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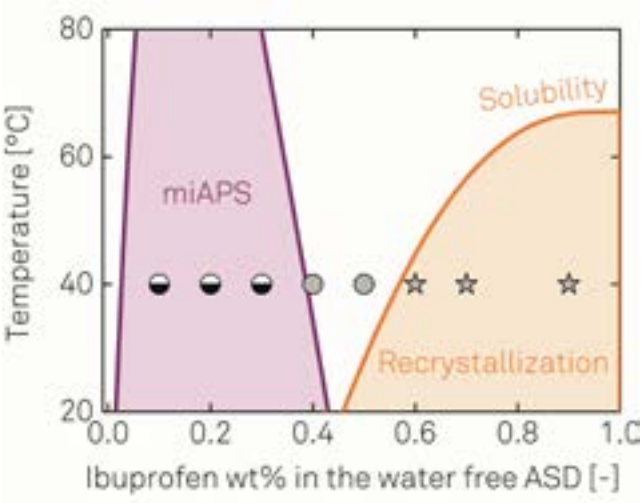
Long-term stability of pharmaceutical formulations - prediction of recrystallization and amorphous-amorphous phase separation

Christian Luebbert and **Gabriele Sadowski**
TU Dortmund University, Germany

Numerous recently-developed Active Pharmaceutical Ingredients (APIs) have a low solubility in water leading to insufficient absorption and bioavailability. To overcome this solubility limitation, APIs are molecularly dispersed in hydrophilic polymers. The resulting formulations are denoted as Amorphous Solid Dispersion (ASDs). For the administration of new pharmaceutical formulations, long-term stability tests are imposed by regulatory authorities at defined conditions of temperature and humidity (25°C, 60% relative humidity (RH) for 12 months tests and 40°C, 75% RH for accelerated six-months tests). Recrystallization of the amorphous API and/or moisture-induced amorphous-amorphous phase separation (miAPS) might occur during storage indicating the thermodynamic instability of the ASDs. Long-term stable formulations are nowadays identified by trial-and-error principles. The aim of this work was to a-priory estimate the long-term stability of ASDs by applying advanced thermodynamic methods1 and thus to reduce the experimental effort for finding promising polymeric carriers suitable for formulation development. In order to validate the thermodynamic predictions, ASDs with different API/polymer compositions were prepared and subjected to two years enduring long-term stability tests at the aforementioned conditions. Recurring PXRD measurements were performed to detect recrystallization and Raman mapping was applied to quantify miAPS. Water sorption was observed as function of time using a magnetic suspension balance. Water sorption and thereby induced phase transitions (recrystallization/ miAPS) could be predicted in quantitative agreement with the experimental data. This study showed that results of long-term stability tests can be predicted correctly in early stages of drug development and that promising polymer candidates for long-term stable ASDs can be identified prior to long-term stability tests by thermodynamic modeling.



Biography

Christian Luebbert graduated in Chemical Engineering at TU Dortmund University, Germany in 2014. During his work as Research Assistant at the Laboratory of Thermodynamics, he focuses on the physical long-term stability of amorphous pharmaceutical formulations. With his expertise, he contributes from an engineering point of view to pharmaceutically highly relevant development of formulation strategies for poorly water-soluble drugs.

Christian.luebbert@bci.tu-dortmund.de