ABSTRACT

Poorly water-soluble drugs such as Candesartan cilexetil and Camptothecin analog offer challenges in developing a drug product with adequate bioavailability. The bioavailability of these drugs is dissolution limited following oral administration. The objective of this study was to develop a tablet dosage form for these drugs incorporating drug nanoparticles to increase their saturation solubility and dissolution velocity for enhancing oral bioavailability while reducing variability in systemic exposure. Drug nanoparticles were prepared using a wet bead milling technique and the milled nanosuspensions were converted into solid intermediate using either a spray drying or spray granulation process. The nanosuspensions were characterized for particle size before and after drying process. The drug nanoparticles were evaluated for solid-state transitions before and after milling using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). The surface morphology of drug nanoparticles was evaluated by Scanning Electron Microscopy (SEM). The dried granules were blended with extra granular excipients for tableting. The saturation solubility and dissolution characteristics of the nanoparticle tablet formulations were investigated and compared with micronized and ‘as-is’ drug formulations to ascertain the impact of particle size on drug dissolution. The systemic exposures of nanoparticle formulations were evaluated in male Wistar rats for assessing increase in the rate and extent of drug absorption. The results demonstrated that there were no solid-state transitions upon milling; the scanning electron micrographs illustrate, the recrystallization of water soluble carrier creates a highly hydrophilic environment around the drug preventing particle interaction and aggregation, there was a significant enhancement in dissolution rate for tablet dosage
form incorporating drug nanoparticles as compared to the un-milled and micronized drug. Systemic exposure studies in rats indicated significant increase in the rate and extent of drug absorption for nanoparticle formulations. The manufacturing process described herein is relatively simple and scalable indicating its general applicability to enhance dissolution and bioavailability of poorly soluble compounds.