Abstract

Title of thesis: Polymeric stabilizers maintaining the saturation solubility of itraconazole nanocrystals after dissolution process

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The increase of bioavailability of poorly water soluble drugs is still an issue. One of the techniques improving aqueous drug substance solubility, and consequently enhancing bioavailability, is formation of nanoparticles. However, the bioavailability is determined by the concentration of the dissolved drug achieved at the time of absorption. This fact emphasizes the importance of the maintenance of the high solubility until the absorption area is reached. Sufficiently stabilised nanocrystalline drugs offer a solution to this problem. In this thesis, the solid nanoparticle formations of an antifungal agent itraconazole (ITZ) are presented. Wet milling was employed to create the nanosuspension stabilised by binary mixture of stabilisers or by a single stabiliser. An aggregation inhibitor Poloxamer 407 (F127) in the combination with a polymeric precipitation inhibitor hydroxypropyl methylcellulose (HPMC) or polyvinyl pyrrolidone (PVP) at different ratios, or a single precipitation inhibitor, were utilised. The nanoscale was determined by dynamic light scattering (DLS) measurements and the crystalline state was confirmed by differential scanning calorimetry (DSC). The solubility tests showed the importance of utilised stabilisers over particle size within nanoscale. The highest solubility levels and the most successful maintenance of high solubility values were obtained in samples containing a single polymeric precipitation inhibitor, followed by binary mixtures with F127 exceeding the amount of HPMC/PVP. The order can be concluded: HPMC>PVP>F127+HPMC>F127+PVP. The physical state (predissolved/solid) of the precipitation inhibitor influences the solubility level. Hygroscopic properties of PVP enhance its affinity to water and thereby increases solubility, the addition of solid excipient is more beneficial. Postmilling addition of the precipitation inhibitor impacts on the concentration of dissolved drug positively.

Keywords: itraconazole, nanosizing, supersaturated state, polymeric precipitation inhibitors