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Evaluation of High Shear Granulation (Lab-Scale vs. Pilot-Scale) for Extended Release Tablets Containing Carbopol® 971P NF Polymer

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PURPOSE

To evaluate the aqueous granulation process for guaifenesin formulations containing mid or high levels of Carbopol® 971P NF polymer (10% or 20% w/w) and to determine the effect of processing equipment (lab- vs. pilot-scale) on the granule and tablet properties and on drug release.

METHODOLOGY

Materials

Guaifenesin (Delta Synthetic Co. Ltd., Taiwan), Carbopol 971P NF polymer (Lubrizol Advanced Materials, Inc., Cleveland, OH), Emcocel® 50M microcrystalline cellulose (JRS Pharma LP, Patterson, NY), lactose monohydrate (Kerry Bio-Science, Norwich, NY), and magnesium stearate (Ferro Corporation, Walton Hills, OH).

Methods

Guaifenesin, a non-ionic water soluble drug (solubility 1:33), was chosen as a model drug 600-mg dose (75.0% w/w of the tablet weight). Carbopol 971P NF polymer was investigated at a 20% and 10% w/w inclusion level – Table 1.

Table 1. Composition (% w/w) of guaifenesin 600-mg ER tablets

Ingredient (% w/w)	20% CBP 971P NF	10% CBP 971P NF
Guaifenesin	75.00	75.00
Carbopol® 971P NF polymer (CBP 971P NF)	20.00	10.00
Emcocel® 50M microcrystalline cellulose	4.50	5.00
Lactose monohydrate	0.00	9.50
Magnesium stearate[a]	0.50	0.50
Total	100.00	100.00

[a] *Magnesium stearate was added post granulation.*

The drug and excipients were granulated with 7% (w/w) of deionized water under different impeller speeds in a single-stage agglomeration process in two bottom-drive granulators (Table 2) with different capacities (4-L vs. 25-L) and impeller/chopper design – Table 3.

Table 2. Process equipment

Items	Pilot-Scale	Lab-Scale
Bottom-drive high shear granulator	Freund-Vector GMXB-Pilot-25L	Glatt Tabletop TMG-4L
Wet mill	Quadro® Comil® (Model U10)	N/A
Fluidized bed dryer	Freund-Vector VFC-15M–20L	Aeromatic-Fielder AG – model Strea-1

Table 3. Granulation conditions for guaifenesin formulations

Processing/Formulation	20% 971P NF - Pilot-Scale	20% 971P NF - Lab-Scale	10% 971P NF - Pilot-Scale	10% 971P NF - Lab-Scale
1. Dry mixing				
Impeller speed (m/s)	3.3			
Chopper speed (rpm)	500			
Mixing time (min.)	3.0			
2. Spraying				
Spray rate (% w/w/min.)	1.95			
Impeller speed (m/s)	2.2–5.5		3.3	
Chopper speed (rpm)	750			
Time (min.)	~3.6			
Total water added (% w/w)[b]	~7			

[b] *based on a 4-kg (pilot-scale) or 600-g (lab-scale) batch size*

All granules were dried in a fluid bed to a moisture content of less than 2%. The dried granules were sized (#18-mesh), blended with magnesium stearate and compressed into capsule-shaped tablets (800-mg target weight, compression force 10 kN). The formulation (20% 971P NF) manufactured under an impeller speed at 3.3 m/s was evaluated under different compression forces (7.5 – 20 kN).

The guaifenesin formulations were evaluated for granule and tablet properties and on the drug release (USP apparatus 2; media – pH 6.8 buffer and/or 0.1N HCl).

RESULTS

Granule Distribution

The granules manufactured in the pilot- and lab-scale equipment under different impeller speeds had relatively similar particle size distribution. The particle size distribution of granules before and after sizing through an 18-mesh screen is summarized in Figures 1-2.

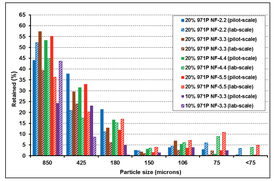

Fig. 1. Particle size distribution of guaifenesin granules before sizing through 18-mesh screen

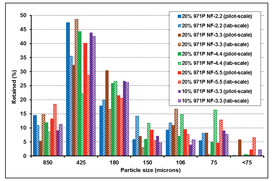

Fig. 2. Particle size distribution of guaifenesin granules after sizing through 18-mesh screen

Granule Properties

All formulations had good flow properties (Table 4), and high impeller speed produced slightly denser granules.

Table 4. Blend properties of guaifenesin formulations

Formulation	Flodex (mm)	Flow rate (g/sec)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibility index
20% CBP 971P NF formulation:						
20% 971P NF-2.2 (pilot-scale)	9	5.68	0.430	0.555	1.29	22.48
20% 971P NF-2.2 (lab-scale)	16	6.10	0.396	0.470	1.19	15.79
20% 971P NF-3.3 (pilot-scale)	16	5.53	0.428	0.571	1.33	24.93
20% 971P NF-3.3 (lab-scale)	6	6.60	0.416	0.483	1.16	13.92
20% 971P NF-4.4 (pilot-scale)	5	7.77	0.459	0.565	1.23	18.73
20% 971P NF-4.4 (lab-scale)	16	5.20	0.451	0.562	1.25	19.72
20% 971P NF-5.5 (pilot-scale)	6	8.28	0.497	0.656	1.32	24.21
20% 971P NF-5.5 (lab-scale)	14	7.18	0.463	0.562	1.21	17.59
10% CBP 971P NF formulation:						
10% 971P NF-3.3 (pilot-scale)	12	5.67	0.424	0.557	1.31	23.86
10% 971P NF-3.3 (lab-scale)	8	6.89	0.427	0.527	1.23	19.01

Tablet Properties

All formulations tableted under 10 kN compression force at 30 rpm had acceptable tablet properties (Table 5).

