INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

Name of the Student	:	Soumi Das
Roll Number	:	146122025
Programme of Study	:	Ph.D.

Thesis Title: Design and Synthesis of Biomolecular Amphiphiles for Effective and Stimuli Responsive Delivery of Anti-Tumor Agents

Name of Thesis Supervisor(s)	:	Dr. Lal Mohan Kundu
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SHORT ABSTRACT

The substance in this thesis bearing the title "**Design and Synthesis of Biomolecular Amphiphiles for Effective and Stimuli-Responsive Delivery of Anti-Tumor Agents"** is compiled in five chapters based on the outcome of experimental results, performed during my Ph.D. tenure.

The first chapter (**Chapter 1**) presents a brief introduction about anticancer drug delivery systems (DDS), especially where the therapeutic molecules are covalently conjugated to DDS. The necessity of DDS in anticancer research and its evolution during the last few decades is discussed elaborately in this chapter. The significance of chemistry in bioconjugation of drugs, synthesis and designing versatile molecules for drug delivery is reviewed. Along with this, the generation of various nanostructures due to the self-assembly properties of this kind of drug conjugates is also explored extensively.

C**hapter 2** describes the design and synthesis of a peptide 5-Fluorouracil (5-Fu) conjugate that can self-assemble to form hydrogel. A photolabile *o*-nitrobenzyl linker was utilized to accomplish a photo-controlled release of hydrophilic 5-Fu from the peptide-5-Fu conjugate. With a careful choice of the peptide sequence, the peptide-drug conjugate was able to form a hydrogel within a narrow pH window (pH 6.0 - 8.0). MTT assay of the peptide-drug conjugate in HeLa cells inferred almost no cytotoxicity up to a high concentration of 110 µM. The gelator prodrug

releases 5-fluorouracil in a controlled, dose-dependent manner under irradiation. The formulation and synthesis of the drug-amphiphile with a cleavable linker, solvent dependent behavior of the amphiphile, physical characteristics and properties of the gel were elaborately studied using NMR, FTIR, CD, HPLC and FESEM. Radiation-induced, controlled release of the therapeutic agent, cytotoxicity in tumor cell lines were also validated.

Chapter 3 demonstrates the procedure of fabrication of nanoparticles from the 5-Fu conjugated peptide amphiphile synthesized in chapter **1**. The covalent conjugation of 5-Fu with the peptide provided better control over the release of 5-Fu and also dramatically reduces the possibility of leaching of the drug. The prepared nanoparticles were also made efficient for passive targeting by PEG 6000 coating on its surface. Successful encapsulation of a second therapeutic agent, camptothecin (CPT), within the nanoparticles was also achieved. The stimuli-responsive release of 5-Fu was carefully monitored by HPLC, NMR, and UV-visible spectroscopy. On the other hand, the release of the hydrophobic drug CPT from the nanoparticles was determined to be in a diffusion-controlled fashion. The cytotoxicity of the nanoparticles due to the release of two drugs was monitored minutely.

Chapter 4 introduced the design and synthesis of dual-responsive, dual drug carrier nanoparticles. Chemically modified palmitic acid containing a disulfide bond, was covalently tethered to 5-Fu through the cleavable linker. Nanoparticle formulation from the self-assembly of the molecule was carried out by the nanoprecipitation method. The novelty of the new amphiphile is that, its self-assembly property can be disrupted by cleaving the disulfide bond in presence of glutathione (GSH), an enzyme, overexpressed In tumor cells. Hydrophobic drug camptothecin was efficiently encapsulated in the nanoparticles. The release of 5-Fu was monitored in a photoresponsive manner, whereas, the non-covalently bound camptothecin could be released from the nanoparticles by the action of GSH. The synthesized amphiphile was proved to be fairly nontoxic in HeLa cell lines up to a very high concentration of 1.1 mM.

Chapter 5, the design of a low molecular weight hydrgelator containing a biomarker biotin covalently tethered to 5-Fu is demonstrated for targeted delivery of 5-Fu. The synthesized molecule formed hydrogel at pH 7. The hydrogel also can effectively entrap another water-soluble chemotherapeutic agent doxorubicin hydrochloride (DOX). The release of 5-Fu was observed in a light-dependent manner, whereas sustained-release of DOX was recorded from the hydrogel. The controlled and sustained release of both the drugs were monitored by UV-Vis,

fluorescence spectroscopy and ^{1}H NMR study. The hydrogel properties and the factors responsible for self-assembly were also identified. The 5-Fu conjugate was also proved to be non-toxic up to a high concentration such as 80 µM.

Chapter 6 represented the conclusion and future perspective of the thesis**.**

Every chapter contains a brief introduction of related works in literature, description of the current result and discussions, experimental section, required references, along with all characterization data of the synthesized compounds.