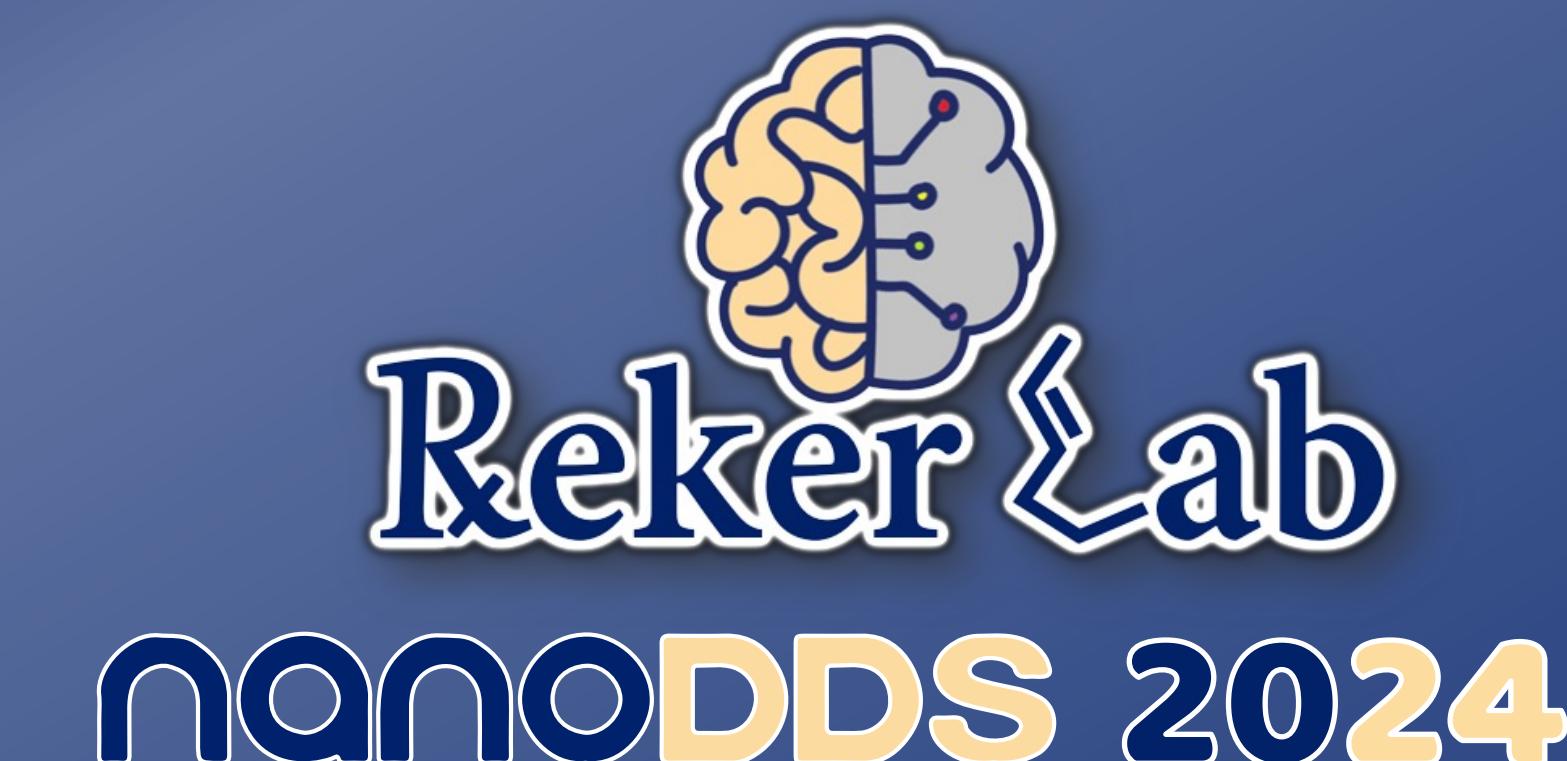


# TuNaAI: a hybrid kernel machine to design tunable nanoparticles for drug delivery

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