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

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by

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Chapter 8
Conclusions and Future Scopes

8.1 Conclusions

In conclusion, this study provides a comprehensive understanding of molecular mechanisms governing gold nanocrystal nucleation and growth and controlled drug delivery systems. We conducted a comprehensive molecular dynamics simulation-based investigation to gain a deeper understanding of this growth process. This investigation allowed us to construct a detailed free energy landscape, enabling us to decipher the intricate mechanism governing the growth of nanocrystals on the gold (111) surface in the presence of CTAB surfactant. Notably, our findings indicate the presence of a formidable energy barrier associated with this process. Even larger nucleates encounter similarly steep energy barriers. Nucleates find a pathway into the spherical micelles' core, potentially allowing their growth to continue. This intriguing revelation opens the door to manipulating and directing nanocrystal growth through external means that elongate or distort the shape of the micelles.

Through molecular dynamics simulations, we demonstrated the role of CTAB micelles as templates for gold nucleation and further explored how co-surfactants like oleylamine (OLA) and hexadecanethiol (HDT) enhance micelle dynamics, reduce energy barriers, and improve nucleation efficiency. A gold nucleate would require an additional energy of 10.36$\pm$0.3 kcal/mol to break the strong layering of micelle and water on the substrate. To reduce this barrier, we are investigating oleylamine (OLA) as a co-surfactant with CTAB, forming cylindrical micelles. This approach aims to lower the energy barrier and enhance nucleate release efficiency. The co-surfactant OLA reduced the energy barrier to 8.42$\pm$0.3 kcal/mol, which was instrumental in reducing these challenges, enabling effective nucleate

release and adsorption. Further, the addition of co-surfactant HDT significantly reduced the energy barrier for nucleate release to 2.83±0.12 kcal/mol. However, a significant energy barrier persists despite these improvements, largely due to hydration layers and micelle reorganization requirements. Reducing this energy barrier is crucial for optimizing nucleation and growth processes.

Further, the role of surface functionalization in tuning the interaction dynamics between nanoparticles and surfaces was analyzed. Introducing the hexadecane thiol layer significantly increases the energy barrier compared to an unfunctionalized surface, demonstrating the importance of steric and hydrophobic effects in modulating interaction forces. These findings provide valuable insights into the molecular-level mechanisms governing nanoparticle-surface interactions and offer guidelines for designing functionalized surfaces to optimize nanomaterial synthesis and surface engineering. The thiol layer reduces the energy barrier; the Optimum surface density is 3.34×10^{-6} mol/m^2. This behaviour highlights the importance of optimizing the thiol surface density to balance stability and efficiency during nanoparticle synthesis. Overall, the results underscore the critical role of surface functionalization in promoting thermodynamic favorability and facilitating micelle-mediated nucleation processes.

Furthermore, we extended our study to the reverse drug release process from chitosan-based matrices. In this study, the release of an encapsulated MTX within the CS-STPP matrix was studied to understand the release of the drug using molecular dynamics simulations. A thorough analysis of the potential of mean force, calculated using advanced sampling techniques – Umbrella Sampling and WHAM analysis- indicated the energetic feasibility of releasing the drug into the aqueous solution from a CS-STPP matrix Encapsulating methotrexate (MTX) in a chitosan-stabilized system revealed an energy barrier of 81.1±0.81 kcal/mol for release in aqueous solution. We have calculated the potential of mean force to understand the energy landscape in the aqueous medium or ethanol-water solution. We have observed that the free energy in the ethanol-water solution reduced to 52.4±1.83 kcal/mol as compared to an aqueous solution, further reduced to 5.33±1.77 kcal/mol after replacing cross-linker STPP with Chloride ions.

8.2 Future Scope

Several key areas can be explored to enhance our understanding and application of micelle-driven nanocrystal growth. The knowledge from the thesis work can be utilized in many directions. Some of them are –

- Integrate artificial intelligence (AI) with molecular dynamics (MD) and other simulation tools to predict nucleation pathways and growth kinetics during nanoparticle formation, enabling more precise control over the synthesis process.
- Machine learning (ML) could be leveraged to reverse-engineer surfactants for the tailored synthesis of poly elemental nanoparticles, opening new possibilities in advanced material design.
- Exploring diverse solvent systems and crosslinking agents could optimize drug delivery applications, expanding the scope of micelle-based systems in pharmaceuticals and nanomaterials synthesis and delivery.

These advancements would significantly enhance micelle-mediated processes' efficiency, versatility, and applicability, driving innovation in nanotechnology and material science.

—— End-of-the-thesis ——

List of Publications

1. Mona Vishwakarma, Debdip Bhandary, Estimation of the Energy Barrier for a Co-Surfactant-driven Gold Nanocrystal Nucleation and its Growth on a Surface: A Molecular Dynamics Investigation, **Journal of Molecular Liquids**, Volume 430, 30 Apr 2025, 127708, 0167-7322, https://doi.org/10.1016/j.molliq.2025.127708

2. Mona Vishwakarma, Debdip Bhandary, Controlled Released Dynamics of Methotrexate from Chitosan-based Capsules: A Detailed Energy Landscape Analysis, **Colloids and Surfaces A**: Physicochemical and Engineering Aspects, Volume 703, Part 2, 20 November 2024, 135403, https://doi.org/10.1016/j.colsurfa.2024.135403

3. Mona Vishwakarma, Debdip Bhandary, Micelle-mediated growth of gold nanocrystals on a surface, **Computational Material Science**, Volume 243, July 2024, 113147, https://doi.org/10.1016/j.commatsci.2024.113147

4. Mona Vishwakarma, Debdip Bhandary, Self-assembly driven ripening of nanocrystals, Proceedings of CUChE Alumni Symposium 2022, 2 (1), 2022, 59-63, [ISBN: 978-81-954649-1-3], https://cucheaa.com/template/Symposium2022/p10.html

5. Mona Vishwakarma, Debdip Bhandary, Thiol-Mixed Co-Surfactant Interactions and Their Role in Facilitating Energy Barrier Reduction, (*under preparation*)

6. Mona Vishwakarma, Debdip Bhandary, Role of Thiolated Layer on Gold Surface in Micelle-mediated Nucleation and Growth of Gold Nanocrystals, (*under preparation*)