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RESEARCH PAPER

Comparison of Low Shear, High Shear, and Fluid Bed Granulation During Low Dose Tablet Process Development

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ABSTRACT

Three processing methods were compared to develop a low dose (0.1%) immediate release tablet. Similar formulations were used to evaluate low shear, high shear, and fluid bed granulation methods. For each granulation process, the drug was dissolved or suspended in the granulating fluid and sprayed into the granulator. Both water and methanol were evaluated as granulating fluids. The low shear granulation was performed in a Patterson-Kelley V-Blender with I-bar. The high shear granulation was performed in a GRAL (top entry impeller) and a Diosna (bottom mounted impeller). Fluid bed granulation was also performed using top-spray. Acceptable content uniformity was obtained using each technology. The type of granulator and granulating solvent affected the granulation particle size distributions and bulk/tap densities. However, the addition of extragranular microcrystalline cellulose minimized the effect of variable granulation properties and allowed similar tablets to be produced from each granulation process.

Key Words: Low shear; High shear; Fluid bed granulation; Extragranular microcrystalline cellulose.

INTRODUCTION

During process manufacturing development of a low dose tablet, content uniformity is the main technical challenge. To achieve acceptable content uniformity, a granulation process is generally utilized. There are a variety of granulation processes that can be utilized. Granulation processes are grouped as either ''wet'' or ''dry.'' Dry granulation is comprised of processes such as slugging or chilsonation. Wet granulation encompasses a large range of technologies including blenders with a liquid dispersion bar, high shear mixers with an impeller and chopper blade, and fluid beds with top or bottom spray and possibly a rotating bottom disk.

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Literature addresses each type of granulation process individually and in detail.[1,2] However, cross-comparison of different granulation technologies using the same formulation is not widely discussed. One example found in the literature was a comparison between different types of high shear mixers using a Fielder, Diosna, Lodige, and Gral.[3] A comparison was also found between a horizontal and vertical high speed mixer by evaluating granule growth using lactose and dicalcium phosphate.[4,5] Another reference compared granules of lactose and calcium phosphate prepared by pan granulation or a massing and screening process using a z-blade mixer and an oscillating granulator.[6] Granules from each technique were compared for particle size, porosity, strength, shape, and compressibility. In another experiment, a statistical comparison of a high-shear vs. low-shear granulation was performed using common excipients, but the excipient levels were varied in the design of experiments in addition to the mixer type and compression pressure.[7] Visavarungroj and Remon studied the binding properties of cross-linked starch by comparing the product from a high shear mixer and a planetary mixer.[8] A planetary mixer and a high shear mixer (Glatt Powrex) were also compared with respect to the influence of percent water addition in the preparation of a controlled-release matrix tablet containing hydroxypropylmethylcellulose (HPMC) and a high-dose, highly water-soluble drug.[9]

A comparison, using a sematilide hydrochloride formulation, of moisture-activated dry granulation in a planetary mixer was performed vs. traditional wet granulation in a planetary mixer, roller compaction, and direct compression.[10] The moist granulation technique was also compared to wet granulation and direct compression using an acetaminophen formulation.[11] The effect of manufacturing process on the initial dissolution of theophylline was also investigated using direct compression, wet granulation, extrusion-spheronization, dry granulation, and spray-drying.[12] Gao et al. performed a comparison of fluid bed and high shear granulation related to a high dose, poorly water soluble, low density micronized drug.[13] Granulation comparison studies help the process engineer to choose from many available technologies in an effort to develop the most robust process for the target formulation.

The purpose of this study was to identify the most robust granulation process for a low dose, soluble active. The low shear granulation was performed in a Patterson-Kelley V-Blender with I-bar. The high shear granulation was performed in a GRAL (top entry impeller) and a Diosna (bottom mounted impeller). Fluid bed granulation in a Glatt was performed using top-spray. The attributes monitored were granulation particle size distribution, granulation and blend density, tablet content uniformity, tablet disintegration time, and tablet friability.

EXPERIMENTAL

Materials

The formulation in Table 1 was used for the experiments. It consisted of drug, lactose monohydrate (Hollandse Melksuikerfabriek, Uitgeest, Holland), microcrystalline cellulose PH102 (FMC, Philadelphia, PA), povidone (Plasdone K29-32, International Specialty Products, Wayne, NJ), crospovidone (Polyplasdone XL, International Specialty Products), and magnesium stearate (Peter Greven, Bad Münstereifel,

Table 1. Drug product formulation.

