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In silico approaches for understanding the role of intermolecular interactions in formulations and combination therapies: implications for ADME properties optimization

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The pharmacokinetic properties and overall therapeutic efficacy of active pharmaceutical ingredients (APIs) depend not only on their inherent molecular characteristics but also critically on their interactions with other components in formulations or combination therapies. Optimizing the absorption, distribution, metabolism, and excretion (ADME) profile of an API requires detailed insights into its intermolecular binding within complex multi-component mixtures. However, understanding these interactions experimentally remains challenging. Computational chemistry techniques offer a powerful *in silico* approaches to model API interactions and predict their impacts on pharmacokinetics. Molecular dynamics simulations and molecular docking can provide information on atomistic level on API binding modes and dynamics within formulations or drug combinations. These methods have recently revealed molecular features of drug-excipient stabilization, permeation enhancement, and synergistic effects that underlie improved *in vivo* ADME properties. Furthermore, structure-based formulation design facilitated by computational modeling has enabled understanding of favourable interactions. Overall, emerging *in silico* strategies to elucidate intermolecular interactions influencing API pharmacokinetics can guide rational design of formulations and combination therapies for optimizing therapeutic delivery. Case studies will illustrate applications including predicting drug-polymer miscibility, modeling unimicelle encapsulation, and designing synergistic combinations of antibiotics and cationic peptides with improved permeability. The promise and current limitations of these approaches will also be examined.