- Peanut oil
- Sesame oil
- Buffers at various pHs

5.2.1 Solubility Modulation

Poorly soluble compounds represent an estimated 60% of compounds in development and many major marketed drugs. It is important to measure and predict solubility and permeability accurately at an early stage and interpret these data to help assess the potential for the development of the candidates. This requires the development of an effective strategy to select the most appropriate tools to examine and improve the solubility in each phase of development and the optimization of solid-state approaches to enhance solubility, including the use of polymorphs, cocrystals, and amorphous solids. All of these would affect the dissolution rates and bioavailability that can be studied with nanocrystal technology.

With this trend of increasingly insoluble drugs stretching resources, many companies are now reevaluating their strategy. They know that there are many available technologies to measure and predict and finally improve solubility, and several new techniques are emerging. Studies that encompass this scope would include how membrane permeation of drugs can be enhanced by means of solubilizing agents, how the solid state is characterized and modified to improve solubility and drug performance, how salt screening and selection can impact the dissolution rate and oral absorption, the application of nanocrystal technology to increase dissolution rate, and the analysis of the use of pharmaceutical co-crystals in enhancing drug properties.

Many different approaches have been developed to overcome the solubility problem of poorly soluble drugs, for example, solubilization, inclusion compounds, and complexation. A basic disadvantage in these formulation approaches is that these can be applied only to a certain number of drugs exhibiting special features required for implementing the formulation principle (e.g., molecule fits into the cavity of the cyclodextrin ring). The use of solvent mixtures is also very limited owing to toxicological considerations. In addition, more and more newly developed drugs are poorly soluble in aqueous media and simultaneously in organic media, thus excluding the use of solvent mixtures. Ideally, the formulation principle should be able to be applied to all or at least most of the poorly soluble drugs.

Solubilizers (e.g., organic solvents, detergents, and Pluronics) are often used to solubilize drugs in aqueous solution without considering their effects on biological systems, such as lipid membranes and multidrug-resistance (MDR) efflux transporters (e.g., P-glycoprotein and MDR1). Liposomal solubilization is an effective approach for the delivery of potent, insoluble drug candidates. An alternative to other methods developed is the production of drug nanoparticles by high-pressure homogenization, either as pearl milling or as the continuous high-pressure homogenization. Of importance is the consideration of metallic contamination during fast speed milling processes to keep it less than 1 ppm. Drug nanoparticles are produced by the dispersion of drug powder in an aqueous surfactant solution; the obtained presuspension is passed through a high-pressure piston-gap homogenizer, for example, 5–20 homogenization cycles at typically 1000–1500 bars, and works on the principle that cavitation occurs in the aqueous phase. The particle suspension has a very high flow velocity when