THERMODYNAMICS OF DRUG POLYMORPHISM: PROBLEMS AND SOLUTIONS

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Bioavailability and biological activity of medical drugs relate to their crystal packing and polymorphic state. Respectively, the search for all possible polymorphs is needed both for drugs available on the market or drug candidates. The problem with this search is that the methods currently used for polymorph screening are based on the kinetic restrictions for crystallization process derived from the Ostwald rule of stages. For metastable crystal forms, these methods often demonstrate poor reproducibility, which brings on the term “disappearing polymorphs”. The present report proposes the use of solid-state processes to reach a reproducible polymorph screening.

Metastable polymorphs can be efficiently prepared using the solid-state exchange/repulsion of guest (solvent) in inclusion compounds (solvates) [1-3]. This process being slow enough brings about mostly thermodynamic control for the formation of the resulting product, which enables milder conditions for the phase transition without collapse to a more stable form [1]. Solid-state processes are much easier to stop on a thermodynamically higher level than crystallization from liquids. Solid-state approach to the polymorph screening makes it more predictable giving crystal forms that were known previously only in mixtures or new polymorphs. This is applicable also for solvates that cannot be prepared by crystallization from solutions. The efficiency of the developed method has been shown for such drugs as indomethacin [1], phenylbutazone [2] and olanzapine [3]. The positive results are achieved without high-throughput screening with quite a few experiments. The preparation of metastable polymorphs by solid-state processes without crystallization from melts or liquid solutions helps to avoid such phenomenon as the oxidation of drug with air oxygen, which may produce toxic or cancerogenic impurities [2,3]. The solid-state processes with thermodynamic control require minimal amounts of solvents and the tested drugs, thus fitting to the concept of green chemistry.

1. K.V. Gataullina, A.V. Buzyurov, A.V. Gerasimov, A.K. Gatiatulin, M.A. Ziganshin, C. Schick, V.V. Gorbatchuk // Crystal Growth & Design, 2023, 23, 7109. https://doi.org/10.1021/acs.cgd.3c00443

2. M.N. Gabdulkhaev, A.V. Simdyanova, D.N. Bolmatenkov, A.T. Gubaidullin, T.A. Mukhametzyanov, M.A. Ziganshin, V.V. Gorbatchuk // CrystEngComm, 2025, 27, 2490. https://doi.org/10.1039/d5ce00094g

3. M.N. Gabdulkhaev, N.F. Idiyatullina, Kh.R. Khayarov, A.O. Surov, M.A. Ziganshin, V.V. Gorbatchuk // Crystal Growth & Design, 2026, 26, 734. https://doi.org/10.1021/acs.cgd.5c01154

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