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Effect of Drug Substance Particle Size on the Characteristics of Granulation Manufactured in a High-Shear Mixer

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ABSTRACT DPC 963 is a non-nucleoside reverse transcriptase inhibitor with low aqueous solubility. The effect of DPC 963 drug substance particle size on the characteristics of granules manufactured by high-shear wet granulation was evaluated. The wet granulation process was used to manufacture a DPC 963 formulation with high drug loading. The formulation was manufactured using drug substance lots with different particle size distributions. Granulation particle size distribution, porosity, and compressibility were determined. A uniaxial compression test was also performed on moist compacts of the formulation prepared with different particle size distributions. Particle agglomeration behavior was affected by drug substance particle size. Granulation geometric mean diameter and fraction with particle size greater than 250 μm was inversely proportional to the drug substance particle size. Mercury intrusion porosimetry revealed higher pore volumes for the granules manufactured using the drug substance with the smaller particle size, suggesting lower tendency for granule densification than for that manufactured with the larger drug substance particle size. Granulation compressibility was also sensitive to changes in drug substance particle size. A decreased drug substance particle size led to increased granulation compressibility. Results from the uniaxial compression experiments suggested that the effect of particle size on granulation growth is the result of increased densification propensity, which in turn results from increased drug substance particle size.

KeyWords: Granulation, Porosity, Compressibility, Particle size

INTRODUCTION

DPC 963 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) [1]. This class of inhibitors targets the reverse transcriptase of the human immunodeficiency virus (HIV), which is critical to the viral replication cycle. Allosteric binding of NNRTIs inhibits the activity of reverse transcriptase. This intervention in the retroviral replication process provides an effective treatment for AIDS and other HIV-related diseases. DPC 963 has a low aqueous solubility of approximately 20 μg/mL and a relatively high projected dose (≥100 mg).

Drug substance particle size can affect processing behavior of a formulation such as granule growth during wet granulation and the resulting granule characteristics. Despite the large number of reports on high-shear wet granulation, few reports address the effect of drug substance particle size on granule growth in high-shear granulation and on granule characteristics (e.g., compressibility and porosity). Granule growth in a high-shear mixer proceeds initially by a nucleation mechanism, whereby liquid bridge bondings are established between particles, which results in nuclei formation. As granulation continues, liquid saturation of the formed nuclei increases as a result of the continued addition of binder solution. After nuclei reach a certain limiting liquid saturation, granule growth by coalescence starts to occur [2]. Coalescence results in rapid granule growth and, as a result, significant increase in granule growth rate. The stress-strain relationship of moist granules is thought to play an important role in granule growth by coalescence [3].

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Area of contact between colliding granules increases as the ability of granules to deform under applied collision force increases, thus resulting in higher probability of successful coalescence. As a result, growth by coalescence is enhanced by lower tensile strength and by granules' higher ability to deform upon application of stress. Properties of the starting material, such as particle size, can affect strength and deformability of moist granules and hence their behavior in the high-shear granulator. Kristensen et al have used a uniaxial compression test to study stress-strain behavior of moist compacts [4, 5]; they defined a critical strain at which stress reaches a maximum value, which they referred to as critical stress. A brittle sample is crushed at the maximum stress, whereas a plastic sample maintains the critical stress at continuing strain. Ouchiyama and Tanaka showed that granule growth by coalescence is expected to increase as the critical stress decreases or the critical strain increases [6]. Granule growth in the high-shear mixer showed good correlation with the critical stress values obtained in the uniaxial compression test. Coalescence was enhanced by the decreased critical stress, which was lowered by the increase in compact porosity. For a given compact porosity, critical stress decreased with the starting material's increased particle size and liquid saturation of the compact [4, 5]. Thus, starting material with small particle size would result in smaller granule size at similar liquid saturation and porosity. On the other hand, material with larger particle size was more easily densified in the high-shear mixer [5]. As porosity decreases, granules gain strength while liquid saturation increases at constant water content. The increased strength is expected to decrease granule growth rate, while increased liquid saturation will be in favor of enhanced coalescence. The effect of particle size on granule growth is, therefore, a function of several interacting factors, the balance of which largely depends on the nature of the material and the experimental conditions. Differences in granule structure and porosity, resulting from changes in starting material particle size, can also affect other characteristics (e.g., compressibility) of the granulation. The purpose of this work was to evaluate the effect of drug substance particle size on the granule growth, porosity, and compressibility for a DPC 963 formulation manufactured by a high-shear wet granulation process. In addition, a uniaxial compression test for moist compacts was performed in an attempt to explain the effect of particle size on the above granulation characteristics.

