CHAPTER-I

INTRODUCTION
Advances in drug discovery technologies have led to identification of a number of compounds with good therapeutic potential. However, because of their complex chemistry majority of these compounds have poor aqueous solubility resulting in reduced and variable bioavailability\textsuperscript{1,2}. The variability in systemic exposure often makes it difficult for dose delineation, results in fed and fast variability and in some instance slower onset of action. These issues may lead to sub-optimal dosing and concomitantly poor therapeutic response. For compounds with poor aqueous solubility that are ionizable, preparation of salts to improve solubility/dissolution rate is a commonly used approach that had limited success. From a product development standpoint, generally a crystalline salt is preferred due to potential physical and chemical stability issues associated with an amorphous drug substance. Identification of a crystalline salt with adequate aqueous solubility requires screening various counter-ions and solvents/crystallization conditions and at times isolation of a crystalline material is difficult. In some instances the salt formed is extremely hygroscopic posing product development and manufacturing challenges\textsuperscript{3}.

The most commonly used approaches include micronisation and solid dispersions of the drug in water-soluble carriers for filling into hard or soft gelatin capsules. Micronisation often results in particles that are < 5 µm with very small fraction that is in sub-micron range. The decrease in particle size results in a modest increase in surface area that may not change the dissolution rate or saturation solubility to significantly impact bioavailability\textsuperscript{4}. 

Solid dispersion compositions comprise of molecular dispersion of the drug in water soluble and lipid-based surface-active carrier that can emulsify, upon contact with the dissolution medium. Formation of molecular dispersions (solid solution) provides a means of reducing the particle size of the compounds to nearly molecular levels (i.e., there are no particles). As the carrier dissolves, the compound is exposed to the dissolution media as fine particles that are amorphous, which can dissolve rapidly and thus absorbed. These formulations are filled in soft or hard gelatin capsules. There are several formulations in the market, e.g., Sandimmune®/Neoral® (cyclosporine microemulsion), Norvir® (Ritonavir) and Fortovase® (Saquinavir). This approach is suitable for highly potent compounds with low dose requirement and thus not applicable for moderately potent compounds where the dose requirement may be high. Thus there is a need for a versatile technology that can resolve formulation issues associated with dissolution and bioavailability enhancement of poorly water-soluble compounds with low or moderate potency.

In recent years an approach that is gaining popularity with formulation scientists for developing a viable dosage form for poorly soluble compounds is to develop a nanoparticle formulation, usually less than 1 μm in diameter. For example, when the particle size of the drug is reduced from 8 μm to 200 nm there is 40-fold increase in the surface area to volume ratio. This increase in surface area can provide substantial increase in the dissolution rate if the formulation disperses into discrete particles. The nanoparticle formulation approach has proven useful and invaluable in all stages of the
drug product development and has opened opportunities for revitalizing marketed products with suboptimal delivery.

Nanoparticle formulation technologies have provided the pharmaceutical industry with new strategies for addressing the issues associated with poorly soluble compounds. For new chemical entities (NCEs) development, the technology has been of great value when it is used as a screening tool during preclinical efficacy and/or safety assessment studies in the early development phase. During later drug product development, robust nanoparticle formulations can be post processed into various types of patient-friendly dosage forms that provide maximal drug exposure. For marketed products requiring life-cycle extension opportunities, nanoparticle formulation strategies provide a means to develop a new drug-delivery platform incorporating existing drug, thus creating new avenues for addressing unmet medical needs. The researches indicate that nanoparticle solutions in drug delivery will capture significant percentage of the total market based on their ability to reduce the product development time to reach the market, extend product life cycles and provide patent protection. The potential benefits of nanotechnology based drug delivery include lower drug toxicity, improved bioavailability and reduced cost of treatment.