Component		Unit (g)	Batch (kg)	%
Drug		0.00025	0.004	0.1
Lactose, monohydrate		0.16575	2.652	66.3
Povidone		0.0050	0.080	2.0
Microcrystalline cellulose		0.0355	0.568	14.2
Microcrystalline cellulose		0.0355	0.568	14.2
Crospovidone		0.0070	0.112	2.8
Magnesium stearate		0.0010	0.016	0.4
Total		0.2500	4.000	100.0
Granulating fluid		total (mL)	granulating (mL)	rinse (mL)
	18%	594.7	446.0	148.7
	20%	660.8	495.6	165.2

Germany). Components in Table 1 above the dotted line were used in the granulation. Components below the dotted line were used in the final blend and lubrication blend. The granulating fluid was either purified water or methanol.

For the fluid bed granulation, the amount of water used was 20% of the dry weight of the granulation excipients and the amount of methanol used was 91%. For all other granulation, the amount of granulating fluid used was 18% of the dry weight of the granulation excipients.

The formulation for this study was developed to provide good compressibility and fast disintegration. Good compressibility was required to make robust tablets that could withstand the stress of a future film-coating process as well as the packaging process into bottles. Fast disintegration was desired because the indication being investigated required fast relief of patient symptoms. Lactose was chosen as the main filler, and microcrystalline cellulose was added to improve compactability and disintegration. Li et al. investigated the role of intra- and extragranular microcrystalline cellulose in dissolution.[14] They found the addition of extragranular microcrystalline cellulose increased dissolution rates and improved compactability. Therefore, the formulation for this study was developed with half of the microcrystalline cellulose intragranularly, to improve granule formation, and half extragranularly to increase dissolution rates and compactabilty.

Equipment

The manufacturing equipment used was an 8 qt. V-blender with I-bar (Patterson-Kelley), a GRAL 25 (Collette), a fluid bed GPCG-5 (Glatt Air Techniques), a Diosna VAC20 (Servolift), a comil (Quadro), and a 10-station Piccola instrumented tablet press (Specialty Measurements, Inc.).

The testing instrumentation used was a STAV 2003 Densifier (J. Engelsmann AG) for tap density at 1250 taps per sample. A sieve shaker (CSC-Meinzer) was used for particle size analysis with U.S.A. Series sieves (20, 40, 60, 80, 100, 170, 230, 325 mesh, and pan). For content uniformity testing, the Zymark Tablet Processing Workstation II (TPWII) running operating software version 2.0 or greater was used with a Thermo Separation Products (TSP) UV 2000 detector and Thermo Separation Products (TSP) P4000 Gradient high-performance liquid chromatography (HPLC) Pump. For disintegration testing a Vanderkamp Tablet Disintegration Tester (Van-Kel Industries, Inc.) was used with a Soft Flo Solid State Temperature Control (Hanson Research). For friability testing an Erweka Friabulator was used.

Manufacturing Process

All manufacturing was completed at Procter & Gamble Pharmaceuticals, Norwich, New York, except for the Diosna which was used at Servolift L.L.C., Rockaway, New Jersey. The drug was dissolved/suspended in the granulating fluid to provide good distribution of the low dose drug in the granulation. Water is the most desirable granulating fluid because it is nontoxic, nonflammable, and easily disposed. However, from preformulation studies with this drug, it was believed that hydrolysis could occur when the drug was in aqueous solution. Therefore, a nonaqueous granulating fluid was also investigated. There was no appreciable solubility of the drug in ethanol, so methanol was the most desirable nonaqueous granulating fluid. The experiments in this study were performed using water or methanol as the granulating fluid.

Granulation processing in the V-blender and GRAL consisted of the following steps (and approximate manufacturing times) shown in Fig. 1: initial blend (5 min), preparation of the granulating solution (15 min), granulation (15 min), wet screening (5 min), drying (30 min), milling (15 min), final blending (15 min), lubrication blending (5 min), and tableting (60 min). All granulations used the same milling, final blending, lubrication blending, and tableting operations. For the process using the Glatt fluid bed and Diosna VAC20, the drying was performed in the same equipment as the granulation, therefore wet screening was not performed. Tableting was performed using a 250-mg target tablet weight and a compression force of 10 kN, which produced tablets of 12–15 kp hardness and 3.95–4.02 mm thickness.

