AN INTEGRATED SYSTEM FOR SOLVENT SOLUBILITY, SINGLE CRYSTAL GROWING, AND POLYMORPH SCREENING OF PHARMACEUTICAL DRUG SUBSTANCES

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Abstract: We would like to present an integrated system that can be used to generate solvent solubility data, and carry out automated crystallization experiment via slow evaporation, and vapor diffusion techniques. Both crystallization techniques are commonly used to grow single crystals for structure solutions. The system is based on a customized Gilson 215 liquid handler with online vortex and filtration modules. The system first delivered solvent or solvent mixtures to powder samples dispensed into either vials or 96-well plate on a sample rack. The mixtures were then allowed to equilibrate with shaking, then filtered through 5um filters to a 96-well collection plate with glass vial inserts (500ul). An aliquot of the filtrate (50ul) was transferred to HPLC vials on rack, and diluted for solubility analysis by HPLC; another fraction of the filtrate (200ul) was transferred to a customized 96 well plate for vapor diffusion experiment; the left over filtrate in the collection plate was sealed with polyethylene mat lids with pin hole on each well position. The vapor diffusion plate and the slow evaporation plate were then left to equilibrate, or evaporate slowly in lab hood for a week. Crystals formed in the wells were then inspected for single crystal suitability, and if powder, checked by PXRD for polymorphs. We have tested the system with commercial compounds such as chloramphenicol, cimetidine, and acetaminophen, as well as our proprietary drug candidates. The system showed excellent solubility data precision (RSD less than 2% for replicates) and accuracy (correlation coefficient between manual and instrument results was 0.96). It also generated single crystals for all the commercial compounds, and 4 out of 6 proprietary drug candidates we tested with. In addition, we obtained the same polymorphs reported in the literature for cimetidine and acetaminophen, and identified multiple polymorphs, solvates and hydrates for our own drug candidates.