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Enhanced Dissolution of a Porous Carrier-Containing Ternary Amorphous Solid Dispersion System Prepared by a Hot Melt Method

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Abstract

The focus of our study was to employ a solvent-free, thermal process to evaluate the use of a porous carrier in a drug-polymer-porous carrier ternary formulation containing a high drug load (e.g., ≥50% w/w). The purpose of the study was to improve the dissolution properties of the BCS Class II drug, indomethacin (IND), in the ternary formulation. The effect that the selected polymer has on properties of the formulation was studied, and the formulation characteristics of hypromellose (AF15), copovidone (VA64), and polyvinyl alcohol-polyethylene glycol graft copolymer (KIR) was evaluated in order to understand differences in dissolution rates and drug adsorption onto the porous carrier. The ternary formulations were manufactured using a thermal technique that relied on heating and mixing, without the necessity of mechanical shear. All thermally processed granules that employed the porous carrier exhibited immediate release compared to crystalline IND and physical mixtures. In addition, the ternary formulations maintained supersaturation compared to the binary formulations without polymer. The results of this study indicated that the thermally processed ternary formulations containing a porous carrier demonstrated a much improved dissolution profile in non-sink conditions.

Introduction

Solubility is an intrinsic property of each individual drug substance and ultimately affects the drug's intestinal absorption. The biopharmaceutical classification system (BCS) was developed to classify intestinal absorption based on the solubility, intestinal permeability, and dissolution rate of drugs [1]. BCS Class II and IV compounds (low solubility) represent a significant growing percentage of new chemical entities targeted for use in drug development. Thirty-three % of drugs listed in the US Pharmacopeia have poor water solubility, as does almost 40% of the top 200 orally administered drugs on the US drug market, 75% of the drug development candidates, and up to 90% of new chemical entities [2-4]. Due to the overwhelming number of drugs exhibiting solubility limitations, overcoming poor water solubility becomes a limiting factor to achieving enhanced absorption and bioavailability [2].

Because poor water solubility affects numerous compounds in development, many techniques have been developed and reported to enhance solubility. A few of these techniques utilized to enhance solubility include amorphous solid dispersions (ASDs) [5], self-emulsifying drug delivery systems (SEDDS) [6], cyclodextrins [7], nanocrystal technologies [5, 8], solid lipid nanoparticles [9], liposomes [10], and micelles [11]. In particular, ASDs can dramatically enhance the solubility and dissolution rate of BCS II and IV drugs by employing a "spring and parachute" effect [12]. The "spring and parachute" effect occurs as the ASD is placed in the