For the V-blender granulation, the initial blend was 5 minutes with the I-bar on, the liquid addition rate was 60 or 150 mL/min, and the total granulating time was 10 or 15 minutes. The GRAL granulation consisted of a 3-minute initial blend with the impeller on low speed and no chopper. The liquid addition rate was 300 mL/min and the granulation time was 3 or 7 minutes. During granulating when the liquid was being added, the impeller speed was kept low with no chopper. When the liquid addition was complete, the impeller speed was kept low, but the chopper was turned on at high speed until the end of granulation. For the fluid bed granulation, the inlet air temperature was allowed to equilibrate to 40°C. The initial blend in the fluid bed was 1 to 3 minutes using low air velocity. The spray nozzle was placed in the bottom port of the

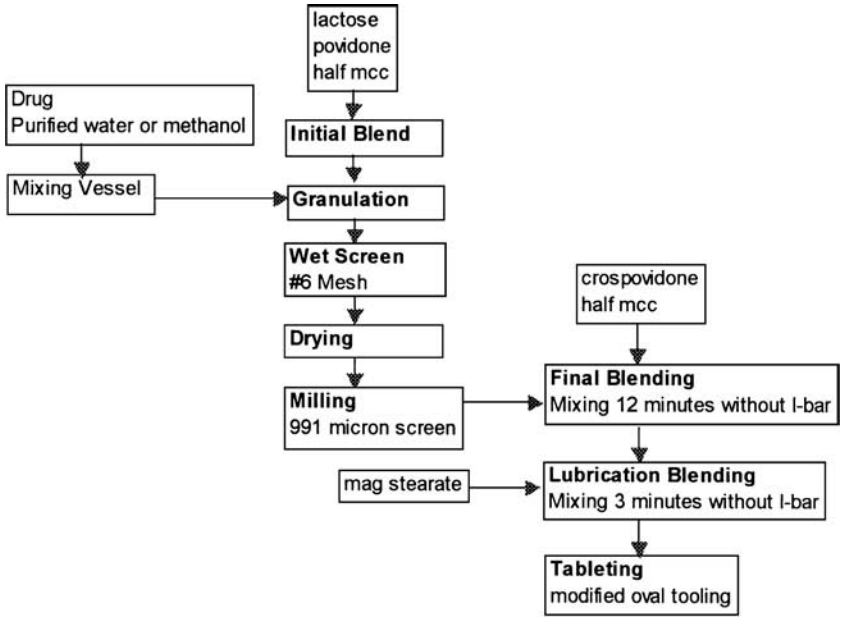

Figure 1. Manufacturing process flowchart.

