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Dry Blending Process Scale-up for a Very Low Dose Drug Candidate

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INTRODUCTION

DMP 543 is a pharmacologically potent compound intended for the potential treatment of Alzheimer's disease. DMP 543, 10,10-bis(2-fluoro-4-pyridinylmethyl)-9(10H)-anthracenone, is poorly water soluble (2.6 μg/mL at ~22° C) and is soluble in methanol and ethanol. DMP 543 contains no ionizable moiety in the pH range of 2-9.2 and exhibits a melting peak at 171° C by differential scanning calorimetric analysis. The drug is unstable in acidic solution. An extremely low strength (0.025-mg capsule with 0.02% drug load in the formulation) was used in clinical studies. Because of the low dose, content uniformity is a major concern in the process development. Proper blending and prevention of segregation, especially when wet granulation is not feasible and powder is cohesive, are required for a successful processing. Particle size distribution, particle shape, surface charge, and cohesiveness of materials have an impact on the mobility of particles and surface adherence to a carrier excipient. The use of a carrier that forms a structured powder with the micronized drug substance adhering on the carrier's surface is critical for a successful formulation and process for a low-dose drug [1]. Electrostatic attraction occurs with particles having a diameter no larger than 2 μm, and Van der Waal forces play a role between particles with a diameter less than 50 μm [2,3]. In addition to the drug substance, the current formulation includes lactose monohydrate (a diluent), sodium starch glycolate (a disintegrant), and magnesium stearate (a lubricant).

Because of stability reasons, a wet granulation process for this potent compound was not an option unless stabilizing agents were added. Therefore, a dry blending process was pursued. In this report, the optimized scaled-up blending process and product evaluation results are presented.

KEYWORDS Dry Blending Process, Low Strength, Process Scale-up, Carrier

EXPERIMENTAL

MATERIALS

Micronized DMP 543 drug substance was manufactured by DuPont Pharmaceuticals at the Deep Water facility in New Jersey. The excipients included lactose monohydrate (Spray Dried 316, Foremost Farms USA, Rothschild, WI), sodium starch glycolate (Explotab® , Penwest Pharmaceuticals, Patterson, NY), magnesium stearate (Mallinckrodt, Cheaterfield, MO), and white opaque #2 and #3 capsules (Capsugel, Greenwood, SC). Milli-Q water (Millipore Corp, Milford, MA) was used for preparing the dissolution medium and the high-performance liquid chromatography (HPLC) mobile phase. HPLC-grade acetonitrile, reagent-grade phosphoric acid 85%, and reagent-grade sodium phosphate, monobasic, monohydrate (all from EM, Gibbstown, NJ) were used in the preparation of the mobile phase for HPLC analysis. Whatman 0.45 μm PVDF (Hydrophilic Polyvinylidine Fluoride membrane) filters (Whatman Science, Ann Arbor, MI) were used for sample filtration.

EQUIPMENT

The following tools and equipment were used during the developmental stage: glass mortar and pestle, Patterson-Kelly Blend Master 8-qt V-Blender, Patterson-Kelly 1-cu-ft and 2-cu-ft V-Blenders (Patterson-Kelley, East Stroudsburg, PA), Gallay Blender 113L (Gallay Containers & Systems LTD, Birmingham, UK), Turbula Shaker/Mixer Model T2C

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(Willy A. Bachofen AG, Maschinenfabrik, Germany), Zanasi ZA5 Capsule Filler (Nuova Zanasi IMA Group, Ozzano Emilia, Italy), Bosch 400 Ccapsule Filler (Bosch, Waiblingen, Germany), Se-Jong SF-30 Capsule Filler (Se-Jong Machinaery Co LTD, Kyoungki-Do, Korea), and JEOL JSM 840 Scanning Electron Microscope (Japanese Electron Optics Laboratories, Tokyo, Japan).

FORMULATION

The capsule formulation for different product strengths is given in **Table 1**.

