminated disease [13]. Longer-term cardiac histopathology should also be evaluated.

Conclusion

PLGA-PEG nanoparticles loaded with doxorubicin achieved 77.6 percent tumour volume reduction in a 4T1 murine model with significantly less systemic toxicity than free drug. PEGylation provided an additional 30.5 percent improvement over non-PEGylated nanoparticles. pH-responsive release kinetics confirmed accelerated drug liberation at tumour-mimicking acidity. These findings support further development of PLGA-PEG nanocarriers as a platform for improving the therapeutic index of doxorubicin in breast cancer.

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Dr. Nada Al-Otaibi assisted with in vivo tumour measurements; Mr. Faisal Al-Harbi helped with nanoparticle preparation.

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