

**High throughput screening for pre-formulation polymorphs and salt forms:  
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A high throughput automated crystallization system was developed for polymorph and salt selection studies of drug compounds. Arrays of crude compound are automatically dispensed to a library array. For salt selection studies, arrays of crude salts are synthesized by adding molar equivalent amounts of API (typically 5mg/crystallization) and acids or bases. A diverse set of recrystallization solvents is added to the array of materials and the samples are heated for two hours to equilibrate. Each hot solution is filtered using a heated multi-tip needle and dispensed into daughter plates that allow up to 3 different recrystallization processes to be carried out simultaneously. The robot performs about 300 crystallizations per cycle including evaporation, controlled cooling, and precipitation. A unique feature of this system is the Universal Substrate™ that makes it possible to prepare and analyze samples without manual manipulation. Solids are screened and analyzed using birefringence, Raman spectroscopy, XRD, and melting point. All data is stored in the database and can be viewed using the Symyx' Renaissance® software data browser. Raman and XRD spectra are sorted into groups with the aid of Symyx' Spectra Studio™ software. Crystallizations of selected wells are run in scintillation vials on 10 to 50mg scale. Birefringence, Raman, XRD, DSC, TGA, and <sup>1</sup>H-NMR are used to identify the forms found on the library. A single set of crystallizations using ephedrine led to the characterization of 7 salts including toluenesulfonate, phosphate, L-tartrate, methanesulfonate, chloride, bromide, and methylsulfate.