EXPERIMENTAL

Materials

DPC 963 was supplied by the Chemical Process R & D of DuPont Pharmaceuticals Company and was used as received unless otherwise stated. Drug substance lots SQ963-010 and SQ963-011 were used. SQ964, the inactive enantiomer of DPC 963, was used for some experiments as a model compound (lot SQ964-001). SQ964 has identical physical chemical properties as DPC 963. Excipients used included microcrystalline cellulose (FMC Corporation, Philadelphia, PA), lactose monohydrate (Foremost, Rothschild, WI), sodium lauryl sulfate (Ruger Chemical, Irvington, NJ), magnesium stearate (Mallinckrodt, St Louis, MO), and croscarmellose sodium (FMC Corporation).

Equipment

The equipment train used to manufacture DPC 963 batches includes the Key KG-1 high shear granulator (Key International, Englishtown, NJ), VWR model 1450 vacuum oven (VWR Scientific, West Chester, PA), Turbula mixer (Willy A. Bachofen AG, Basel, Switzerland), and Carver press (Fred S. Carver Inc., Menomonee Falls, WI).

Manufacturing of drug product by the wet granulation process

Granulation was carried out in a Key KG-1 granulator (1 L bowl) at a batch size of 120 g. Drug loading in the formulation was 50% wt/wt. Avicel PH102 was blended with DPC 963 and a portion of croscarmellose sodium in the granulator, with an impeller speed of 650 rpm and a chopper speed of 3000 rpm, for 2 minutes. The granulating solution was prepared by dissolving the sodium lauryl sulfate (SLS) in water. The granulating solution was then added to the blend in the granulator (impeller speed maintained at 650 rpm and chopper speed at 3000 rpm) at a rate of 10 g/min using a peristaltic pump. The amount of water in the added granulating solution represented 21.2% of the total amount of solids in the formulation. Additional water

was added to the granulator in 20-g portions with 1 minute of mixing (wet massing) between additions. The total quantity of added water was identical for all batches. The granulation was screened through 10-mesh screen and dried in a vacuum oven at 40°C to a moisture content of 1.0% to 2.0%. The dried granulation was screened through a 25-mesh screen and then blended with lactose monohydrate and the remaining quantity of croscarmellose sodium for 15 minutes using a Turbula mixer. Magnesium stearate was added to the granulation and blended for 3 minutes. Finally, the granulation was compressed to 200 mg tablets (100 mg strength) using the Carver press to a target hardness of 63 N using 10/32 inch standard concave round tooling.

Drug Substance Particle Size Distribution

Drug substance particle size distribution was determined using the Aerosizer Mach 2 (Amherst Process Instruments, Cambridge, MA) equipped with an AeroDisperser, sensor, vacuum, and data acquisition/analysis ability, which all were controlled by a microprocessor. The sample was suspended as dry powder using a sample holder with a medium cup and a medium opening. Run time was 200 to 400 seconds using 1100 V.