Table 5. Physical properties of guaifenesin tablets manufactured under 10 kN compression force at 30 rpm

Formulation	Weight (mg)	SD	Thickness (mm)	SD	Breaking force (KP)	SD	Friability 100 rot.	Friability 300 rot.
20% CBP 971P NF formulation:								
20% 971P NF-2.2 (pilot-scale)	804.43	6.21	7.42	0.02	17.40	0.92	0.187	0.400
20% 971P NF-2.2 (lab-scale)	802.43	6.47	7.46	0.04	12.97	0.78	0.164	0.353
20% 971P NF-3.3 (pilot-scale)	804.92	3.77	7.38	0.03	16.71	0.81	0.164	0.359
20% 971P NF-3.3 (lab-scale)	803.57	4.69	7.42	0.03	14.58	0.77	0.106	0.388
20% 971P NF-4.4 (pilot-scale)	806.75	4.40	7.54	0.05	13.36	0.90	0.264	0.483
20% 971P NF-4.4 (lab-scale)	801.27	4.49	7.43	0.04	13.32	0.58	0.227	0.497
20% 971P NF-5.5 (pilot-scale)	803.44	8.29	7.40	0.03	15.27	1.86	0.302	0.609
20% 971P NF-5.5 (lab-scale)	800.62	3.90	7.31	0.21	13.14	1.69	0.269	0.527
10% CBP 971P NF formulation:								
10% 971P NF-3.3 (pilot-scale)	799.77	5.04	7.21	0.03	20.38	1.20	0.322	0.355
10% 971P NF-3.3 (lab-scale)	800.95	4.53	7.19	0.04	19.03	0.71	0.102	0.199

The formulation (20% CBP 971P NF) granulated under an impeller speed at 3.3 m/s (pilot- or lab-scale) was further evaluated for the effect of compression forces (7.5 – 20 kN) and pre-compression force on tablet properties (Table 6). The tablets produced under low compression force had lower friability at 300-rotation than those produced under high compression force (15 kN for lab-scale and 20 kN for pilot-scale). Addition of a pre-compression force (PCF up to 750 N) significantly improved the tablet friability (at 300 rotations).

Table 6. Physical properties of formulations obtained at 3.3 m/s impeller speed (effect of compression force and pre-compression force)

Formulation	Weight (mg)	SD	Thickness (mm)	SD	Breaking force (KP)	SD	Friability 100 rot.	Friability 300 rot.
20% 971P NF-7.5 kN (pilot-scale)	814.58	8.79	7.63	0.03	14.63	1.04	0.230	0.520
20% 971P NF-7.5 kN (lab-scale)	800.66	5.28	7.66	0.03	12.37	0.87	0.226	0.514
20% 971P NF-10 kN (pilot-scale)	804.92	3.77	7.38	0.03	16.71	0.81	0.164	0.359
20% 971P NF-10 kN (lab-scale)	803.57	4.69	7.42	0.03	14.58	0.77	0.106	0.388
20% 971P NF-15 kN (lab-scale)	804.59	4.16	7.17	0.03	15.11	0.88	0.132	failed
20% 971P NF-15 kN–750 N (lab-scale)	801.13	3.60	7.06	0.02	19.75	1.70	0.170	0.237
20% 971P NF-20 kN (pilot-scale)	805.78	4.08	6.97	0.05	18.51	1.48	0.190	failed
20% 971P NF-20 kN–750 N (pilot-scale)	794.18	7.03	6.85	0.05	21.65	2.88	0.137	0.306

Drug Release

Tablets manufactured under 10 kN compression force at 30 rpm were tested in both dissolution media (pH 6.8 phosphate buffer and 0.1N HCl). A similar release profile was observed for the tablets manufactured under different impeller speeds (Figures 3-4). In pH 6.8 phosphate buffer, the drug release from pilot-scale batches was slightly faster than from lab-scale batches.

The drug release of tablets manufactured in different granulator size was not affected by compression force and pre-compression force (Figure 5).

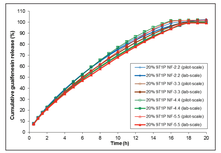

Fig. 3. Effect of impeller speed on drug release in pH 6.8 phosphate buffer from guaifenesin tablets with 20% CBP 971P NF compressed at 10 kN (n=6 ± SD)

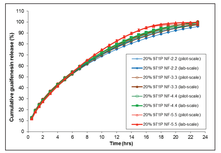

Fig. 4. Effect of impeller speed on drug release in 0.1N HCl from guaifenesin tablets with 20% CBP 971P NF compressed at 10 kN (n=6 ± SD)

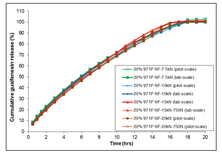

Fig. 5. Effect of compression force, pre-compression force and tableting speed on guaifenesin release in pH 6.8 phosphate buffer from formulation with 20% 971P NF granulated at 3.3 m/s impeller speed (pilot- or lab-scale) (n=6 ± SD)

CONCLUSION

Extended release guaifenesin tablets containing mid and high levels of Carbopol 971P NF polymer (10% or 20%) as a matrix forming excipient could be produced by high shear aqueous granulation in two bottom-drive granulators with different capacities (4-L vs. 25-L) and impeller/chopper design (either pilot- or lab-scale). The process condition obtained from lab-scale could be applied directly to pilot-scale process. Similar granulation conditions could be used for the two polymer levels.

All formulations granulated with 7% water at the same spray rate (1.95% w/w/min.) under different impeller speeds (2.2–5.5 m/s) gave similar granule and tablet performance.

The impeller speeds, compression force, and pre-compression force had no major impact on the drug release.

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