Dynamic plantwide modeling, uncertainty and sensitivity analysis of a pharmaceutical upstream synthesis: Ibuprofen case study

A dynamic plantwide model was developed for the synthesis of the Active pharmaceutical Ingredient (API) ibuprofen, following the Hoescht synthesis process. The kinetic parameters, reagents, products and by-products of the different reactions were adapted from literature, and the different process operations integrated until the end process, crystallization and isolation of the ibuprofen crystals. The dynamic model simulations were validated against available measurements from literature and then used as enabling tool to analyze the robustness of design space. To this end, sensitivity of the design space towards input disturbances and process uncertainties (from physical and model parameters) is studied using Monte Carlo simulations. The results quantify the uncertainty of the quality of product attributes, with particular focus on crystal size distribution and ibuprofen crystalized. The ranking of the most influential parameters on the chosen quality attributes is presented, with crystal growth and water concentration being the most influential ones. The total amount of saturated solvent, which propagates from upstream processes, has been shown to highly influence the total mass of crystal produced, and the target specifications for the API as well. This dynamic plantwide modeling coupled with Monte Carlo simulations is valuable to improve design and optimization of pharmaceutical processes at early stages, especially to bottleneck the design space against a range of uncertainties and disturbances.