Supersaturated controlled release matrix using amorphous dispersions of glipizide

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Abstract

Spray dried dispersions (SDDs) of glipizide, a BCS Class II model drug, were prepared using various grades of hydroxypropyl methylcellulose acetate succinate (HPMCAS) and copovidone S-630 as carriers. The SDDs appeared as a single amorphous phase with up to 60% drug loading level as revealed by X-ray powder diffraction (XRPD), modulated differential scanning calorimetry (mDSC) and scanning electron microscopy (SEM). Supersaturated micro-dissolution testing of various SDDs in fasted state simulated intestinal fluid showed prolonged supersaturation state (up to 180 min) with solubility increases of 5.2–13.9 fold relative to crystalline drug under similar conditions. Solubility and stability characteristics of the most desirable SDDs in terms of relative dissolution AUCs (AUC<sub>SDD</sub>/AUC<sub>crystalline</sub>) and supersaturated concentration ratios (C<sub>50</sub>/C<sub>max</sub>) were determined. Results show that HPMCAS-based SDDs achieve a higher degree of supersaturation compared to Copovidone S-630 and that SDDs comprising HPMCAS-M and HPMCAS-H maintained stable supersaturated concentration. Dissolution data showed that SDD-loaded CR tablets provide stable supersaturated concentration within the hydrated matrix with increased rate and extent of drug dissolution over 24 h. Co-existence of HPMCAS and HPMC within the hydrating matrix showed strong suppression of drug crystallization and allowed achievement of zero-order and slow-first order release kinetics.

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1. Introduction

The main emphasis during the drug synthesis process is to ensure production of a well-defined solid form of the drug substance having high purity and degree of crystallinity, although many compounds may exist in different polymorphic forms, hydrates (solute), desolvated solvate or in an amorphous state. Each of these forms has different thermodynamic properties that will impact its melting points, solubility, stability, X-ray diffraction profiles as well as bioavailability and may undergo spontaneous changes during manufacturing, processing, and compression stage or even during storage. Most of crystalline compounds under development are classified as BCS class II (70%) and BCS class IV (20%), while 30% and 10% of marketed drugs are classified as BCS class II and IV respectively (Di et al., 2012; Williams et al., 2013). Among many solubilization methods documented amorphous systems have proven to enhance both solubilization and bioavailability of poorly soluble compounds due to their higher enthalpy, entropy and free energy relative to crystalline structures (Leuner and Dressman, 2000). The solubility advantage of amorphous systems versus their crystalline counter parts has been found to be between 10 and 1600 fold (Hancock and Parks, 2000). Multiple important drug products are marketed in amorphous forms for immediate release and absorption, including Accolate<sup>®</sup> (zafluralikast), Cefin<sup>®</sup> (cefuroxime axetil), Accupril<sup>®</sup> (quinapril HCl), and Virapect<sup>®</sup> (nelfinavir mesylate). However enhanced solubilization of poorly soluble compounds based on amorphous property of the drug-carrier for inclusion into a controlled release delivery system remains a challenge. Problems such as dissolution stability and potential precipitation from a supersaturated state to equilibrium solubility level within the delivery system itself as well as during prolonged dissolution, transit in the GI tract and exposure to GI milieu are of chief concerns during delivery system development and evaluation. Drug dissolved within the hydrated matrix can reach supersaturated state and in-situ precipitation to crystalline state results in suppression of solubility over prolonged release period.

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