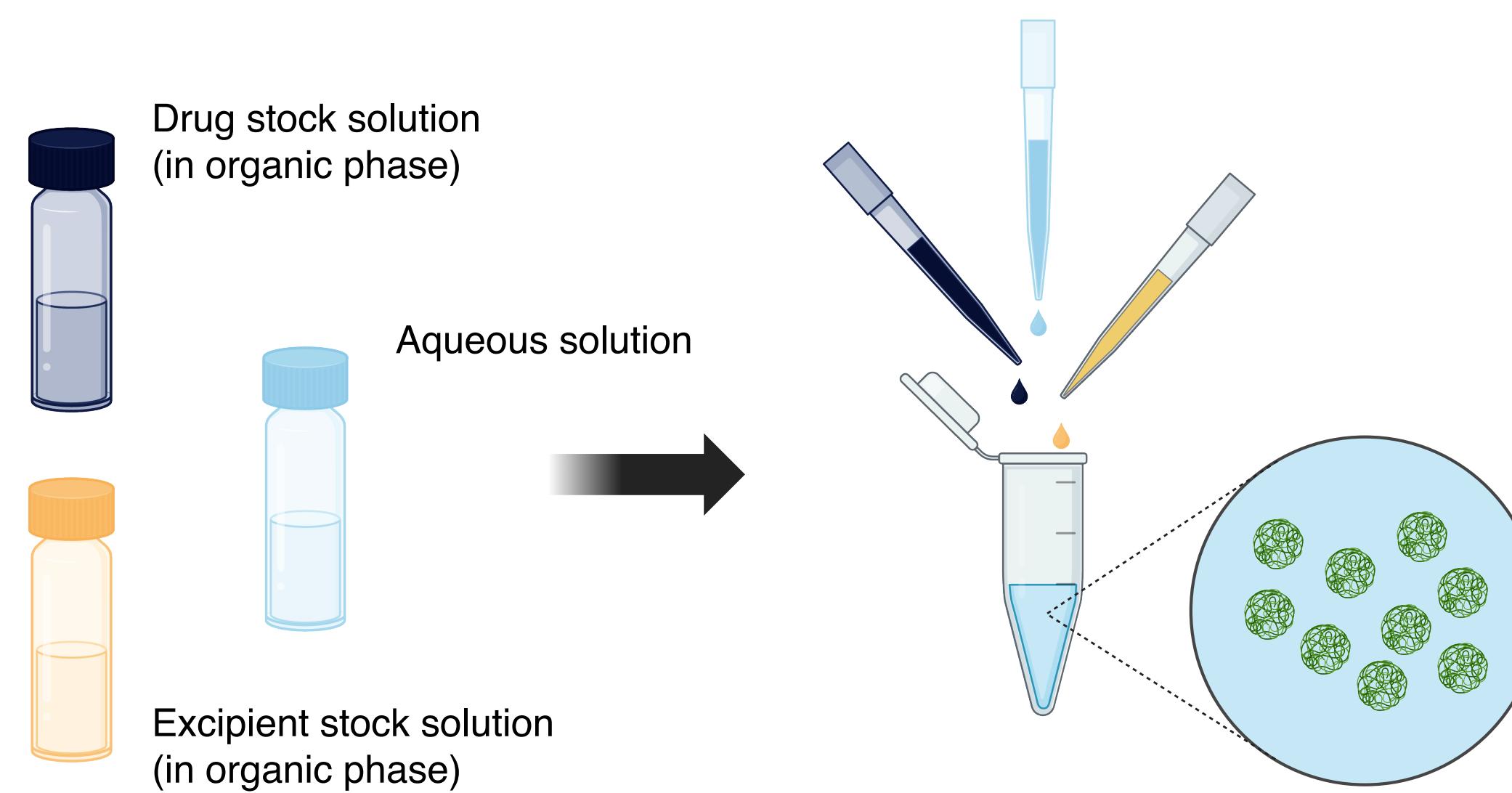
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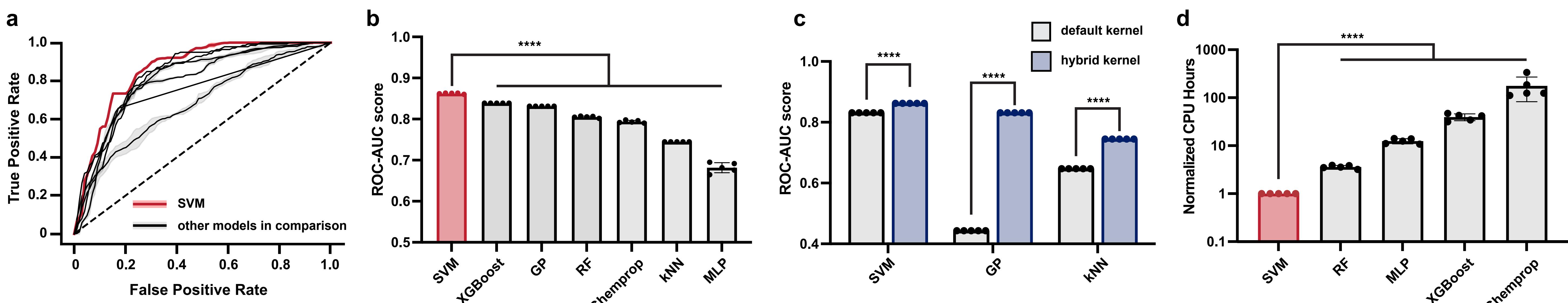
## 1 Introduction

