pH-Dependent Molecular Dynamics Simulations of Active Pharmaceutical Ingredient Precipitation and Dissociation

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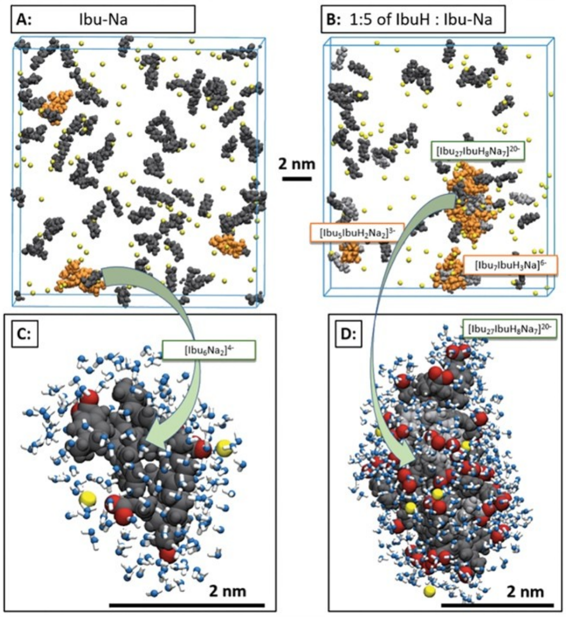

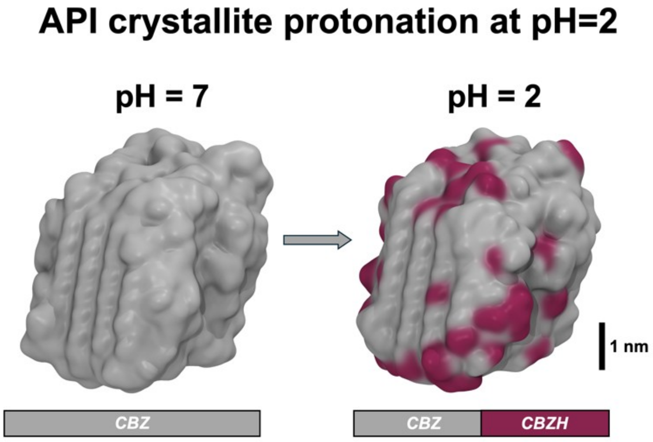

Modern pharmacology must integrate sometimes controversial aspects of drug discovery and formulation into collaborative research and development efforts, such as contrasting precipitation environments with the area of application and the favorable solubility of precipitates. The success of a new active pharmaceutical ingredient (API) candidate critically depends on its bioavailability, especially considering that a significant proportion of newly developed APIs fall under the biopharmaceutical classification system (BCS) class II substances, which are primarily limited by solubility. In many cases, this restricts drug uptake in the bloodstream after the dissolution of the API crystals in the gastrointestinal system. The need for molecular-scale insights becomes particularly evident for contrasting systems precipitated in an aprotic solvent while featuring constituents that can be protonated once the tablet reaches the intestinal system. Quantification and control of acid-induced precipitation and dissociation are critical to provide well-defined kinetics of drug release to the patient [1].

Conversely, our comprehension of crystal dissolution remains relatively limited and generally depends on the premise of a simple reversal of the growth process, namely ion-by-ion or molecule-by-molecule dissolution. However, in real-world situations, the dissolution of an API constitutes a complex, multi-faceted process, which may encompass the wetting of a solute phase, successive solvent penetration into the solute, initial fragmentation of crystals into crystallites, followed by the de-aggregation or dissolution of APIs into the solvent. This presentation focuses on the final stage of the dissolution process, which entails the disintegration of a small API crystal into the solvent to elucidate the underlying mechanisms or driving forces that facilitate acid-induced API crystallite dissolution [2,3].

[1] H. Lu, M. Macht, R. Rosenberg, et al., *Small,* **2024**, *20*, 2307858.

[2] A. Gadelmeier, M. Macht, D. Zahn, *J. Pharm. Sci.*, **2022**, *111(10)*, 2898-2906.

[3] P. Duchstein, M. Macht, D. Zahn, *CrystEngComm*, **2025,** Advance Article.