453e Formation Mechanism and Properties of Nanoparticles Produced by Supercritical Fluid Extraction of Emulsions

Boris Y. Shekunov, Pratibhash Chattopadhyay, Jeff Seitzinger, Robert Huff, and Adam Gibson

This work aims to evaluate a new method for production of pure drug and composite (e.g. polymer-drug) nanoparticles intended for different drug delivery systems. The technique developed, supercritical fluid extraction of emulsions (SFEE), involves a continuous or batch extraction of the oil-in-water (o/w) emulsions using a stream of supercritical carbon dioxide. Model drugs indomethacin and ketoprofen were encapsulated into biodegradable polymers poly(lactide-co-glycolide) (PLGA) and polymethacrylate (Eudragit RS). In another group of experiments, compounds cholesterol acetate (CA), griseofulvin (GF) and megestrol acetate (MA) were taken as an example of poorly water-soluble molecules. All particles were obtained in the form of aqueous nanosuspensions. A mechanistic study was conducted on the effect of the process condition (flow rates, pressure, temperature) and emulsion characteristics (concentration, phase composition, choice of surfactants) on the particle size and purity. These nanoparticles were also produced in several batches in order to compare their dissolution behaviour with micronized materials.

The fundamental mechanism of this process is outlined. The particle size (within 50 –1000 nm in this study) was controlled mainly by the emulsion droplet diameter, but also influenced by the polymer and drug concentrations and emulsion solvent fraction. The mass transfer of the organic solvent proceeds by two parallel pathways: (a) by direct extraction upon contact between SC CO2 and the organic phase and (b) diffusion of the organic solvent into water followed by consequent extraction of the solvent from the aqueous phase into SC CO2. There is also an inverse flux of CO2 into the droplets leading to expansion of the organic phase and creating local supersaturation and precipitation of drugs. Although the solvents used to form the emulsions are considered to be “immiscible” with water, there is always a finite solubility in the aqueous phase. This solubility may significantly increase the rate of mass-transfer from the emulsion droplets into the aqueous phase. After the solvent extraction is completed, the nanoparticles remain in the aqueous phase, stabilized by the surfactant. The surfactant molecules present around the emulsion droplet act as protective layer and prevent particle growth by agglomeration or by a thermodynamic “ripening” effect.

Dissolution studies indicated a sustained release for encapsulated materials for several hours consistent with their size. These particles were amorphous in nature. For pure drugs, crystalline nanoparticles produced a 5-10 fold increase in the dissolution rate compared with micronized powders. Theoretical calculations indicated that this dissolution was governed mainly by the surface kinetic coefficient and the specific surface area of the particles produced. It was observed that the necessary conditions for a reliable and scalable process was the sufficient emulsion stability during the extraction time. The importance of fundamental mechanistic understanding is indicated.

It is suggested that SFEE technology offers an alternative to both current microencapsulation and micronization processes, with significant advantages in terms of product quality, processing time and scale up.