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Evaluation of Three Amorphous Drug Delivery Technologies to Improve the Oral Absorption of Flubendazole

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ABSTRACT

This study investigates 3 amorphous technologies to improve the dissolution rate and oral bioavailability of flubendazole (FLU). The selected approaches are (1) a standard spray-dried dispersion with hydroxypropylmethylcellulose (HPMC) E5 or polyvinylpyrrolidone-vinyl acetate 64, both with Vitamin E d-α-tocopheryl polyethylene glycol succinate; (2) a modified process spray-dried dispersion (MPSDD) with either HPMC E3 or hydroxypropylmethylcellulose acetate succinate (HPMCAS-M); and (3) confining FLU in ordered mesoporous silica (OMS). The physicochemical stability and *in vitro* release of optimized formulations were evaluated following 2 weeks of open conditions at 25°C/60% relative humidity (RH) and 40°C/75% RH. All formulations remained amorphous at 25°C/60% RH. Only the MPSDD formulation containing HPMCAS-M and 3/7 (wt./wt.) FLU/OMS did not crystallize following 40°C/75% RH exposure. The OMS and MPSDD formulations contained the lowest and highest amount of hydrolyzed degradant, respectively. All formulations were dosed to rats at 20 mg/kg in suspension. One FLU/OMS formulation was also dosed as a capsule blend. Plasma concentration profiles were determined following a single dose. *In vivo* findings show that the OMS capsule and suspension resulted in the overall highest area under the curve and C_{max} values, respectively. These results cross-evaluate various amorphous formulations and provide a link to enhanced biopharmaceutical performance.

Introduction

Studies indicate that drug candidates are becoming increasingly difficult to formulate as a function of 3 confluent trends: (1) the use of high throughput screening to identify drug leads; (2) the nature of drug candidate isolation from chemical processes, which biases systems to complex forms; and (3) the nature of contemporary drug targets, which often diverge from the chemical space that is known to provide useful oral bioavailabilities.[1,2] Although conventional formulation strategies are initially sought based on their lower developmental risk and cost, often these approaches do not provide for adequate exposure in preclinical and clinical assessments. There is a strong industrial sensitivity toward aggregating the risk of new drug delivery systems. Therefore, the aim of this

Abbreviations used: ACN, acetonitrile; API, active pharmaceutical ingredient; AUC, area under the curve; C_{max}, maximum drug concentration; DCM, dichloromethane; FA, formic acid; FeSSIF, fed state simulated intestinal fluid; HPMC, hydroxypropylmethylcellulose; HPMCAS, hydroxypropylmethylcellulose acetate succinate; MPSDD, modified process spray-dried dispersion; NH_4Ac, ammonium acetate; OMS, ordered mesoporous silica; P_{app}, apparent permeability coefficient; PK, pharmacokinetic; PVP VA, polyvinylpyrrolidone-vinyl acetate; RH, relative humidity; RS, reference solution; SDD, spray-dried dispersion; SSDD, standard spray-dried dispersion; T_g, glass transition temperature; T_m, melting temperature; TPGS, tocopheryl polyethylene glycol succinate.

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study was to evaluate the biopharmaceutical performance of 2 emerging drug delivery technologies with a more conventional approach as a performance-based drug development risk assessment with flubendazole (FLU) as the model compound.

FLU belongs to the group of benzimidazole carbamates and was first marketed as Fluvermal® by Janssen Pharmaceutica in the mid-1970s as an anthelminthic agent against gastrointestinal parasites. In an early 1980s study in Mexico, FLU demonstrated superior activity compared with diethylcarbamazine against the filarial parasite, *Onchocerca volvulus*, after 12 months of follow-up.[3] Although this study had some limitations (i.e., the total exposure from 5 weekly injections was not assessed), the activity of FLU was supported by the absence of recurrent dermal microfilaria, a surrogate marker for living worms capable of reproduction. It was recently estimated that 26 and 129 million people (mainly in sub-Saharan Africa) are infected with the filarial diseases onchocerciasis and lymphatic filariasis, respectively.[4,5]

As Fluvermal was originally designed to treat gastrointestinal parasites, systemic uptake was not required. Also, it is well known that orally administered methylcarbamate benzimidazole results in poor systemic exposure in most species.[6] Therefore, the first step was to re-formulate FLU to improve the dissolution rate, solubility, and therefore the systemic exposure, which is necessary to target the filarial larvae and adult worm. Here, we evaluate 3 amorphous drug delivery technologies to achieve this.

Solid dispersions were first defined in 1971 as one or more active ingredients in an inert carrier or matrix in the solid state.[7] Due to advances in manufacturing process technologies, solid dispersions are now routinely produced by spray drying as a means to enhance the dissolution rate and solubility of poorly soluble compounds.[8] Here, the resulting active pharmaceutical ingredient (API) is molecularly dispersed within the polymeric carrier matrix.[8-10] Following exposure to aqueous media, the API is released in its supersaturated state as individual molecules and/or fine colloidal particles and the polymeric carrier impedes precipitation, leading to its enhanced performance.[9,11,12] Examples of marketed solid dispersions include Sporanox® and Kaletra®.

