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Supersaturated controlled release matrix using amorphous dispersions of glipizide

Zheng Lu[a], Yonglai Yang[b], Rae-Ann Covington[b], Yunxia (Vivian) Bi[b], Thomas Dürig[b], Marc A. Ilies[a], Reza Fassihi[a,*]

[a] School of Pharmacy, Temple University, 3307 N. Broad Street, Philadelphia, PA 19140, USA
[b] Ashland Specialty Ingredients, 500 Hercules Road, Wilmington, DE 19808, USA

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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 ($AUC_{(SDD)}/AUC_{(crystalline)}$) and supersaturated concentration ratios (C_{180}/C_{max}) 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.

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 (solvate), 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® (zafirlukast), Ceftin® (cefuroxime axetil), Accupril® (quinapril HCl), and Viracept® (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.

* Corresponding author.
E-mail address: reza.fassihi@temple.edu (R. Fassihi).

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Amorphous systems can be produced in the presence of a polymeric carrier or suitable excipients by any one of the methods such as spray drying (Caron et al., 2011; Dontireddy and Crean, 2011; Haque and Roos, 2005; Ueno et al., 1998; Yonemochi et al., 1999), freeze drying (Dontireddy and Crean, 2011; Haque and Roos, 2005; Ihli et al., 2013; Imamura et al., 2008), melt extrusion (Lakshman et al., 2008), vapor condensation, casting, super-cooling of melt, milling (Caron et al., 2013; Caron et al., 2011; Gupta et al., 2003; Mallick et al., 2008), co-grinding, compaction of crystals and during manufacturing processes (Hancock and Zografi, 1997). The choice of polymer is a critical factor when developing amorphous solid dispersion. Various water-soluble polymers such as polyvinylpyrrolidone (PVP) and poly (vinyl-pyrrolidone-co-vinyl-acetate) (PVP-VA) (Martinez-Oharriz et al., 2002; Matsumoto and Zografi, 1999; Weuts et al., 2005), poly (ethylene glycol) (PEG) (Law et al., 2004; Verheyen et al., 2002) and hydroxypropyl methylcellulose (HPMC) (Kushida and Gotoda, 2013; Miyazaki et al., 2011) or enteric polymers such as hydroxypropyl methylcellulose phthalate (HPMCP) (Miyazaki et al., 2011) and hydroxypropyl methylcellulose acetate succinate (HPMCAS) (Friesen et al., 2008; Tanno et al., 2004) have demonstrated use in application of amorphous solid dispersions. HPMCAS is an enteric polymer with a Tg around 120 °C and solubility above pH 5. The amphiphilic nature of HPMCAS allows it to interact with water-insoluble drug through its hydrophobic regions whereas its hydrophilic groups can interact with aqueous environments and form stable colloidal species maintaining the supersaturated state. When HPMCAS is ionized (pH > 5), the negative charges on its succinate groups can minimize the formation of large polymer aggregates through electrostatic repulsion and stabilize drug-polymer colloids (Friesen et al., 2008). HPMCAS can provide different solubility and dissolution profiles as the ratio of succinoyl and acetyl substitutions changes. These unique properties of HPMCAS relative to many other polymers make it an ideal candidate for solid dispersion preparation. Its ability to dissolve in a wide range of organic solvents also contributes to its processability and feasibility when using spray-drying technique. Copovidone S-630 (copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a ratio of 3:2 by mass) is another polymeric candidate that can be used in spray-dried dispersion. The combination of vinyl pyrrolidone and vinyl acetate monomers in a single polymer chain makes copovidone possessing both hydrophilic and hydrophobic properties. This amphiphilic nature makes it a highly effective polymeric carrier with stabilizing potential for solid dispersion application.

Hence, the aim of this study was to develop spray-dried amorphous dispersion (SDD)-loaded controlled release matrix tablets using automated spray dryer and compaction simulator with optimized process parameters. Two types of SDD carriers, namely HPMCAS and Copovidone, were used in order to enhance both solubility and dissolution rate of poorly water-soluble compounds while maintaining the stability of the supersaturated state after dissolution. The unique features of the hydrating CR matrix system consisting of amorphous drug dispersion and potential precipitation inhibition mechanisms are investigated. The drug glipizide a weak acid which tends to have limited solubility and dissolution rate (pKa = 5.9) was chosen as a poorly soluble model compound representing Class-II drug according to the FDA adopted Biopharmaceutics Classification Scheme (CDER, 2015).

2. Materials and methods

2.1. Materials

Glipizide was purchased from RIA International LLC (East Hanover, NJ). HPMCAS (AquaSolve™, H, M and L grades), Copovidone (Plasdone™ S-630) and hydroxypropyl methylcellulose (Benecel™, HPMC K100M, K15M and K4M) from Ashland Specialty Ingredient (Wilmington, DE) were used in this study. Anhydrous lactose (Kerry Bio-science, Norwich NY), microcrystalline cellulose (Avicel® PH 102, FMC BioPolymer, Newark DE) and magnesium stearate were used for matrix tablet preparation. The properties of polymers used for preparation of spray-dried dispersion are summarized in Table 1.

2.2. Preparation of spray-dried dispersions (SDDs)

Solid dispersions of glipizide were prepared by spray drying method. 20%, 40% and 60% (w/w) drug loads were used to represent low, medium and high drug content solid dispersions. Briefly, glipizide powder and polymers (HPMCAS-H, M and L or Copovidone S-630) with defined ratios were dissolved in the mixture of dichloromethane: methanol (DCM:MeOH, 2:1 w/w) at total solid content of 3.75% (w/w). The solutions were spray-dried using GEA Niro A/S spray dryer (SD Micro™, Denmark) equipped with a 1.0 mm two-fluid nozzle and operated in an open cycle configuration under pre-determined process conditions. The inlet and outlet temperature of drying chamber were controlled within 90–96 °C and 55–60 °C, respectively. The feed solution was pumped at a rate of 16–18 g/min with atomizing gas flow rate of 1.5–1.7 kg/h. The overall process gas flow rate was maintained at 25.4–-25.6 kg/h. The resultant solid dispersions were dried in the vacuum for 16 h (40 °C). SDD compositions were expressed in terms of the weight percentage (wt%) of drug in the spray-dried dispersion. For example, 20% glipizide:HPMCAS-H SDD consists of 1 part (by weight) glipizide and 4 parts (by weight) HPMCAS-H polymer.

Table 1
Properties of polymers used for solid dispersion preparation.

	HPMCAS-H	HPMCAS-M	HPMCAS-L	Copovidone S-630
Appearance	White to off-white powder (F type) or granules (G type)			White powder
Weight average molecular weight (g/mol)	75,100	103,200	114,700	47,000
Average particle size (microns)	≤10 (F type)	≤10 (F type)	≤10 (F type)	65–75
Viscosity	2.4–3.6[a]	2.4–3.6[a]	2.4–3.6[a]	25.0–31.0[b]
Glass transition temperature, Tg (°C)	122	120	119	109
Acetyl content	10–14%	7–11%	5–9%	
Succinoyl content	4–8%	10–14%	14–18%	

[a] NF/EP/JP viscosity method, measured for a 2% solution at 20 °C, unit: mPa s.
[b] K-value viscosity, calculated from the kinematic viscosity of a 1% aqueous solution.