Table 1. DMP 543 Capsule Formulations, 0.025- and 0.1-mg Strengths

Ingredient	0.025-mg Strength Amount (%)	0.1-mg Strength Amount (%)
DMP 543	0.02[1]	0.04[2]
Lactose monohydrate, NF	97.23	97.21
Sodium starch glycolate, NF	2.00	2.00
Magnesium stearate, NF	0.75	0.75
Total	100.00	100.00
Fill weight Capsule size	120 mg #3	240 mg #2

[1]A 2%-9% excess of drug was added to the formulation.
[2]A 2% excess of drug was added to the formulation.

Lactose monohydrate (~97%) was used as a bulking agent, sodium starch glycolate was used as a disintegrant, and magnesium stearate served as a lubricant.

Selection of Mixing Method and Bottle Type for Pre-Blend

The effect of the mixing method for the pre-blend of DMP 543 and lactose, at a ratio of 1 to 200, on the potency and content uniformity of the capsules was examined using trituration in a glass mortar and pestle, and turbular mixing in a plastic bottle or a glass bottle.

The number of lactose rinses required to minimize the drug loss to the bottles was investigated using methanol to extract the drug from the bottles after 2 and 4 lactose rinses.

Process

Geometric mixing of the drug substance and lactose monohydrate in various sizes of mixer/blenders was used for the dry blending process. A small fraction of lactose (0.4%-4% of total lactose) was triturated in a mortar and pestle, and then mixed with the drug substance in a glass bottle using a turbular mixer. The drug to triturated lactose ratios were 1:99 to 5:95, depending on the batch size. The 400-g blend mixed using turbular mixer was then transferred from the glass bottle to an 8-qt V-blender with I-bar installed. The glass bottle was rinsed with fresh lactose 4 times. The lactose rinses and fresh lactose were then geometrically blended with the initial pre-blend in the 8-qt V-blender. The second pre-blend from the 8-qt V-blender was transferred to either a 1-cu-ft V-blender, a 2-cu-ft V-blender, or a 113-L Gallay tote bin, depending on the batch size (10-, 20-, or 50-kg, respectively). The 8-qt V-blender was rinsed 4 times with lactose. Again, the lactose rinses and fresh lactose were geometrically blended with the second pre-blend. The final blend was encapsulated after the disintegrant and lubricant were blended in.

Sampling

The final powder blend (1 to 3 times unit dose) was sampled using a thief from 10 different locations (5 from top, 3 from middle, and 2 from bottom) of a V-blender for blending uniformity test for a 10-kg and a 20-kg batch size. The final powder blend (1 to 3 times unit dose) was removed from 12 different locations (from 4 segments of top, middle, and bottom sections) of a Galley tote bin for a 50-kg batch size.

Ten even fractions of capsules were collected throughout the encapsulation process per batch. One capsule was arbitrarily removed from each fraction of collected capsules for the content uniformity test.

Scanning Electron Microscopy

Scanning electron microscopy was conducted by mounting the sample on a sample holder and sputter coated with gold/palladium prior to examination, using JEOL JSM 840.

Assay and Degradation Determination

Capsules were extracted in aliquots of an acetonitrile/water mixture (50:50, vol/vol) for 30 minutes. After extraction, samples were centrifuged and/or filtered with 0.45 µm Whatman PVDF filters for HPLC analysis.

HPLC was performed on a system including a programmable pump (Waters 510 HPLC pump system, Waters, Milford, MA), an autosampler (Waters™ 717 Plus, Waters, Milford, MA), a variable wavelength UV absorbance detector (Spectroflow 757, Waters, Milford, MA) set at 260 nm, a Hewlett Packard Zorbax® C8 (25 cm x 4.6 mm) column (Hewlett Packard, Valley Forge, PA), and a column oven (Waters, Milford, MA) at 35°C. An isocratic method was used for assay, using a mixture of acetonitrile, pH 4.6, 10 mmol sodium phosphate buffer (60:40, vol/vol) as a mobile phase at a flow rate of 1.0 mL/min. A gradient method was used for degradants determination. Mobile phase A (10 mmol sodium phosphate buffer) and mobile phase B (acetonitrile:water, 70:30, vol/vol) at a flow rate of 1.5 mL/min were used. The results were obtained using a data acquisition and analysis program (Multichrom® software, VG Instruments, Altrincham, UK).

