and Wu (1991). Their conclusion was that the crystal growth of theophylline monohydrate is controlled by a surface reaction mechanism rather than by solute diffusion in the bulk. Further, they found that the data was described by the screw-dislocation model and by the parabolic law, and they concluded that a defect-mediated growth mechanism occurred rather than a surface nucleation mechanism.

Impurities and Crystal Growth

The addition of foreign agents (dispersing agents, growth inhibitors, surface active agents, etc.) to a system before or during crystallization can profoundly influence or interfere with the nucleation processes and with the diffusion of molecules to the surface of the growing crystal. Very small quantities of additives may adsorb into the growing crystal lattice and alter the character of the crystal surface by any one or combinations of the following mechanisms:

1. Changing the properties of the formulation (i.e., surface tension, ionic strength, or the macroscopic solubility, c_s)
2. Altering the adsorption layer at the solid–liquid interface, therefore affecting the integration of growth units
3. Undergoing selective adsorption onto the crystal face, exerting a blocking effect
4. Being adsorbed onto growth steps, disrupting the flow of growth layers across the surface
5. Being adsorbed at kinks on the crystal face, causing rough faces to flatten out
6. Altering the surface energy of a crystal face, which may change its degree of solvation

Since many undesirable changes in pharmaceutics arise from nucleation and crystal growth, impurities (either added intentionally or inadvertently) can modulate or suppress these processes. This may give rise to inhibition of crystal growth in suspensions, emulsions, and ointments, and may also inhibit polymorphic transitions.

PARTICLE SIZE REDUCTION METHODS

There has been a long history of the use of particle size reduction and deaggregation techniques in the pharmaceutical industry, and extensive reviews of these techniques and their theories have been provided previously (Parrot, 1974; Chaumeil, 1998; Merisko-Liversidge et al., 2003; Patravale et al., 2004; Rabinow, 2004; Rasenack and Muller, 2004; Moschwitzer and Muller, 2006). The size reduction processes of interest here are mechanical in nature and capable of reducing drug particle size into the ultrafine range (particle diameter <10 μm).

Particle size reduction can be achieved by two methods:

1. Precipitation—substance is dissolved in appropriate solvent.
2. Mechanical methods—mechanical force is introduce by using different kind of equipments (mills), which is commonly used in the pharmaceutical industry.

There are multitudes of milling techniques/equipment available for the reduction of drug particles into the ultrafine range (Moschwitzer and Muller, 2006). All the techniques fall under two broad categories: dry milling (the size reduction is carried out in the dry state of the particle) and wet milling (size reduction is carried out with the particles being suspended in a liquid medium). A brief discussion of four such techniques (fluid energy milling, ball milling, media milling, and Microfluidizing®) follows. Besides these techniques, modern methods such as those that use supercritical fluids in the micronization process are getting increasingly popular. The most widely applied techniques of this category include the rapid expansion of supercritical solutions (RESS) process, the supercritical antisolvent (SAS) method, and the particles from gas-saturated solutions (PGSS) method. Discussion of these techniques would be out of the scope of this chapter.