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Optimizing early phase development of amorphous solid dispersion formulation thorough application of modeling tools

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Statement of the Problem: Amorphous Solid Dispersion (ASD) is an established formulation technique for improving the bioavailability of poorly water-soluble Active Pharmaceutical Ingredients (APIs) by increasing solubility, wettability and dissolution rate. Successful manufacturing of ASD formulation by Hot Melt Extrusion (HME) requires selection of e.g. the right API load, excipients, and processing temperature. API load is also crucial in determining important quality attributes of the drug product such as long term physical stability to ensure consistent product performance during its self-life. Identifying the possible maximum drug load limit and excipients for HME feasibility and risk assessment, and long-term physical stability of the manufactured ASD can be quite challenging whereby several extrusion trials are required in addition to prolonged stability studies. Exploring the optimal design space during early phase of formulation development by this approach requires significant amount of resources including API which may be limitedly available during this phase.

Methodology & Theoretical Orientation: As an API-sparing approach, novel empirical model and the rigorous thermodynamic Perturbed Chain Statistically Associating Fluid Theory (PC-SAFT) were applied to model ASD phase diagram of several formulations to effectively and quickly explore the design space to optimize formulation development. These were followed up with HME manufacturing and long-term stability studies (up to 18 months) of the formulations under ICH conditions to verify the model-predicted results. Several APIs and polymeric excipients including Soluplus, Copovidone, PVP, and HPMCAS were used in the studies.

Findings: The modeling tools were found to be very suitable in estimating extrusion temperature required for generating crystal-free ASD formulations as well as predicting their physical stability under different storage conditions, i.e., temperature and relative humidity.

Conclusion & Significance: Recent advances in predictive ASD phase diagram modeling proved to be reliable tools for excipient selection, HME temperature prediction, and designing ASD formulations for maximum drug load and physical stability. Applying these tools enables successful ASD formulation optimization using less resources and materials.

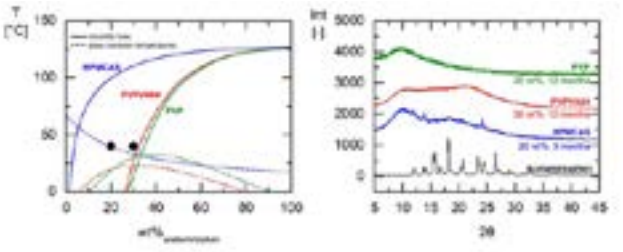

Fig 1. *Left:* Phase behavior of Acetaminophen/PVP, Acetaminophen/Copovidone, and Acetaminophen/HPMCAS at 40°C/75% RH. The solid and dashed lines show solubility prediction using PC-SAFT and glass transition temperature prediction by Gordon-Taylor equation, respectively. *Right:* XRPD diffractograms of crystalline Acetaminophen and its ASD formulations with the three polymers after storage at 40°C/75% RH.

Biography

Samuel Kyerematen is a Senior Scientist in the Global Pharmaceutical Sciences Division at AbbVie Deutschland in Ludwigshafen. His research activities focus on scientific advances in the understanding of amorphous molecular solids, and development and application of models in predicting with confidence the preferred composition, manufacturing process, and stability of amorphous solid dispersion formulations. His current responsibilities at AbbVie Deutschland include leading the Material Science Group that supports formulation development, and mentoring Doctorate research students and other scientists within the company. He received his Doctorate in Polymer Science from Martin-Luther-Universität in Germany.

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