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Development of amorphous solid dispersion formulations of a poorly water-soluble drug, MK-0364

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ABSTRACT

The goal of this study was to demonstrate that MK-0364 solid dispersions can be developed as a means to increase the solubility and bioavailability of a poorly water-soluble drug, MK-0364. The potential solid dispersions would enable an oral solid dosage form as a monotherapy or combination product of MK-0364. Preliminary screening included sample preparation *via* a solvent casting method, physical characterization, and *in vitro* dissolution testing. Lead formulations were subsequently manufactured using hot melt extrusion (HME) and spray-drying (SD). All HME (without polyvinyl pyrrolidone) and SD formulations exhibit characteristics of a single phase glass including an amorphous halo when analyzed with X-ray powder diffraction (XRPD), a single glass transition temperature (T_g) measured with differential scanning calorimetry (DSC), and supersaturation when dissolved in dissolution media. The oral absorption of MK-0364 from selected HME and SD formulations in monkeys results in marginally greater exposure with a consistently longer T_{max} relative to a liquid filled capsule reference. Based on the processability, physical characterization, *in vitro* dissolution, and animal pharmacokinetic results, copovidone- and hydroxypropyl methylcellulose acetate succinate (HPMCAS)-based solid dispersion formulations are viable product concepts. The physical stability of both the solid dispersion formulations was also evaluated for 54 weeks under different conditions. The copovidone-based solid dispersion requires protection from moisture.

1. Introduction

Drugs with poor aqueous solubility have low or erratic absorption and, consequently, poor and variable bioavailability. Several common formulation approaches to increase the drug solubility/bioavailability include the use of cosolvents, surfactants, cyclodextrins (Loftsson and Brewster, 1996; Rajewski and Stella, 1996; Stella and Rajewski, 1997), salt formation, pH adjustment, particle size reduction, or lipid-based formulations. Solid dispersions or, more specifically, solid solutions of drugs in polymers as alternatives can be produced using cost effective manufacturing technologies adapted from other industries (*e.g.*, extrusion and spray drying), enable solid products directly suitable for fixed dose combinations, and do not require prohibitively expensive excipients (*e.g.*, hydroxypropyl-beta-cyclodextrin).

Solid dispersions have been used for dissolution or bioavailability enhancement since the 1960s. Solid dispersions are defined as the solid state dispersions of one or more compounds in an inert matrix (Chiou and Riegelman, 1971). Early solid dispersions using low molecular weight matrices such as urea and succinic acid increased the dissolution and absorption of sulfathiazole (Goldberg et al., 1965; Sekiguchi and Obi, 1961), chloramphenicol (Goldberg et al., 1965), griseofulvin (Chiou and Niazi, 1976; Goldberg et al., 1966b), and acetaminophen (Goldberg et al., 1966a). More recent solid dispersions using high molecular weight matrices such as polyethylene glycols, cellulose derivatives, acrylics (polyacrylates, polymethacrylates), and polyvinyl-based polymers not only enhanced the dissolution and bioavailability but also provided good physical stability of several compounds (Al-Obaidi and Buckton, 2009; Andrews et al., 2009, 2010; Curatolo et al., 2009; Dong et al., 2008; Friesen et al., 2008; Kennedy et al., 2008; Konno et al., 2008; Leuner and Dressman, 2000; Serajuddin, 1999).

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Table 1
Summary of MK-0364 SC formulations.

Component	SC 1 (%)	SC 2 (%)	SC 3 (%)	SC 4 (%)	SC 5 (%)	SC 6 (%)	SC 7 (%)	SC 8 (%)	SC 9 (%)	SC 10 (%)
MK-0364	10	10	10	10	10	10	10	10	10	10
Polysorbate 80	NA	NA	NA	NA	3	NA	NA	NA	NA	NA
Sorbitan monooleate	NA	NA	NA	NA	3	NA	NA	NA	NA	NA
Vit E TPGS	NA	NA	NA	NA	NA	10	NA	NA	NA	NA
Poloxamer 407	NA	NA	NA	NA	NA	NA	10	15	NA	NA
Polyoxyl 35 castor oil	NA	NA	NA	NA	NA	NA	NA	NA	6	NA
Sodium lauryl sulfate	NA	NA	NA	NA	NA	NA	NA	NA	NA	10
Eudragit® L100-55	90	NA	NA	NA	NA	NA	NA	NA	NA	NA
HPMCP HP-55	NA	90	NA	NA	NA	NA	NA	NA	NA	NA
HPMCAS-LF	NA	NA	90	NA	NA	NA	NA	NA	NA	NA
Copovidone	NA	NA	NA	90	84	80	80	75	84	80

Additionally, solid dispersions are suitable for the production of a wide variety of solid oral dosage forms. For example, the melted drug/matrix can be extruded and shaped as films, sticks, granules, pellets, powders, or individual unit dosage forms (*e.g.*, injected molds). Alternatively, solid dispersions can be used as intermediates to be further processed into conventional tablets as immediate or modified release formulations. Several commercially available products are based on solid dispersions such as Gris-PEG® (griseofulvin/PEG), Certican® (everolimus/HPMC), Isoptin-SRE® (verapamil/HPC/HPMC), ProGraf® (tacrolimus/HPMC), Cesamet® (nabilone/PVP), and Kaletra® (lopinavir/ritonavir/copovidone).