One limitation of this technique is that both the API and polymer must be soluble in the liquid phase. Because this solvent must easily evaporate for particle formulation to occur, a low vapor pressure is also necessary. For compounds with low solubility in solvent systems that meet the previously mentioned criteria, or to avoid non-compendial solvents, heat can be used to increase the solubility. The level of heat that is required for total solubilization depends on many factors. For compounds with solubility limitations similar to FLU, an in-line heat exchanger can be used to heat the sample above the boiling point of the solvent. The in-line heat exchanger technology was chosen based on the very limited exposure (<30 s) that is required to completely dissolve the API. Using heat to increase solubility in volatile organic solvents has associated risks. Particle size and morphology of the ingoing API can have an effect on the dissolution kinetics during heating and can require longer residence times in the heat exchanger. Chemical stability during heating is also a consideration. However, due to the limited time the spray solution is exposed to the elevated temperature, thermal chemical degradation is typically not observed. Once the API has been dissolved in the heat exchanger, a specialized atomizer (termed a flash nozzle) is used. This nozzle is unique to the heating process based on atomization taking place by flash boiling of the solvent.[13,14]

Adsorption onto ordered mesoporous silica (OMS) is another example of a new enabling technology that improves the performance of poorly soluble compounds by improving their dissolution rate and solubility and thereby enhancing oral bioavailability.[15-17] It is increasingly attracting the attention of industrial scientists due to several factors such as its burgeoned interest in the academic world.[18,19] Their cylindrical and uniform-sized pore structure serves as the key attribute to improve the dissolution rate of poorly soluble compounds. A concentrated drug solution is loaded into the pores through capillary forces. The dissolved API is added in cycles to allow solvent evaporation, leading to a confined amorphous API.[20] When the mesopore size is only a few times larger than the drug molecule, the confined API is unable to crystallize, thus exhibiting a higher free energy and consequently higher solubility when compared to its crystalline counterpart.[21,22]

Formulations from each drug delivery technology were screened using a variety of solid-state characterization tools and *in vitro* dissolution experiments in biorelevant media. The physical and chemical stability of the formulations following 2 weeks of open storage at 25°C/60% RH and 40°C/75% RH was also assessed. Finally, the 2 lead formulations from each amorphous technology were selected to evaluate systemic exposure in rats. The results from this study provide further insight into industrial formulation considerations of these emerging technologies while linking them to their *in vivo* performance.

Materials and Methods

Powder Manufacturing

Standard Spray-Dried Dispersions

The feedstock solution was prepared by dissolving either a 1/9/0.5 or 1/3/0.15 weight ratio of FLU (Shaanxi Hanjiang Pharmaceutical Group, Hanzhong City, China)/polymer/Vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS; Barentz NV, Zaventem, Belgium) in 1/9 (wt./wt.) 98%-100% formic acid (FA; Merck, Overijse, Belgium)/dichloromethane (DCM; Merck). The selected polymers were either hydroxypropylmethylcellulose (HPMC E5; Dow Chemical, Terneuzen, The Netherlands) or polyvinylpyrrolidone-vinyl acetate 64 (PVP VA 64; Kollidon®64, BASF, Ludwigshaven, Germany). A Büchi 290 (Flawil, Switzerland) equipped with an inert loop was used to spray dry in closed loop conditions with an inlet and outlet temperature of 65°C and 45°C, respectively, and a spray rate of 8 g/min under nitrogen flow. The damp powder was removed from the collector and dried ≤20 h in a vacuum oven (Heraeus, Liederkerke, Belgium) set to 45°C and 200 mbar under nitrogen flow. To investigate the influence of drying time, the 1/3/0.15, FLU/HPMC E5/Vit. E TPGS was also dried for 5 days under the same conditions.

Modified Process Spray-Dried Dispersions

The stock suspension was prepared by suspending FLU and polymer in the appropriate solvent systems at the various ratios of FLU/polymer. Formulations containing hydroxypropylmethylcellulose acetate succinate-M (HPMCAS-M; Shin-Etsu, Tokyo, Japan) were suspended in 9:1 acetone:water (Honeywell Burdick & Jackson, Muskegon, MI) and formulations containing HPMC E3 (Dow Chemical, Midland, MI) were suspended in 9:1 methanol:water (Honeywell Burdick & Jackson). The approach for ensuring complete dissolution of the API in this spray-drying process is 2-fold. First, the solubility for the given solvent system and temperature is previously determined prior to the modified spray-drying process. To ensure dissolution, a process temperature that is slightly higher than the temperature at which the solubility was observed is selected. Second, the lack of crystalline material present in the final dispersion is evidence that complete dissolution of the API was achieved in the heat exchanger. The material was prepared by spray drying using a modified spray dryer similar in scale to a ProCepT (Zalzate, Belgium). The spray-drying equipment was