ESTIMATION OF THE ENERGY BARRIER FOR MICELLE-MEDIATED NUCLEATION GROWTH ON SURFACES: STRATEGIC REDUCTION AND APPLICATION IN DRUG DELIVERY

Thesis submitted in partial fulfilment

for the Award of Degree

Doctor of Philosophy

by

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CERTIFICATE

It is certified that the work contained in the thesis titled "*ESTIMATION OF THE ENERGY BARRIER FOR MICELLE-MEDIATED NUCLEATION GROWTH ON SURFACES: STRATEGIC REDUCTION AND APPLICATION IN DRUG DELIVERY*" by *Ms. MONA VISHWAKARMA* has been carried out under my supervision and that this work has not been submitted elsewhere for a degree.

It is further certified that the student has fulfilled all the requirements of Comprehensive, Candidacy and SOTA.

21/05/2025

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DECLARATION BY THE CANDIDATE

I, *MONA VISHWAKARMA*, certify that the work embodied in this thesis is my own bona fide work and carried out by me under the supervision of *DR. DEBDIP BHANDARY* from July 2019 to Jan 2025, at the *DEPARTMENT OF CHEMICAL ENGINEERING & TECHNOLOGY, Indian Institute of Technology (Banaras Hindu University) Varanasi*. The matter embodied in this thesis has not been submitted for the award of any other degree/diploma. I declare that I have faithfully acknowledged and given credits to the research workers wherever their works have been cited in my work in this thesis. I further declare that I have not willfully copied any other's work, paragraphs, text, data, results, *etc.*, reported in journals, books, magazines, reports, dissertations, theses, *etc.*, or available at websites and have not included them in this thesis and have not cited as my own work.

Date: May 21, 2025
Place: Varanasi, India

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It is certified that the above statement made by the student is correct to the best of my knowledge.

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ABSTRACT

Poly elemental nanoparticles (PENPs) offer multi-functionality with exceptional properties such as high mechanical strength, thermal stability, and fatigue resistance, but their synthesis is energy-intensive and challenging. A solution-based approach using micelles (CTABs) mediated nucleation and growth is investigated to address this. The free energy of gold nucleation to be grown on a gold surface within a spherical micelle is estimated using the Umbrella Sampling method. An energy barrier of 10.36 ± 0.3 kcal/mol inhibited the nucleate-engulfed micelles from delivering the nucleate to the surface. Structural analysis showed that the spreading of micelle is essential to the discharge of engulfed nucleate. Adding a co-surfactant, oleylamine (OLA), with the primary surfactant, CTAB, formed a stable cylindrical micelle in water, which could reduce the energy barrier for the abovementioned purpose. The energy barrier decreases to 8.42±0.3 kcal/mol in this case. Micelle deformation, influenced by OLA, facilitates nucleate release onto the surface, followed by an energy increase due to nucleate-surface interactions. However, a significant energy barrier persists despite these improvements, mainly due to hydration layers and micelle reorganization requirements. Reducing this energy barrier is crucial for optimizing nucleation and growth processes. The strong affinity between alkyl thiols and gold atoms was utilized to engineer the micelle's behaviour further. Hexadecane thiol molecules were infused into the micelle, and a subsequent reduction in the energy barrier was obtained (2.83±0.12 kcal/mol). To make the process spontaneous, the energy barrier, due to strong water layering, has to be removed. A sparingly dispersed monolayer of thiols was introduced on the targeted surface. The decrease in the potential of mean force (PMF) and negative free energy changes demonstrated that thiol-functionalized surfaces can make the process spontaneous. The surface density of thiols was further varied to

optimize the energy barrier, and found that 3.34×10^{-6} mol/m^2 was the optimum density. Finally, we extended our study to the reverse drug release process from chitosan-based matrices. Encapsulating methotrexate (MTX) in a chitosan-stabilized system revealed an energy barrier of 81.1 ± 0.81 kcal/mol for release, which reduced to 52.4 ± 1.83 kcal/mol upon adding ethanol as a co-solvent. Further, it decreased to 5.33 ± 1.77 kcal/mol after replacing cross-linker STPP with Chloride ions. This highlighted the significant impact of solvent composition and cross-linkers like STPP on drug encapsulation and release.

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