made its mark and is influencing every segment and subspecialty. Particle size reduction (or often referred to as micronization) offers a significant opportunity for formulators to solve the product development hurdles inherent with poorly water-soluble active pharmaceutical ingredients (APIs).

In the case of formulations intended for oral administration, poorly water-soluble APIs typically suffer from an inadequate or highly variable rate and/or extent of drug absorption (sometimes as a function of food in the stomach, i.e., fed/fasted variability). Particle size reduction of the API before formulating will significantly increase the specific surface area and subsequently the rate of dissolution of the drug in the gut milieu. Therefore, in the case of poorly water-soluble APIs for which absorption is dissolution limited, particle size reduction may result in significant improvement in the rate and extent of drug absorption such that the bioavailability requirements of the drug are met.

In the case of formulations intended for intravenous administration, size reduction of APIs to nanometer-sized particles render a sterile, aqueous dispersion of such particles infusible. Indeed, particle size reduction methodologies have advanced to the point where nanometer-sized crystalline API particles can be realized. This size reduction approach provides a valuable formulation alternative to the traditional formulation approach of ensuring that a drug is solubilized before intravenous administration. It alleviates the potential issues associated with utilizing high concentrations of aqueous compatible cosolvents and surfactants to solubilize the drug.

In addition, size reduction can also enhance delivery of poorly water-soluble APIs to the respiratory tract. Specifically, aerosolized particles should have aerodynamic diameters in the range of 1–5 μm. With larger particles, deposition occurs primarily on the back of the throat, which can lead to systemic absorption and undesired side effects.

This chapter will provide a theoretical basis for the use of size reduction techniques to solve the formulator's challenge with poorly water-soluble APIs. It will also describe various methodologies available for size reduction, and will outline capabilities and limitations of each. Finally, several examples will be presented where size reduction techniques to nanoparticle sizes have been successfully applied to poorly water-soluble APIs. These examples will include drugs intended for oral and parenteral administration.

THEORY

There are a number of physicochemical properties of an API that are impacted upon size reduction, which need to be considered while resolving pharmaceutical problems related to solubility limitations. Clearly, dissolution rate and its dependence upon particle size reduction is one of those critical properties (Ross and Morrison, 1988; Rabinow, 2004; Kocbek et al., 2006). For example, in the case of oral administration of a poorly water-soluble API, the increase in dissolution rate attendant with size reduction provides for more drug in solution, and available for absorption, during its gastrointestinal transit (Chaumeil, 1998; Merisko-Liversidge et al., 2003; Patravale et al., 2004; Pouton, 2006). In the case of intravenous administration, the dissolution rate will, to a large extent, determine the distribution kinetics and hence availability of drug to interact with pharmacological receptors at the molecular level. Therefore, dissolution phenomena and its dependence on particle size are critical to understanding the value of size reduction to pharmaceutical applications (Setnikar, 1977; Rasenack and Muller, 2002; Merisko-Liversidge et al., 2003; Mosharraf and Nystrom, 2003). This section will focus on and review the theoretical aspects of dissolution, crystal growth, and solubility of crystalline APIs with an emphasis on how these properties are affected by particle size diminution (Noyes and Whitney, 1897; Brunner and Tolloczko, 1900; Nernst, 1904; Hixson and Crowell, 1931; Tawashi, 1968; Anderson, 1980; Cammarata et al., 1980; Valvani and Yalkowsky, 1980; Braun, 1983; Greco Macie and Grant, 1986; Zipp and Rodriguez-Hornedo, 1989; Abdou, 1990; Grant and Higuchi, 1990; Sokoloski, 1990; Grant and Chow, 1991; Ragnarsson et al., 1992; Canselier, 1993; Lu et al., 1993; Yao and Laradji, 1993; Yonezawa, 1994, 1995; Lindfors et al., 2006a, b). The relevance of particle size reduction of crystalline APIs to the improvement of bioavailability (Moschwitzer and Muller, 2006) will also be addressed.