RESULTS AND DISCUSSION

Blending of the drug substance and lactose at a ratio of 1 to 200 in a glass mortar and pestle followed by multiple rinses with lactose resulted in capsules with 100% potency. Because this method is not practical for large-scale manufacturing, turbular mixing in different types of bottles was examined. Also, because the DMP 543 dose is very low, full recovery after pre-blending of lactose and drug substance is very critical. Pre-blending of lactose and DMP 543 in a glass bottle followed by 2 rinses of the bottle with lactose resulted in capsules with a 96% potency. However, pre-blending in a plastic bottle using turbular mixing followed by 2 rinses of the bottle with lactose resulted in a capsule assay value of only 75%. More drug was recovered from the glass bottle (B, **Table 2**) than from the plastic bottle (A, **Table 2**) after the lactose-rinsed bottles were subjected to the methanol extraction. This suggests that the drug loss to the plastic bottle was not recoverable by methanol, although the drug substance was freely soluble in methanol. It is possible that, because of the hydrophobic nature of DMP 543, the drug dissolved in methanol was then irreversibly sorbed to the plastic material. Furthermore, only 0.4% of drug was lost to the walls of the glass bottle, and a complete recovery of the drug was achieved provided the glass bottle was subjected to 4 lactose rinses (C, **Table 2**). Therefore, a total of 4 lactose rinses to the glass bottle were selected in the pre-blending step.

Table 2. Drug Recovery From Different Types of Bottles by Solvent Extraction of a 0.025-mg Strength Capsule

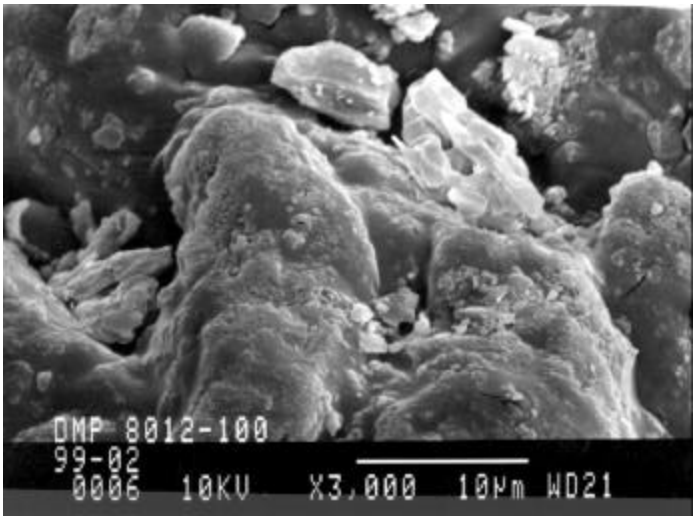
Batch, Type of Bottle	% Recovered	No. of Lactose Rinses	Assay (%)
A, Plastic bottle	0.24	2	74.7[1]
B, Glass bottle	2.4	2	96.2[1]
C, Glass bottle	0.4	4	108.1[2]

[1]A 6% excess of drug was added in this batch (0.48-kg size). A 2-qt V-blender was used after turbular mixing.
[2]A 9% excess of drug was added in this batch (10-kg size). An 8-qt V-blender was used after turbular mixing

When scaling up to batch size larger than 10 kg, it was found that using a small amount of triturated lactose (0.4%-2% of total lactose) enhanced its carrier efficiency. As shown in **Table 3**, the low assay value of batch D was probably due to some drug substance concentrated in a certain portion of blend that was not sampled for assay (the 10 samples tested representing 0.012% of the entire batch).

Batch E was prepared by mixing the drug with a small fraction of triturated lactose that distributed the cohesive drug substance better, and this resulted in an accountable potency, although the content uniformity was still not acceptable (**Table 3**). Effectively, with lactose triturated and turbular mixing time extended from 20 to 30 minutes, batch F resulted in an excellent content uniformity with a 100% accountable potency and a small RSD (0.9%, **Table 3**).

