

Mechanistic Generative Design for Continuous Pharmaceutical Manufacturing: Coupling Explainable Molecular Graphs, CFD, and Autonomous Experimentation

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Abstract

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This study proposes an integrated mechanistic generative-design framework for continuous pharmaceutical crystallization by combining explainable molecular graph generation, molecular-to-process property translation, computational fluid dynamics (CFD) digital twins, reduced-order surrogate modeling, process analytical technology, and constrained Bayesian optimization.

The framework was evaluated using a structured proof-of-concept dataset containing 180 molecular candidates, 540 formulations, 1,800 CFD simulations, 240 autonomous experimental records, and 80 optimization iterations. The closed-loop system improved the hypervolume indicator from 0.0917 to 0.8976 and reduced yield-surrogate RMSE from 8.18% to 1.72%. The study demonstrates how manufacturability can be incorporated into molecular design through physics-informed and explainable AI approaches.