- Drug-excipient nanoparticles are an emerging drug delivery platform.
- They are known for facile synthesis through **self-assembly**, **high drug-loading capacity**, and a rational design process informed by **machine learning**<sup>1,2</sup>.
- However, their simple synthesis (Fig. 1) also prevents tuning of material composition.



**Figure 1.** Schematic of the drug-excipient nanoparticle synthesis protocol. The **drug** and **excipient** are dissolved in an organic solvent (e.g., DMSO) and mixed in **equimolar amounts**. The mixture undergoes phase reversal upon the addition of an **aqueous solution**, leading to the self-assembly of **nanoparticles**.

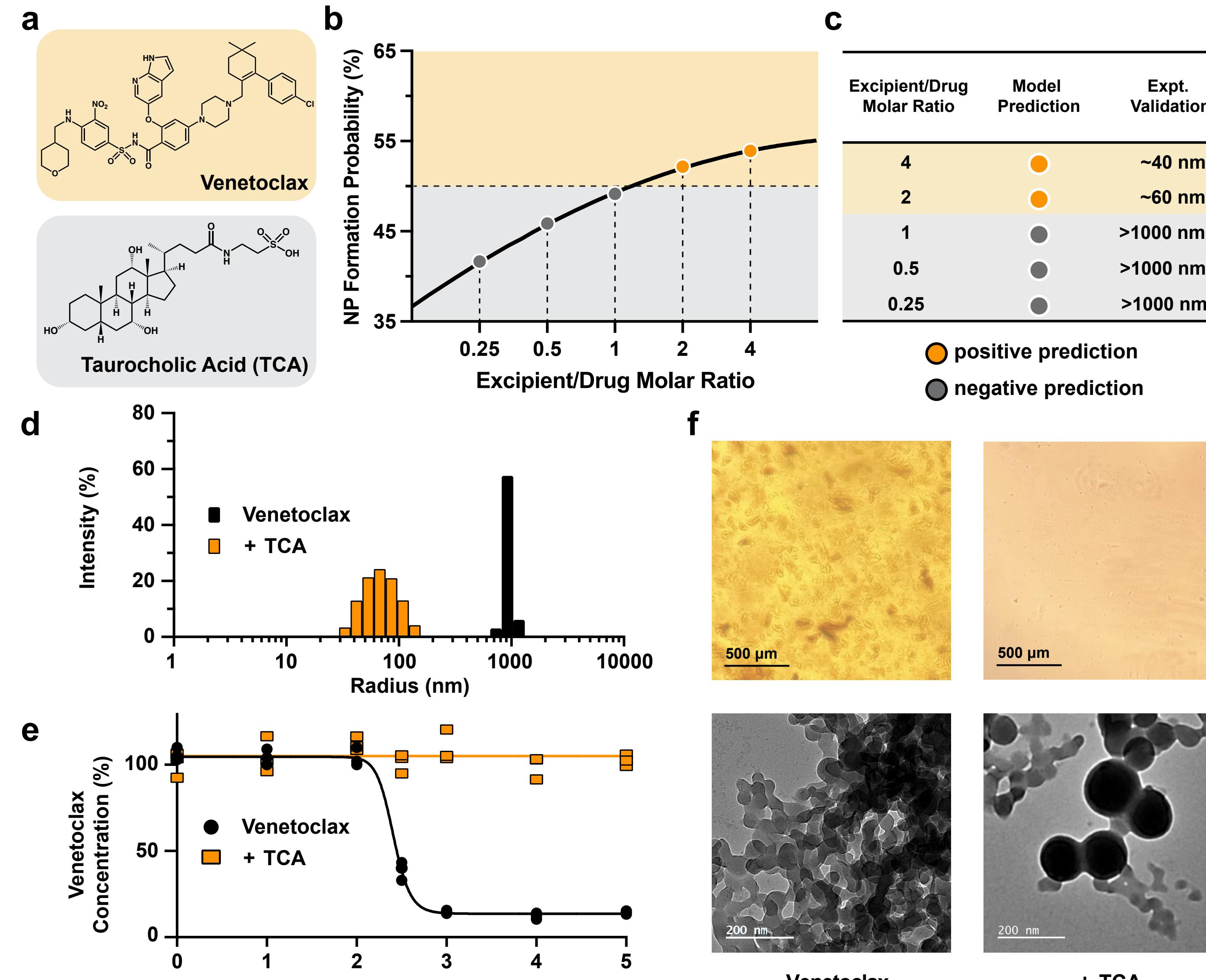
## 3 Kernel Machine Evaluation



**Figure 4.** Evaluation of the hybrid kernel machine on predicting nanoparticle formation. ROC curves (a) and ROC-AUC scores (b) of surveyed models in the leave-one-pair-out validation test. Overall best performing SVM is shown in red and other models in black. The diagonal, dashed line represents random guessing (ROC-AUC score=0.5). The lightly colored area around the solid lines indicates the standard deviation of five independent repeats. SVM, support vector machine; GP, Gaussian process; RF, random forest; kNN, k-nearest neighbors; MLP, multi-layer perceptron. c, ROC-AUC score improvements of kernel-learning models. Models with default kernels (SVM and GP, RBF kernel; kNN, Minkowski distance) are denoted in gray, and the deployments of the hybrid kernel for SVM, GP and kNN are colored in blue. d, Comparison of computational cost (quantified by CPU hours normalized on SVM, except for Chemprop which is accelerated using GPU resources) of each method. Unpaired t test ( $\alpha = 0.05$ ); \*\*\* $p < 0.0001$ .

