

Rational screening in solid form selection

Arjen van Langevelde, Erwin Blomsma, Stéphanie Mulder

Avantium Technologies BV, Zekeringstraat 29, 1014 BV Amsterdam, The Netherlands

Purpose

The solid-state properties of drug substances have a profound effect on the pharmacological profile of the final drug products. As a consequence, selection and control of the solid form of the drug substance is a major issue throughout the whole drug development life cycle and production. Therefore, the solid state of the drug substance is one of the focal points during pre-formulation.

Selection as well as production of the most appropriate solid form of a drug substance demands a thorough understanding of its solid-state behavior. However, many parameters are involved in crystallization processes. To cover this complex n -dimensional parameter space by systematic variation of the parameters (=the combinatorial approach) requires a huge amount of crystallization experiments to be performed. Although high-throughput crystallization approaches running hundreds of thousands of experiments may secure this precise mapping, numerous meaningless experiments will be performed as well.

Methods & Results

To maximize the information that is obtained from the crystallization experiments, descriptor technology and multivariate statistics are used. Using this rational screening approach solvents for crystallization screens are selected, inducing at least the same variation in the crystallization study as in regular high-throughput screening, but significantly fewer experiments are to be performed.

In these high-throughput polymorph and salt screens a minimal amount of product (< 5 gram) is used in approximately thousand crystallization experiments covering a wide parameter range. Dedicated screening and analytical technology has been developed to allow these small-scale experiments. Several challenges from managing and analyzing small samples sizes to handling large amounts of data will be highlighted.