The research described here involves the development of amorphous solid dispersion formulations of a poorly water-soluble drug, MK-0364, to increase its solubility and bioavailability. The potential solid dispersions would enable an oral solid dosage form as a monotherapy or combination product of MK-0364. The evaluation of this system included initial preparation *via* solvent casting, physical characterization, and *in vitro* dissolution testing prior to identifying lead formulations for further development *via* hot melt extrusion (HME) and spray-drying (SD). During HME and SD formulation development, physical characterization, *in vitro* dissolution testing, and *in vivo* evaluation were conducted to select the best candidates for subsequent physical stability studies.

2. Materials and methods

2.1. Materials

All chemicals were analytical grade or ACS reagents. MK-0364 was obtained from Merck & Co., Inc. Polysorbate 80 (Tween 80™, Croda, Inc., Edison, NJ), sorbitan monooleate (Span 80®, Uniqema, New Castle, DE), polyvinyl pyrrolidone (PVP or Plasdone® K-29/32, ISP Corporation, Wayne, NJ), methacrylic acid copolymer (Eudragit® L100-55, Evonik Degussa Corporation, Piscataway, NJ), caprylic/capric glycerides (Imwitor® 742, Sasol North America, Inc., Westwood, NJ), acetone, methanol, hydrochloric acid, and water were used as received. D-α-Tocopheryl polyethylene glycol 1000 succinate (vitamin E TPGS) and butylated hydroxylanisole (BHA) were purchased from Eastman Chemical Company (Kingsport, TN). Hydroxypropyl methylcellulose (HPMC, Pharmacoat grade 606), hydroxypropyl methylcellulose phthalate (HPMCP HP-55) and hydroxypropyl methylcellulose acetate succinate (HPMCAS-LF) were purchased from Shin-Etsu Chemical Co., Ltd., Japan. Copovidone (Kollidon® VA 64), poloxamer 407 (Lutrol® F 127), polyoxyl 35 castor oil (Cremophor® EL), and sodium lauryl sulfate (Texapon® K 12 P PH) were purchased from BASF Corporation (Florham Park, NJ).

2.2. Preparation of solvent cast (SC) formulations

The SC formulations (Table 1) were prepared by dissolving 2 g of solids in 15 mL of a suitable organic solvent according to the solubility. The solutions were spread into a thin layer in a foil-protected aluminum or stainless steel pan for drying in a vacuum oven. Samples were dried for approximately 30 min at 110 °C/>30 in Hg, transferred from pans to glass vials, and dried for an additional 16 h at 40 °C/ambient.

2.3. Preparation of hot melt extrusion (HME) formulations

Prior to the HME process, all components listed in Table 2 were pre-blended in a Bohle high shear granulator (model BMG, L.B. Bohle, Germany). Polysorbate 80 and sorbitan monooleate were first mixed to obtain a homogeneous solution, whereas vitamin E TPGS was melted in a water bath set at 40–45 °C. Copovidone and MK-0364 were blended in the high shear granulator for 3–5 min with an impeller speed of 300–500 rpm. The surfactants were then added to the granulator over a period of 3–8 min using 300–500 rpm impeller and 1000 rpm chopper speeds, followed by a 2–5 min additional mixing. The wet granulated sample was introduced into a Thermo Scientific 16 mm 25:1 L/D corotating twin-screw extruder (Thermo Fisher Scientific, Inc., Waltham, MA) set at 130–160 °C using a Brabender Technologie single-screw FlexWall® feeder (20% drive command in volumetric mode). The twin-screw extruder screw designs are illustrated in Fig. 1. The resulting extrudate was ambiently cooled and ground in a mortar with a pestle for physical characterization.

2.4. Preparation of spray-drying (SD) formulations

The SD formulations listed in Table 3 were prepared using a Niro SD-Micro™ spray dryer (GEA Processing Engineer, Inc., Columbia,

Table 2
Summary of MK-0364 HME formulations.

Component	Function	HME 1 (%)	HME 2 (%)	HME 3 (%)	HME 4 (%)	HME 5 (%)
MK-0364	Active	10	10	10	10	10
Polysorbate 80	Surfactant	1.5	NA	1.5	1.5	1.5
Sorbitan monooleate	Surfactant	1.5	NA	1.5	1.5	1.5
Vit E TPGS	Surfactant	NA	5	NA	NA	NA
BHA	Antioxidant	NA	NA	0.83	NA	NA
PVP	Polymer	NA	NA	NA	10	20
Copovidone	Polymer	87	85	86.17	77	67