# Tailoring Thermo-responsive Transitions by Engineering the Hydrophobic Core of Polymer Nanoparticles

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Cancer remains one of the most pressing global health challenges and is projected to become the leading cause of death worldwide. While conventional treatments such as surgery, chemotherapy, and radiotherapy have proven effective in slowing tumor progression, they are often accompanied by severe side effects due to non-selective toxicity to healthy tissues. To overcome these limitations, nanocarrier-based drug delivery systems have emerged as promising alternatives, offering the potential to concentrate therapeutics within cancerous tissues and minimize damage to surrounding healthy cells. In particular, stimuli-responsive polymeric nanostructures allow for site-specific drug release triggered by environmental cues such as reduced pH or elevated temperature, both hallmarks of the tumor microenvironment. This study presents the design, synthesis, characterization, and biological evaluation of thermos-responsive polymeric nanoparticles engineered for cancer therapy. Amphiphilic block copolymers were synthesized via Reversible Addition-Fragmentation Chain Transfer (RAFT) polymerization, selected for its ability to finely control polymer architecture, molecular weight, and dispersity. The core hypothesis of this work is that modifications in the hydrophobic segment of thermo-responsive copolymers can significantly affect their Lower Critical Solution Temperature (LCST), thus enabling precise tuning of their temperature-triggered behavior. A copolymer system composed of poly(($C_{12}$-co-MAA)-b-($EG_2$MA-co-NIPAM)) was first examined, showing a sharp thermo-responsive transition near physiological temperature. To enhance the hydrophobic core structure, poly(lactic acid) (PLA) was subsequently incorporated into a novel grafted architecture, resulting in poly((PHEMA-graft-PLA)-b-($EG_2$MA-co-NIPAM)). This design aimed to restore a stable hydrophobic core while preserving thermo-responsive features. Nanoparticles were produced via flash nanoprecipitation, forming well-defined micellar structures. The thermo-responsive properties of the nanoparticles were assessed through Dynamic Light Scattering (DLS) and UV-Vis spectroscopy. Temperature-dependent drug release profiles were studied using a model compound, highlighting the influence of core hydrophobicity on release kinetics. Furthermore, cytocompatibility and cellular uptake were evaluated in vitro. For tracking and imaging purposes, Rhodamine B was covalently attached to the MAA-based copolymer, producing fluorescently labeled nanocarriers with a triggering temperature of 37 °C. Cellular uptake was confirmed by flow cytometry and confocal microscopy, demonstrating the potential of these smart nanostructures for targeted drug delivery applications. Altogether, this work underlines the key role of hydrophobic core engineering in controlling thermo-responsive behavior and paves the way for the rational design of next-generation nanocarriers for cancer therapy.

**Keywords**: *smart polymers, nanoparticles, thermo-responsive drug release, RAFT polymerization, amphiphilic block copolymers, PLA, MAA, POEGMA2, NIPAM, Rhodamine B, fluorescent bioimaging.*