An Extrusion Spheronization Approach to Enable a High Drug Load Formulation of a Poorly Soluble Drug with a Low Melting Surfactant

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ABSTRACT: Vitamin E tocopherol polyethylene glycol succinate (TPGS) is a non-ionic surface active agent, known to enhance the bioavailability of lipophilic compounds via wettability, solubility, and in some cases permeability enhancement. MK-0536 is an anti-retroviral drug with poor wettability and solubility and a high dose. Based on pharmacokinetic studies in dogs and humans, use of vitamin E TPGS in oral solid formulations of MK-0536 provides desired PK characteristics. The use of vitamin E TPGS, however, in solid dosage forms is limited because of the processing challenges resulting from its waxy nature and low melting temperature (~37°C). The current study, for the first time, demonstrates the use of an alternative low pressure extrusion and spheronization approach to enable high loadings of the poorly soluble, poorly compactable drug and relatively high levels of vitamin E TPGS. This approach not only aided in mitigating processing challenges arising from most high energy process steps such as milling, compression, and coating, but also enabled a higher drug load formulation that provided superior bioperformance relative to a conventional high shear wet granulated formulation. An encapsulated dosage form consisting of pellets prepared by extrusion spheronization with 75% (w/w) MK-0536 and 10% (w/w) vitamin E TPGS was developed. J Pharm Sci 104:3752–3759, 2015
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INTRODUCTION

A majority of the drug candidates in discovery possess poor aqueous solubility and hence present bioperformance challenges.[1] Among the various approaches to improve solubilization, use of surfactants to improve wettability and solubility is well studied.[2] Vitamin E d-alpha tocopherol polyethylene glycol succinate (vitamin E TPGS) is a nonionic surfactant that has been widely reported to enhance bioperformance of poorly soluble compounds by increasing solubility and permeability.[3–8] In a clinical study involving pediatric liver transplant patients, Sokol et al.[8] demonstrated a 40%–72% reduction in the cyclosporine dosage, as a result of vitamin E TPGS co-administration. The enhancement in cyclosporine bioavailability was explained based on micelle formation and p-glycoprotein (P-gp) inhibition. Yu et al.[7] demonstrated that vitamin E TPGS enhances the absorption flux of amprenavir by increasing its solubility and permeability. Other studies have reported that TPGS enhanced the bioavailability of paclitaxel as a result of solubility and permeability enhancement.[4,5] In the current study, plasma exposures for the poorly wetting, poorly soluble compound, MK-0536 were roughly tripled in beagle dogs with the use of vitamin E TPGS relative to a simple drug in capsule formulation.

Despite these reports on the utility of vitamin E TPGS in solubility and permeability enhancement, formulation/drug delivery approaches with vitamin E TPGS have been mainly confined to solid dispersions,[9,10] emulsions and nanodelivery systems.[11–15] Reports describing conventional oral solid formulations of lipophilic compounds containing significant amounts of vitamin E TPGS are very limited.

Because of the waxy nature and low melting temperature (~37°C) of vitamin E TPGS, use of this surfactant in significant quantities in solid oral dosage forms is quite challenging. Danjo et al.[16] have reported tableting challenges, especially tablet sticking to lower punch well below the melting point of a low melting excipient, butyl p-hydroxybenzoate. Potential localized melting of vitamin E TPGS during other energy intensive processes, apart from compression, such as granulation milling and tablet coating also pose a significant challenge. Furthermore, the waxy nature of TPGS can compromise the mechanical strength of the tablets. For the first time, a relatively recent report described systematic evaluation of monolithic and bilayer tabletability of wet granulation based tablet formulations of a drug candidate containing up to 40% (w/w) drug load and 10% (w/w) vitamin E TPGS.[17] A more recent study[18] describes the processing challenges with tableting TPGS formulations and demonstrated the applicability of Aeropril® 300 in boosting tensile strength of placebo tablet formulations containing 10% (w/w) vitamin E TPGS. Li and coworkers used up to 8% (w/w) TPGS levels in a low drug loading (DL) formulation containing less than 7% (w/w) of a lipophilic API.[19]

The current study is a first of its kind in that it describes the use of relatively high levels of vitamin E TPGS (10%, w/w) for bioperformance enhancement of a poorly wetting, poorly soluble and poorly compactable drug candidate (MK-0536) at a high DL of 75% (w/w) in an oral solid dosage form, while addressing formulation challenges. An extrusion spheronization approach has been proposed as a unique approach that circumvents the aforementioned processing challenges while accommodating very high loading of the lipophilic active moiety, MK-0536 and relatively high levels of vitamin E TPGS.

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MATERIALS AND METHODS

Materials

Vitamin E TPGS was obtained from Eastman Chemical Company (Kingsport, Tennessee). Microcrystalline cellulose (Avicel PH101) and Croscarmellose sodium (CCNa) were obtained from FMC Biopolymer (Newark, DE). Lactose monohydrate-312 from Foremost Farms (Baraboo, WI), hydroxypropyl cellulose (HPC) – Klucel EXF from Hercules Inc. (Wilmington, DE) and sodium stearyl fumarate from Spectrum Inc. (New Brunswick, NJ) were other excipients used.

