STUDY OF THE CRYSTALLIZATION PROCESS OF THE ANTIVIRAL DRUG TECOVIRIMAT USING THE MOLECULAR DYNAMICS METHOD

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The active ingredients of drugs are often solid phases. However, the polymorphism inherent in molecular crystals necessitates strict control over the polymorphic composition of active substances during drug production, as different solid forms can vary significantly in their physicochemical properties. Precipitation from solution is a widely employed method for producing solid pharmaceutical forms, where the formation of specific polymorphs primarily depends on the properties of the chosen solvent. Currently, identifying the crystallization conditions for particular polymorphs remains purely empirical. It is generally accepted that the precipitation process involves the formation of molecule clusters that gradually grow into crystal nuclei. The structure of these clusters is believed to dictate the architecture of the resulting solid form.

Molecular dynamics (MD) simulation, is well-suited for investigating processes occurring in solution. MD provides a comprehensive set of atomic coordinates, enabling the extraction of detailed information regarding molecular orientation, cluster size and morphology, and intermolecular interactions—both within solute clusters and with the surrounding solvent. Furthermore, these simulations allow for the calculation of various thermodynamic properties. Such data are essential for analyzing of a specific solvent influence on cluster architecture and, consequently, the structure of the resulting solid phase.

The antiviral drug Tecovirimat, having six known solid forms, was selected as the object of this study [1]. Using MD simulations, we constructed models of Tecovirimat solutions in various solvents and at different concentrations. The conformations of individual Tecovirimat molecules were investigated as well as mutual molecular orientation. Furthermore, the structure and stability of the resulting molecular associates in solution were examined. Finally, a comparative analysis was performed between the MD simulation data and experimental X-ray diffraction data for Tecovirimat. The correspondence between the structure of clusters and the precipitated solid form was shown.

1. Tyavanagimatt S. R. et al. Polymorphic forms of ST-246 and methods of preparation: pat. 9339466 USA. - 2016.

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