

PARTICLE DESIGN FOR DRUG DELIVERY SYSTEMS

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For many new drugs, as well as reformulations of established molecules, the need for improved and efficient drug delivery systems is apparent. With over 80% of drugs administered as solids in particulate form, attention has been increasingly focused on methods which enable critical particle properties to be engineered with regard to drug delivery, dosage form design and bioperformance of final products. For example, in respiratory drug delivery, effective deep lung deposition is achieved with particles sized between 1 and 5 microns. Indeed the general trend is to use ultra-fine particles as a means to overcome the major challenges of many new drug molecules and macromolecules – such as poor aqueous solubility which frequently leads to low bioavailability.

Current methods of forming fine particles, such as solvent crystallization or precipitation followed by harvesting, drying and milling (or micronisation), are capable of achieving the targeted particle size, but this multistage processing sequence coupled with the high energy input on milling often damages the crystals, creates amorphous domains, and leads to highly charged and cohesive materials as well as reducing chemical and physical stability. Additionally, particles can vary from batch to batch causing problems in down stream processing and product uniformity. Also the stringent pharmaceutical controls on purity, solid state chemistry, including polymorphic purity, and residual solvent levels must be met. Current crystallization practice, with continuing challenges in particle formation and process control and scale-up, remains the process of choice for particle formation but has limited scope in particle engineering and design. New approaches are required.

In recent years interest in supercritical fluid (SCF) methods for engineering drug particles with well defined crystallographic, chemical and physical properties has grown. Of the various methods proposed, the SEDS™ (Solution Enhanced Dispersion by Supercritical fluids) process has been shown to have the widest applications in pharmaceutical particle design. In this technique, the SCF is used as a dispersing antisolvent and as a medium for extracting the solvent for efficiently precipitating the solute from an organic or aqueous solution. Various materials, ranging from inorganic and organic small molecular weight drugs to proteins and polymers, as well as drug-excipient coformulations, have been processed successfully, with efficient and batch consistent manufacture of particles in the 0.5 to 30 microns size range with narrow size distributions, and controlled solid state properties, high purity and low residual solvent levels. The process has been scaled to a manufacturing capacity preparing materials for clinical trials under cGMP.

This presentation will discuss the need for particle design for drug delivery systems and, following a brief review of supercritical fluid methods, highlight several areas where this new approach has successfully addressed current pharmaceutical challenges in formulation and performance of drug delivery systems. Future perspectives will also be presented.