Active compound, MK-0536, is an internal Merck compound. MK-0536 is a BCS class II weak acid with a p*K*a of 8.62 and clog *P* of 1.32. Solubility of MK-0536 is ~0.12 mg/mL across the physiological pH range. The compound was classified as highly permeable based on the results of a prior *in situ* rat intestinal perfusion study (P_{eff} 3.7×10^{-5} cm/s for both MK-0536 and high permeability marker metoprolol).

Methods

High Shear Wet Granulation

The early clinical formulation at 25% (w/w) DL containing 10% (w/w) TPGS, similar to that used in first in human (FIH) studies, was prepared by conventional high shear wet granulation (HSWG) and encapsulation. The composition details are provided in Table 1. A Diosna P1–6 high shear granulator was fitted with a 2 L bowl (200 g batch size) and the intragranular components (all components except vitamin E TPGS and sodium stearyl fumarate) of the formulation were dry mixed for 3 min and a 20% (w/w) aqueous solution of vitamin E TPGS, used as granulating fluid, was atomized onto the powder bed at 40 g/min and the impeller and chopper were operated at 300 and 1500 rpm, respectively. The granulation run averaged 2.5 min and no wet massing was used. For granule encapsulation, the granulation was tray dried in the oven at 30°C for 16 h and the dried granules were manually screened through an 850 μm sieve and manually encapsulated into hard gelatin capsules. For a true head to head comparison, a benchmark HSWG formulation with the highest achievable drug load of 61.5% (w/w) (compositionally similar to the 25%, w/w DL formulation except the higher amount of API replacing the diluent) was also prepared as per the above procedure to compare against the 75% (w/w) DL extrusion spheronization formulation. This high drug load HSWG formulation was also attempted to be encapsulated, although unsuccessfully, on a Bonapace InCap automatic encapsulation equipment (dosing disk type) into size 0 capsules.

Table 1. Formulation Composition for a 25% (w/w) Drug Load Wet Granulation Formulation with Increasing Levels of Vitamin E TPGS at 2%, 5%, and 10% (w/w)

Composition	% (w/w)		
MK-0536	25	25	25
Vitamin E TPGS	2	5	10
Lactose monohydrate	25	25	25
Microcrystalline cellulose (Avicel PH101)	40	37	32
Hydroxypropyl cellulose	3	3	3
Croscarmellose sodium	3	3	3
Sodium stearyl fumarate	2	2	2
Total	100	100	100

Extrusion Spheronization

The extrusion and the spheronization processes were run on a Fuji Paudal low pressure extruder MG-55, and a QJ230T marumerizer. The extrusion process involved axial extrusion with a dome die having a pore size and die thickness of 1.0 mm each. The extruder was operated at 50 rpm. The extrusion–spheronization experiments were conducted at controlled room temperature of 21°C. Prior to extrusion spheronization, the components were high shear wet granulated with a 20% (w/w) aqueous TPGS solution (as in section *High Shear Wet Granulation*) and the wet granulated mass was transferred directly from the high shear granulator into the hopper of the MG-55. The extrudates that were generated were gently transferred into the QJ230T bowl operating at 1200 rpm. A small amount of microcrystalline cellulose (~0.5%, w/w of the batch) was sprinkled during spheronization (through the lid port) to prevent agglomeration. Upon 90–120 s of spheronization, the spherical beads are unloaded and tray dried in a convection oven at 30°C for 16 h. The extrusion spheronization beads were characterized for size and roundness by optical microscopy in conjunction with Image Pro Plus® image analysis software.

X-Ray Diffraction for Crystallinity Evaluation

X-ray powder diffraction (XRPD) was performed to verify crystallinity of the API, post extrusion spheronization and to ensure that significant amount of amorphous API was not generated as a result of solubilization in vitamin E TPGS. XRPD was performed in the transmission mode with a Philips X'Pert X-ray diffractometer, which was equipped with a Cu Kα source (λ = 1.54056 Å) operating at a tube load of 40 kV and 40 mA. Each sample was scanned between 2° and 40° (2θ) with a step size of 0.02° and a scan rate of 2 s/step.

Pharmacokinetic Evaluation in Beagle Dogs

Fasted male Beagle dogs (Marshall Farms) weighing approximately 10 kg were used for the studies described herein. All animals were housed in an AAALAC-accredited facility in accordance with the USDA guidelines. The Guide and Animal Welfare regulations were followed in the conduct of the animal studies. Veterinary care was given to any animals requiring medical attention. Studies were conducted under a protocol approved by the Merck IACUC. Three to six dogs were dosed with each formulation (detailed number of animals provided in respective tables/figures). After an overnight fast, each dog was given a MK-0536 test formulation (at 10 mg/kg, each capsule was filled based on corresponding animal body weight the day before the study), immediately followed by 3.5 mL/kg of water. The 10 mg/kg dose was selected based on the high end of the projected Phase I clinical dose range for MK-0536 (on a mg/kg basis). Because of the flat pH solubility profile of the compound across the physiological pH range, no pretreatment (e.g., pentagastrin) to control stomach pH of the dogs, was employed for the studies. Food was returned at 4 h after dosing. Blood was drawn from a catheter placed into the cephalic vein at predose and at predetermined time intervals post dose and plasma was separated by centrifugation. For analysis, the plasma samples were extracted using protein precipitation. Plasma extracts were injected onto a Waters Atlantis dC18, 2.1 × 50 mm^2, 5 μm HPLC