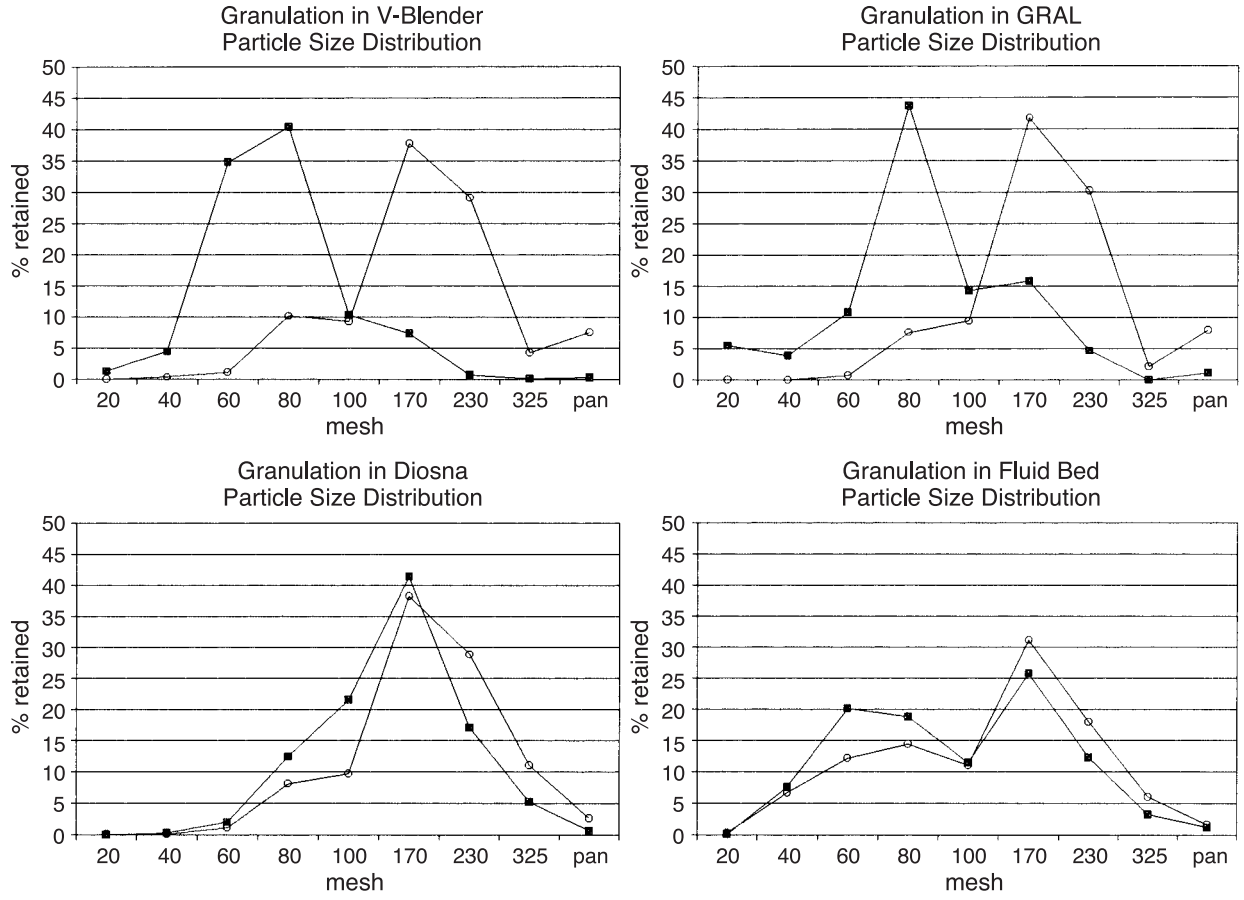

Figure 2. Granulation particle size distributions, with water (■) or methanol (○).

fluid bed. The fluid addition rate was 80 mL/min for water with a granulation time of 8–9 minutes. The fluid addition rate was 300 mL/min for methanol with a granulation time of 10–15 minutes. When the liquid addition began, the air velocity was increased so that the fluidizing excipients covered the nozzle. At the end of the liquid addition, the air velocity was decreased for drying. For the Diosna granulation, the liquid addition rate was 300 mL/min and the granulating time was 7 minutes. The impeller speed was 150 rpm and the chopper speed was 3000 rpm.

RESULTS AND DISCUSSION

Granulation Particle Size Distribution

Particle size distribution (PSD) of the granulation, after drying and prior to milling, was tested for each process. Representative PSDs of granulation from the V-blender, GRAL, Diosna, and fluid bed processes are shown in Fig. 2.

The V-blender and GRAL processes produced granulations with similar particle size distribution when methanol was used as the granulating fluid. When water was used, the GRAL granulation had significantly less material retained on the 60-mesh screen compared to the V-blender granulation. For the V-blender process, the processing parameters (fluid addition rate, amount of fluid, granulation time, and blender and I-bar speeds) were kept the same whether water or methanol was used as the granulating fluid. With processing parameters the same for both water and methanol, it can be seen from Table 2 that there is a solvent effect on the granulation particle size distribution. When water is used, larger granules result. The solvent effect on particle size was also observed for the GRAL granulations, where the processing parameters (liquid addition rate, amount of liquid, granulation time, and impeller and chopper speeds) were kept constant.

For the Diosna process, the processing parameters (fluid addition rate, amount of fluid, granulation time, and impeller and chopper speeds) were kept the same whether water or methanol was used as the granulating fluid. The type of solvent did not have as great an effect on the Diosna granulation particle size distribution when compared to the V-blender and GRAL. However, there was still a larger percentage of

Table 2. Granulation and final blend bulk and tap densities.