Physical Testing of Granulation and Tablets

a. Particle size distribution of granulation

Particle size distribution of the final lubricated granulation was determined by mesh analysis using an Allen Bradley Sonic Sifter (Allen Bradley, Milwaukee, WI) equipped with a series of 6 screens and a pan. An approximately 10 g sample was tested with a pulse setting of 5, sift setting of 5, and a total sifting time of 5 minutes.

b. Bulk and tapped density of granulation

Bulk density of the lubricated granulation was evaluated by determining the weight of 10 mL of granulation in a graduated cylinder. The tapped density was determined using a Vankel tap density tester, Model 50-1200 (VanKel, Edison, NJ), which provides a fixed drop of one-half inch at 300 taps/min. A volume measurement was taken when the height of granulation in the 10-mL measuring cylinder has reached a constant value (approximately 200 to 300 taps).

c. Moisture determination of granulation

Loss on drying from approximately 5 g of in-process samples taken during drying was measured at 105°C using a Computrac MAX 50 (Arizona Instruments, Phoenix, AZ).

d. Granulation compressibility

Compression profiles were obtained by compressing the granulations on the Carver press using different compression forces. The hardness of the resulting tablets was determined using a Vanderkamp VK200 Tester, Model 40-2000 (VanKel, Edison, NJ).

e. Porosity of granulation and tablets

Pore volume distribution was determined by mercury intrusion porosimetry for the tablets and the granulation fraction retained on a 100-mesh screen. Incremental pore volume was determined at different pressures ranging from 0.5 to 60,000 psi, which corresponds to pore diameters between 360 μm and 0.003 μm.

Uniaxial compression test

Stress-strain relationships were obtained for moist compacts of the formulation. Formulation components were dry blended in the high-shear granulator. A sample of the resulting powder mixture was removed and wetted to target moisture by spraying it with SLS solution and mixing it very gently to achieve uniform water distribution in the sample. A cylindrical mass was formed using die and flat-faced punches 1.27 cm in diameter on an Instron model 5567 (Instron Corporation, Canton, MA) equipped with a 30 kN load cell. The Instron cross head was programmed to travel downward at a speed of at 2.5 mm/min until the target compact height was achieved. The mass of the moist sample and the height of the compact were chosen so that compacts with specified porosity (on the dry basis) were obtained. The compact was removed from the die, and stress-strain relationship for the formed compact was then determined by loading the compact between the flat-faced plates of the Instron and then driving the upper plate downward at a constant rate of 2.5 mm/min. The applied force and displacement were obtained and converted to the corresponding stress and strain values, respectively.

RESULTS AND DISCUSSION

Effect of drug substance particle size on granulation compressibility and size distribution

Particle size distribution of the various drug substance lots used for tablet manufacture is shown in **Table 1.** SQ964, the inactive enantiomer, has identical physical chemical properties as DPC 963. The 2 enantiomers showed identical X-ray powder diffraction pattern, differential scanning calorimetry thermogram, solubility, solution pH, water content, and moisture uptake. Granulation compressibility was dependent on the drug substance particle size. Granulation compressibility increased with the decrease in drug substance particle size (**Figure 1**).

Table 1. Effect of drug substance particle size on granule growth in the high-shear granulator

Drug Substance Lot	SQ964-001	SQ963-010	SQ963-010 (jet milled)	SQ963-011
Drug substance particle size (µm)	10%[a] - 2.9 50%[b] - 5.1 90%[c] - 8.3	10% - 10.5 50% - 21.8 90% - 31.2	10% - 3.3 50% - 9.3 90% - 15.5	10% - 5.4 50% -12.8 90% -21.9
Drug substance surface area (m2/g)	1.36	0.46	ND	1.25
Drug ubstance bulk density (g/mL)	0.12	0.42	0.29	0.32
Normalized granule size[d]	36.9	6.1	19.1	9.6

[a]10% of the particles smaller than this number.
[b]50% of the particles smaller than this number.
[c]90% of the particles smaller than this number.
[d]Normalized granule size is obtained by dividing the geometric mean diameter of the granulation by the median particle size (D50) of the corresponding drug substance lot.

The effect of drug substance particle size on the resulting granules' particle size distribution was also evaluated. Granule growth in the high-shear mixer increased as the particle size of the drug substance decreased. Granulation manufactured with drug substance lot SQ964-001 showed larger fraction retained on the 40-60 mesh screens (>250 µm) compared to the granulation manufactured using SQ963-010 with larger particle size (**Table 2**).