1a



1b

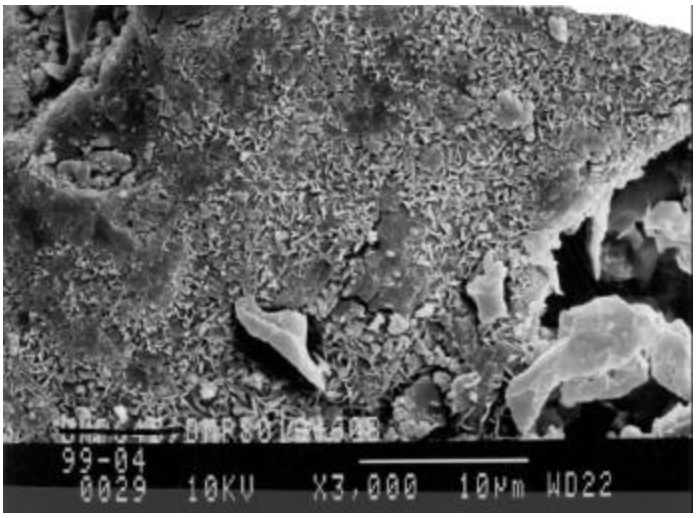


Figure 1. Scanning electron microscope photomicrographs of a placebo powder blend (1a) and an active powder blend (1b) at 3000X magnification with 10-µm reference scale provided.

The initial powder blend was then transferred to an 8-qt V-blender for the next step of geometric blending. It was found that 3 lactose rinses of the V-blender prevented drug loss to the processing container. Approximately 3.3% and 0.4% of drug was recovered in the first and third lactose rinses, respectively.

Table 3. Effect of Trituration and Turbular Mixing Time on Content Uniformity of a 10-kg Batch Size of a 0.025-mg Strength Capsule

Process Parameters					
Batch no.	Step 1: Trituration	Step 2: Turbular Mixing (min)	Step 3: 8-qt V-Blending Time	Step 4: 1-cu-ft V-Blending Time	[1] Assay Mean ± RSD, % (n=10)
D	-	20	[2]	[2]	93.9 ± 2.7
E	lactose	20	[2]	[2]	108.1 ± 14.7
F	lactose	30	[2]	[2]	109.6 ± 0.9

[1]The drug overage in these batches was 9%.

[2]The blending time for all three batches was the same (16 minutes and 18 minutes for step 3 and step, respectively).

Scanning electron microscopy of placebo and active blends (**Figures 1a and 1b**) of a 10-kg batch size showed that the drug evenly distributed on the surface of the lactose. Further scale-up using a 2-cu-ft V-blender or a 113-L tote bin instead of a 1-cu-ft V-blender at Step 4 (**Table 3**) was conducted. Results for a 20-kg batch of 0.025-mg strength capsules and a 50-kg batch of 0.1-mg strength are shown in **Table 4**. Acceptable content uniformity with RSD ≤ 2.2% and 1.6%, respectively, was obtained.

Table 4. Results of Chemical Tests for Two Scale-up Batches[1]

Test	0.025-mg Capsule 20-kg Batch Size	.1-mg Capsule 50-kg Batch Size
Content uniformity of powder blend	101.5 ± 1.3% (n=10)	01.8 ± 0.5% (n=12)
Content uniformity of capsules	101.1 ± 2.2% (n=10)	03.8 ± 1.2% (n=10)
Composite for initial release	101.7 ± 1.0% (n=3)	102.2 ± 1.6% (n=3)
Related substance (RS)	Individual RS: <0.1%Total RS: <0.1%	Individual RS: <0.1%Total RS: <0.1%

[1]A 2% excess of drug was added to the formulation.

In conclusion, using a dry blending process for a very low dose drug is feasible provided that the pre-blending is carefully designed and other process parameters are optimized. Triturated lactose served as an excellent de-agglomerating carrier for micronized, cohesive drug substance at the initial mixing step. This effectively facilitated the distribution of the drug evenly onto the surface of the remaining lactose. A successful scale-up to a 50-kg batch size was demonstrated using this blending process.

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