Process	Sample	Bulk density (g/mL)	Tap density (g/mL)
Wet gran. V-blender	Dry	0.64–0.66	0.73–0.76
	Milled	0.65–0.67	0.75–0.76
	Final blend	0.59–0.62	0.72–0.73
Wet gran. GRAL	Dry	0.62–0.71	0.73–0.80
	Milled	0.62–0.71	0.74–0.83
	Final blend	0.56–0.62	0.69–0.76
Wet gran. Diosna	Dry	ND	ND
	Milled	0.67–0.70	0.85–0.87
	Final blend	0.59–0.61	0.74–0.77
Wet gran. fluid bed	Dry	0.52–0.58	0.64–0.71
	Milled	0.53–0.58	0.65–0.73
	Final blend	0.48–0.53	0.60–0.67
Methanol gran. V-blender	Dry	0.59–0.63	0.75–0.77
	Milled	0.60–0.65	0.75–0.78
	Final blend	0.52–0.56	0.67–0.69
Methanol gran. GRAL	Dry	0.57–0.59	0.71–0.76
	Milled	0.58–0.60	0.72–0.74
	Final blend	0.52–0.54	0.66–0.67
Methanol gran. Diosna	Dry	0.60–0.62	0.81
	Milled	0.62–0.63	0.81–0.82
	Final blend	0.55–0.56	0.71–0.72
Methanol gran. fluid bed	Dry	0.54–0.57	0.66–0.71
	Milled	0.55–0.58	0.63–0.66
	Final Blend	0.49–0.51	0.63–0.66

Note: ND = Not done.

Table 3. Tablet content uniformity results.

Process	Minimum mean tablet assay (%)	Maximum mean tablet assay (%)	% RSD
Wet gran. V-blender	96.8	97.8	2.2–2.6
Wet gran. GRAL	97.5	100.8	0.7–1.6
Wet gran. Diosna	99.1	106.1	0.6–1.9
Wet gran. fluid bed	94.8	102.1	0.6–1.3
Methanol gran. V-blender	95.1	95.2	0.8–1.1
Methanol gran. GRAL	96.8	97.0	0.8
Methanol gran. Diosna	96.3	100.1	1.1–1.2
Methanol gran. fluid bed	95.1	99.0	0.7–1.3

granules retained on the larger mesh screens (20–80 mesh) when water was used instead of methanol.

For the fluid bed granulations, different liquid amounts and addition rates were used depending on the solvent. For water, an addition rate of 80 mL/min was used to add 660 mL of water. For methanol, an addition rate of 300 mL/min was used to add 3000 mL of methanol. Table 2 shows that for the fluid bed granulation processes, the resulting particle size distributions were similar for both water and methanol when compared to the differences seen within the V-blender and GRAL granulations. The granulation with water still has a higher percentage of particles retained on two of the coarser screens (9% more on the 60-mesh and 6% more on the 80-mesh). Overall in the fluid bed granulation, using methanol at a faster addition rate and higher amount than water allowed granules to be formed that are similar in size distribution to ones formed with water.

Granulation and Final Blend Density

The bulk and tap density were tested for the granulation after drying and milling. The final blend was also tested. The results are shown in Table 2. The results showed that there was a lower density when methanol was used as the granulating fluid, rather than water, for the V-blender, GRAL, and Diosna processes. The results also show that the densities from the fluid bed process are the same for both water and methanol. Finally, the results show that the density of material from the fluid bed process is lower than from the other processes regardless of the solvent used.

Tablet Content Uniformity

A sample was collected at 3-minute intervals throughout the tableting run, for a total of 10 samples. One tablet from each sample was used for content uniformity testing. Tablets tested from every granulation process met the USP Uniformity of Dosage Units <905> criteria of no tablet outside the range of 85.0% to 115.0% with a relative standard deviation (RSD) of less than or equal to 6.0%. The minimum and maximum mean tablet assay for each process and the % RSD are shown in Table 3.

Tablet Weight, Thickness, and Hardness

As mentioned earlier, 250-mg tablets were compressed at 10 kN for each process studied. Tablets were then tested for weight, thickness, and hardness. The results are shown in Table 4.