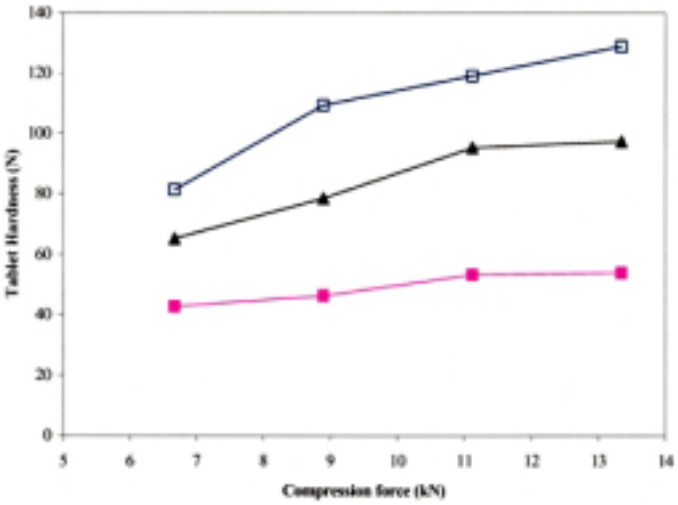

Figure 1. Compression profiles of DPC 963 granulation manufactured using different drug substance lots. SQ964-001, □; SQ963-010 (milled), ▲; SQ964-010, ■.

Table 2. Mesh analysis results for DPC 963 granulation

		Percent Retained	
Mesh Size	Mesh Opening (µm)	SQ964-001	SQ963-010
40	> 425	15.4	9.5
60	250	29.2	14.7
80	180	10.1	11.5
100	150	8.2	6.8
200	75	20.8	30.4
325	45	9.3	17.4
> 325	< 45	6.9	9.6

Geometric mean diameter was 188.4 μm and 132.4 μm for the 2 batches, respectively. Normalized granule size, obtained by dividing the geometric mean diameter of the granulation by the median particle size (D50) of the corresponding drug substance lot, was used as a measure of particle growth in the granulator. Normalized granule size appeared to be inversely proportional to the drug substance particle size (**Table 1**).

Granulation porosity

Granulation porosity increased as the drug substance particle size decreased. Granulation manufactured using SQ964-001 showed higher intragranular pore volume by mercury intrusion porosimetry than for the granulation manufactured using drug substance with larger particle size (SQ963-010). Pore volume for pores in the 1-10 μm diameter range was higher for the SQ964 batch (**Figure 2**).

Higher pore volume for the granulation manufactured using the drug substance lot with small particle size may be the reason for its higher compressibility. The high granulation porosity resulted in an increased fragmentation propensity and volume reduction behavior of the granulation that led to increased compressibility. In agreement with this hypothesis is the fact that tablets compressed using the more porous granulation showed reduced pore volume in the 1 to 2 μm pore diameter range compared to tablets compressed using the less porous granulation under the same compression force (**Figure 3**).

This illustrates the higher tendency of the more porous granulation to densify upon application of the compression force resulting in closer packing of the particles. This is consistent with the finding by Wikberg and Alderborn that demonstrated wider and bimodal pore size distribution for the tablets compressed from granulation with low porosity compared to the narrower and smaller pore size distribution for tablets compressed from the more porous granulation [7].

