INFLUENCE OF ADDITIVES ON THE ANTISOLVENT PRECIPITATION OF STABLE PHARMACEUTICAL NANOPARTICLES

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Background: Low solubility and bioavailability are two major challenges faced by the pharmaceutical industry. Antisolvent precipitation is a fast, cost and energy efficient method used to prepare nanosize drug particles, to increase the solubility and the dissolution rate of poorly water soluble active pharmaceutical ingredients (APIs). Generally different types of additives such as surfactant and polymeric molecules are used to stabilize the nanoparticles during precipitation and subsequent storage or drying stages. Although nanosuspensions are used in some dosage forms, their short shelf life often necessitates separation of the nanoparticles from the solution to prepare dry powders. Freeze drying or spray drying processes can be used but frequently lead to agglomeration. Additives can act as redispersing agents which help to enhance the dissolution rate of agglomerated dry nano/micro particles.

Methods: A systematic investigation of the effect of different additives, before and after nucleation, and process parameters on the antisolvent precipitation of 2 poorly water-soluble APIs, fenofibrate (FF) and dalcetrapib (DCP), was conducted. The produced nanoparticles were isolated to dryness by freeze drying. PXRD, DSC and SEM analyses were performed on freeze dried particles to confirm the morphology and polymorphic form present. In vitro dissolution rate studies of the as received drug, nanosuspensions and freeze-dried particles were compared to probe the influence of additives during the precipitation and freeze drying processes.

Results: It was observed that lowering temperature helps to stabilize nanoparticles produced by antisolvent precipitation. For both APIs FF and DCP, nanosuspensions in the presence of single additives showed multimodal particle size distributions resulting in D[90] values in the micrometre range. In the presence of mixture of surfactant and polymeric additives (e.g. DOSS and PVA), both APIs produced narrower particle size distributions than in the presence of single additives resulting in D[90] values remaining in nanometer range over time (up to 30 mins). From particle size measurements of freeze-dried nanoparticles, it was observed that agglomeration happened during the drying process resulting in micrometer size particles of various habits. Dissolution rates of freeze-dried APIs prepared with additives showed rapid dissolution profiles compared to ‘as received’ API and freeze-dried APIs without additive. Freeze dried dalcetrapib in the presence of multiple additives underwent rapid dissolution similar to the aqueous nanosuspension which can be contributed to the thin needle like morphology of dried dalcetrapib particles.

Conclusions: Additives help in decreasing particle size and stabilizing nanoparticles of FF and DCP. For both APIs a combination of surfactant and polymeric additives are more efficient to stabilize nanosuspension and produce narrow PSD than single additives. Additives had a significant effect on the resulting morphology of dried particles. Additives present in dried APIs act as redispersing agents to increase the dissolution rate. Particle habits have direct effect on dissolution rate.