Table 4. Tablet weight, thickness, and hardness.

Granulation process	Weight (g)	Weight % RSD	Thickness (mm)	Thickness % RSD	Hardness (kp)	Hardness % RSD
Wet gran. V-blender	0.2487–0.2488	0.6–0.7	3.96–3.97	1.1–1.1	13.8–14.0	8.4–10.1
Wet gran. GRAL	0.2479–0.2517	0.6–0.8	3.97–3.99	1.1–1.7	12.1–14.8	8.8–10.4
Wet gran. Diosna	0.2491–0.2503	0.6–0.8	4.02–4.03	1.3–1.4	10.9–11.6	10.6–11.0
Wet gran. fluid bed	0.2453–0.2501	0.6–1.4	3.96–4.04	1.0–1.5	13.3–16.0	7.7–11.7
Methanol gran. V-blender	0.2475–0.2504	0.6–0.9	3.97–3.99	1.3–1.6	12.7–13.7	8.5–11.7
Methanol gran. GRAL	0.2474–0.2490	0.6–0.8	3.98–4.03	1.3–1.6	13.3–14.0	9.3–13.4
Methanol gran. Diosna	0.2480–0.2488	0.9–1.0	4.01–4.03	1.5–1.7	12.0–12.3	12.2–12.5
Methanol gran. fluid bed	0.2475–0.2500	0.6–1.1	3.99–4.04	1.2–1.7	13.7–15.7	7.3–12.0

There was no significant difference in thickness and hardness for tablets made from any of the granulation processes. The addition of half of the microcrystalline cellulose extragranularly in the final blend compensated for variation in granulation particle size distribution and density. All of the final blends had similar compressibility.

Tablet Disintegration and Friability

Tablet disintegration was performed using purified water at 37°C and six tablets sampled during the middle of each tableting run. The apparatus used met USP <701> guidelines with disks. The time recorded was the time for the last tablet to disintegrate. Tablets from each granulation process disintegrated in less than 1 minute. The composite range of disintegration times from the different processes is 12–55 seconds.

Friability was performed according to the USP <1216>. For each test, 26 tablets were friabulated for 100 revolutions. The tablets were sampled during the middle of each tableting run. Tablet friability from all the granulation processes was very low. The composite range including all processes was 0–0.16%. No cracked or broken tablets were observed.

CONCLUSIONS

When formulating for a low dose active and developing a tablet manufacturing process, the formulation used in these studies is a good starting point. This formulation of primarily lactose with microcrystalline cellulose half intragranular and half extragranular yielded similar and acceptable final product using water or methanol as granulating fluids in low shear, high shear, or fluid bed granulation processes. If hydrolysis of the drug in aqueous granulating fluid is a problem, methanol would be an acceptable choice as a nonaqueous granulating fluid. It was also determined that variation in granulation particle size distribution and density may be overcome by spraying the drug in with the granulating fluid and by mixing the granulation with 14% microcrystalline cellulose during the final blend. The additional microcrystalline cellulose in the final blend added robustness in the process and ensured acceptable tablet properties. This approach resulted in tablets with consistently good content uniformity, disintegration, and friability.

When working with essentially a placebo formulation, all granulation processes can result in products with similar properties. The excipients that were used resulted in a robust product that was not significantly affected by the change in granulation process. For a low dose active that is soluble and stable in solution, the type of granulation process is not a key factor in maintaining product quality. The choice of granulation process is not dictated by technical concerns, but rather by other concerns such as process cycle time, containment of potent actives, and accessible equipment. For example, granulation in a fluid bed or other ''one-pot'' system is faster than traditional high shear granulation followed by drying, because it eliminates a wet screening and transfer step. In the case of this study, the fluid bed granulation process allowed for faster fluid addition rates and a much larger amount of methanol could be used, due to evaporation of the fluid during the granulation process. Also, fluid bed granulation or ''one-pot'' systems reduce operator exposure to the active.

In conclusion, for a low-dose, soluble active, acceptable content uniformity was obtained by dissolving the active in the granulating fluid and spraying it onto the excipients. The formulation that was tested produced robust product independent of the granulation method. This allowed for greater flexibility in the choice of process and allowed for additional concerns to be addressed such as cycle time and containment.

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