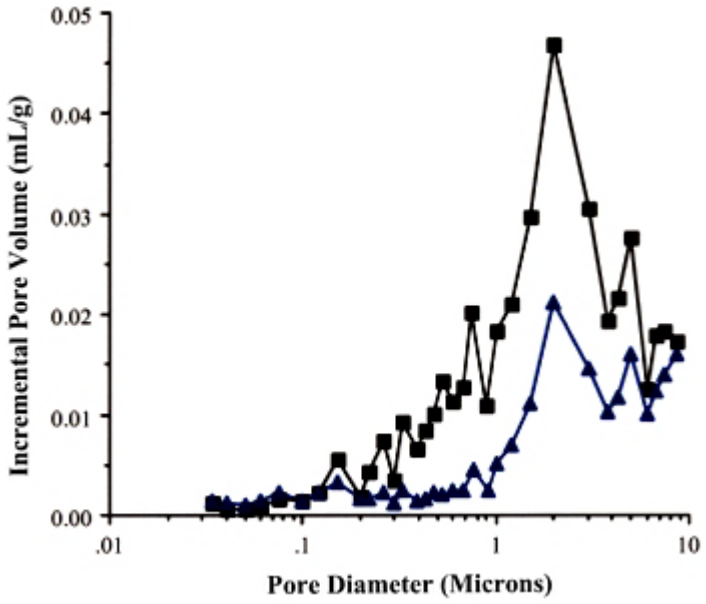

Figure 2. Porosity of DPC 963 granulation fraction retained on 100-mesh screen manufactured using drug substance lots with different particle sizes. SQ964-001, ■ ; SQ963-010, ▲.

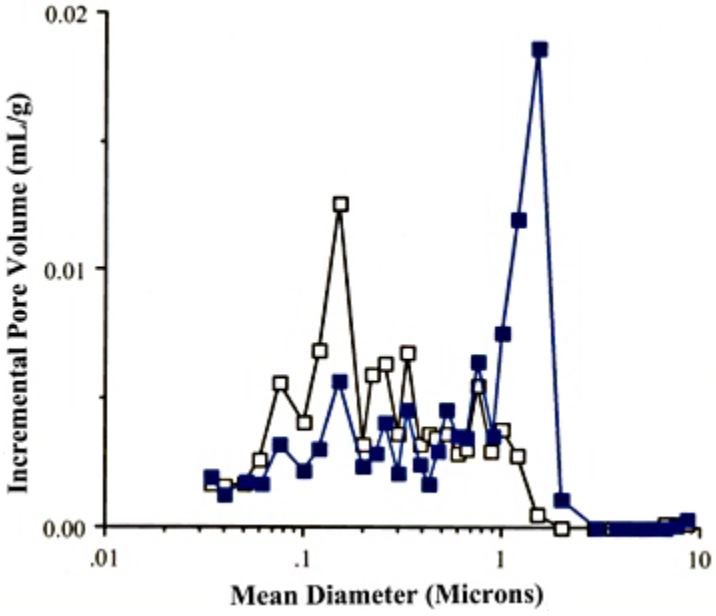

Figure 3. Porosity of DPC 963 tablets compressed using similar compression force and manufactured using drug substance lots with different particle sizes. SQ964-001, ❑ ; SQ963-010, ■.

Uniaxial compression test

Stress-strain profiles were obtained for compacts containing 23% ± 1% water in an attempt to understand the mechanism of particle size effect on the above-mentioned granulation attributes. Compacts were prepared for mixtures manufactured using drug substance lot SQ964-001 (small particle size) and SQ963-010 (large particle size). For each mixture, compacts with approximately 28% and 38% porosity were prepared, which corresponded to pore volumes of 0.25 cm3/g and 0.40 cm3/g, respectively. The higher pore volume is equivalent to the intragranular pore volume of granulation manufactured by high shear using small drug substance particle size, as determined by mercury intrusion porosimetry (the intragranular pore volume was arbitrarily taken as the total pore volume for pores smaller than 10 μm in diameter). The intragranular pore volume for granulation manufactured using a large drug substance particle size was 0.18 cm3/g. This low porosity was not achievable in this test because of practical limitations. Stress-strain profiles for all compacts showed a steady increase in strain as a function of the applied stress until the critical stress is reached. At the critical stress, the sample appeared to exhibit plastic flow, at which point constant stress is more or less maintained at continuing strain (**Figure 4**). Critical stress and strain values and compression forces used to form the compacts are shown in **Table 3**.

