

A Rare Pharmaceutical Mesophase - Avibactam Tomilopil Form 1

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Purpose

Avibactam tomilopil (AVT) is an orally available prodrug of the beta-lactamase inhibitor avibactam. AVT's solid form is novel because it is a thermotropic mesophase, a state of matter that is rarely observed in pharmaceuticals. This work describes the experimental and computational investigations that have been pursued to investigate this novel form.

Methods

Extensive solid-state characterization and computational work has been pursued to characterize this novel solid form and advance understanding of the molecular level structure. This includes extensive solid form screening and characterization (e.g. PXRD, thermal analysis, FT-IR + Raman, and solid-state NMR (including variable temperature and HETCOR analysis)). Computational work includes crystal structure prediction and advanced molecular dynamics simulations.

Results

Extensive experimental work has identified Form 1 as the only viable solid form. PXRD showed generally equidistant spacing between peaks along with disorder. ssNMR observed a single ^1H T1 time, but several ^1H T1 ρ times, indicating heterogeneity on a nanoscale domain size. In some cases, more significant peak shifting was observed in PXRD, Raman, and ssNMR than is normally observed for crystalline material. Lowest energy predicted crystal structures match well with the experimental PXRD pattern. Each of the lowest energy predicted structures have hydrogen bonding present between molecules at the terminal amide group. Analysis of the trajectories from MD simulations show that the hydrophobic tails of the molecule exhibit a higher-than-average degree of dynamic disorder.

Conclusion

A mesophase is a single-phase material with at least one molecular degree of freedom (conformational, positional, orientational) exhibiting both crystalline-like long-range order and liquid-like disorder and mobility. A mesophase differs from an amorphous solid, for example, in that it is a thermodynamically stable single phase. It has been estimated that only 5% of organic molecules can form thermotropic mesophases, and therefore, they are very rarely encountered in pharmaceuticals. Extensive experimental and computational work support the conclusion that AVT Form 1 is a mesophase.

Keywords: mesophase, Materials Science, solid-state, polymorphism