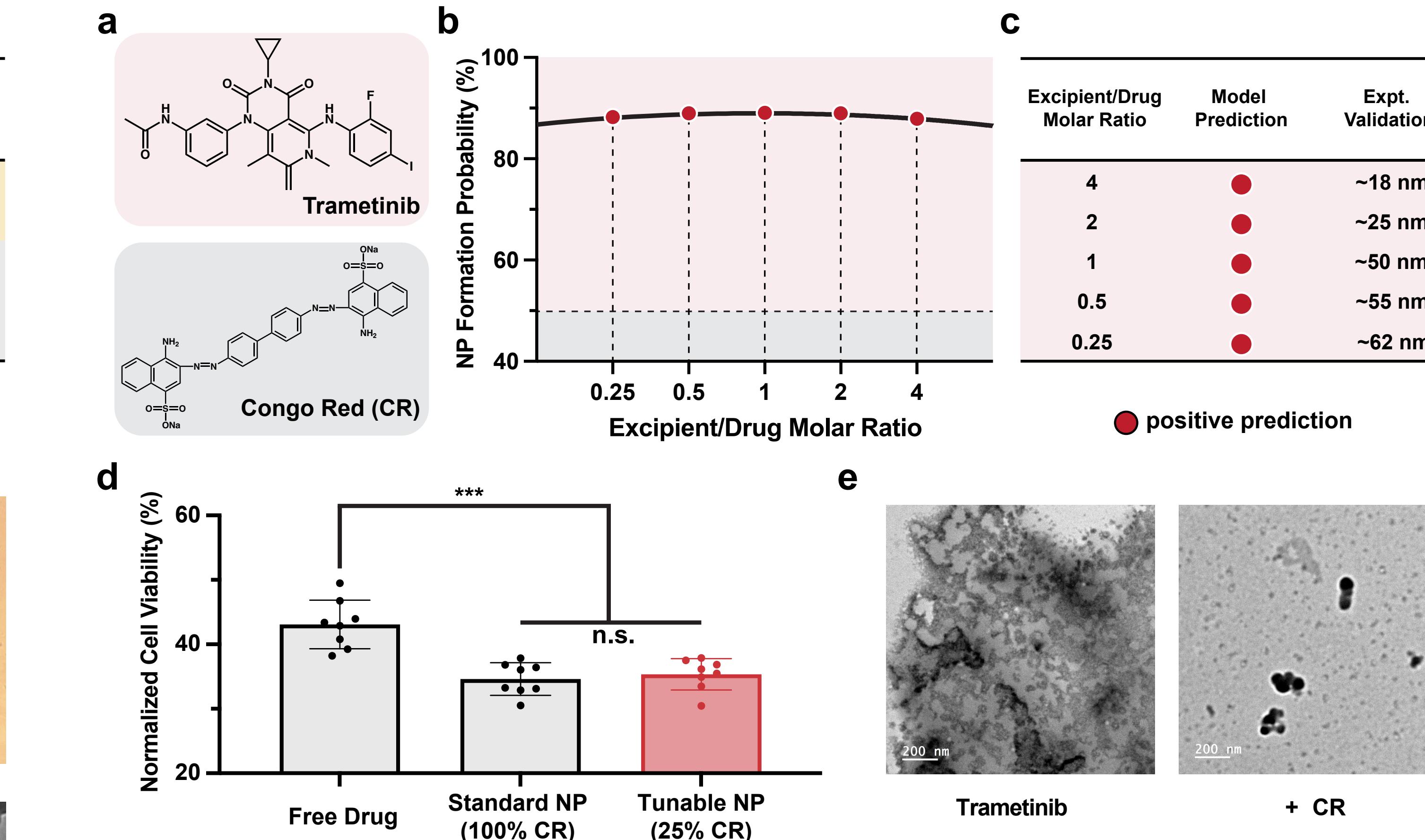
## 4 Prospective Case Validation

### Increasing excipients – formulate hard-to-load drug



**Figure 5.** Venetoclax-Taurocholic Acid (TCA) nanoparticles form when TCA is added more than Venetoclax. a, Chemical structures of drug and excipient. b, Model prediction of Venetoclax-TCA nanoparticle formation. c, Validation of model prediction. d, DLS size results of unformulated and formulated Venetoclax. e, Dispersion stability of Venetoclax alone and Venetoclax-TCA nanoparticles. f, Widefield (top row) and TEM (bottom row) images of 500 $\mu$ M unformulated Venetoclax (left column) and Venetoclax nanoparticles (right column).

### reducing excipients – preserve nanoparticle potency



**Figure 6.** Reducing the amount of Congo Red (CR) does not impair stability or potency of Trametinib nanoparticles. a, Chemical structures of drug and excipient. b, Model prediction of Trametinib-CR nanoparticle formation. c, Validation of model prediction. d, MTT assay results of unformulated and formulated Trametinib. Unpaired t test ( $\alpha = 0.05$ ); \*\*\* $p < 0.001$ ; n.s.,  $p > 0.05$ . e, TEM images of Trametinib alone (left) and Trametinib-CR nanoparticles (right).

## 5 Conclusion

- Introduced the concept of turning drug-excipient nanoparticle by adjusting stoichiometry during synthesis.
- Developed an automated, high-throughput data generation workflow.
- Constructed a bespoke kernel machine to guide the design of tunable nanoparticles.
- Enabled encapsulation of previously inaccessible drugs by rational increase of excipient.
- Computationally guided the reduction of excipient to prepare potent and safer nanoparticles.

## 6 References

- Reker, D. et al. Computationally guided high-throughput design of self-assembling drug nanoparticles. *Nature Nanotechnology* **16**, 725-733 (2021).
- Shamay, Y. et al. Quantitative self-assembly prediction yields targeted nanomedicines. *Nature Materials* **17**, 361-368 (2018).

## Research Supported by



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