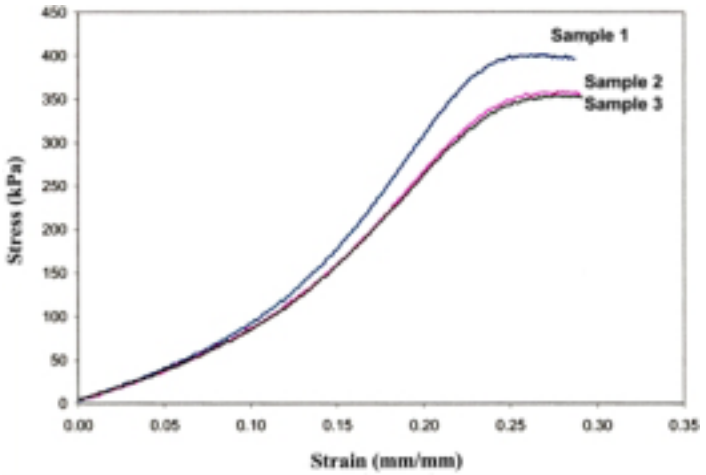

Figure 4. Stress-strain relationship (three replicate samples) for DPC 963 moist compact with 38% porosity prepared using lot SQ964-001.

Table 3. Stress-train parameters[a] for DPC 963 moist compacts

	SQ964-001		SQ963-010	
	28% porosity	38% porosity	28% porosity	38% porosity
Compaction force[b] (N)	9480.3 ± 525.0	681.8 ± 10.4	8296.7 ± 296.1	427.5 ± 12.0
Critical stress (kPa)	456.2 ± 41.7	371.2 ± 26.6	605.0 ± 41.7	374.0 ± 12.1
Critical strain (mm/mm)	0.326 ± 0.014	0.282 ± 0.011	0.400 ± 0.002	0.328 ± 0.009

[a]value ± SD, n=3.
[b]Compression force needed to form a compact with the specified porosity

Compacts prepared using small drug substance particle size demonstrated the higher compression forces required to achieve similar porosity compared to the larger drug substance particle size. This explains the higher porosity for the granulation manufactured using lot SQ964-001 in the high-shear mixer. Under similar forces in the high-shear granulator, formulation manufactured with small drug substance particle size was more resistant to densification, resulting in more porous granulation. Compacts prepared at the high porosity level (37%) using the 2 particle-size distributions showed comparable critical stress values. Because the 2 particle sizes resulted in different granulation porosities, comparison of stress-strain behavior of compacts with different porosities (higher porosity for the small particle size and lower porosity for the large particle size) should be more predictive of coalescence during granulation. The decreased porosity for the granules manufactured with large particle size results in higher liquid saturation than for the more porous granules prepared from the small particle size at constant water content. The decreased porosity is expected to increase the critical stress, whereas the increased liquid saturation is expected to lower the critical stress. The effect of decreased porosity appeared to be more pronounced and the more porous compact for SQ964-001 showed lower critical stress than the less porous compact did for SQ963-010 compact. Because a lower critical stress favors granule coalescence [4, 5], SQ964-001 showed faster granule growth in the high-shear granulator and hence a larger mean diameter and a higher fraction retained on the 40- to 60-mesh screens (>250 μm).

It is noteworthy that the observed effect of particle size on granule growth for DPC 963 is opposite to that reported for dicalcium phosphate [5]. As with DPC 963, the smaller particle size of dicalcium phosphate showed more resistance to densification compared to the larger particle size. Unlike DPC 963, the dicalcium phosphate material with large particle size showed remarkably lower critical stress at a constant porosity and liquid saturation. The effect of particle size on granulation growth in the case of dicalcium phosphate could be explained if the lower critical stress for the material with larger particle size was maintained despite its decreased porosity during granulation compared to the material with smaller particle size.

CONCLUSIONS

DPC 963 granule growth in the high-shear granulator and the resulting granule compressibility and porosity were sensitive to relatively small changes in drug substance particle size. Decreasing the drug substance particle size resulted in more pronounced granule growth and enhanced the porosity and compressibility of the granulation. For compounds such as DPC 963, drug substance particle size needs to be carefully controlled to ensure acceptable and reproducible granulation characteristics.

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