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Processing of Extended Release Tablets Containing Carbopol® 971P NF Polymer by Top-Drive High Shear Granulation

Andrew Stansbrey,[1] Timothy J. Smith,[2] Hong Luo,[1] and Elena Draganoiu[1]

[1]Lubrizol Advanced Materials, Inc., Cleveland, OH, [2]Freund-Vector Corporation, Marion, IA

PURPOSE

To evaluate the aqueous granulation process in a pilot-scale top-drive high shear granulator for guaifenesin formulations containing (10% or 20% w/w) Carbopol® 971P NF polymer and to determine the effect of processing conditions on the granule and tablet properties and on drug release.

METHODOLOGY

Materials

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

Equipment

Pilot-scale top-drive high shear granulator (Freund-Vector GMX-25 equipped with a 25-L vessel, Freund-Vector Corp.), fluidized bed (Freund-Vector VFC-15M equipped with 20-L bowl, Freund-Vector Corp.), QuadroComil U10 with 3/8 inch screen (Quadro Engineering Inc.), automated rotary tablet press (Piccola 469 Tablet Press, SMI Inc.).

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 extended release tablets

Ingredients (% w/w)	20% CBP 971P NF	10% CBP 971P NF
Guaifenesin	75.00	75.00
Carbopol® 971P NF polymer	20.00	10.00
Emcocel® 50M	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 in a two-stage agglomeration process with deionized water (6% or 7% w/w) under different spray rates, impeller and chopper speeds (Table 2).

Table 2. Granulation conditions for guaifenesin formulations

Formulation/Processing	20% 971P NF 3.3/3.3	20% 971P NF 3.3/5.5	20% 971P NF 5.5/5.5	20% 971P NF 3.3/5.5 Low spray rate	20% 971P NF 3.3/5.5 Low water	20% 971P NF 3.3/5.5 High chopper	10% 971P NF 3.3/5.5
CBP 971P NF (%)	20	20	20	20	20	20	10
Target water (%)	7	7	7	7	6	7	7
1. Granulation Process:							
Dry blending							
Impeller/chopper speed (mps[b]/rpm)				3.3/0			
Time (min.)				3.0			
Agglomeration 1							
Impeller/chopper speed (mps[b]/rpm)	3.3/0	3.3/0	5.5/0	3.3/0	3.3/0	3.3/0	3.3/0
Spray rate (% w/w/min.)	1.95	1.95	1.95	1.42	1.62	1.95	1.95
Water added (% w/w)[c]	~3	~3	~3	~3	~3	~3	~3
Time (min.)	1.5	1.5	1.5	2.0	1.5	1.5	1.5
Agglomeration 2							
Impeller/chopper speed (mps[b]/rpm)	3.3/1500	5.5/1500	5.5/1500	5.5/1500	5.5/1500	5.5/3000	5.5/1500
Spray rate (% w/w/min.)	1.95	1.95	1.95	1.42	1.62	1.95	1.95
Water added (% w/w)[c]	~4	~4	~4	~4	~3	~4	~4
Time (min.)	2.2	2.2	2.2	3.0	2.2	2.2	2.2
Wet Massing							
Impeller/chopper speed (mps[b]/rpm)	3.3/1500	5.5/1500	5.5/1500	5.5/1500	5.5/1500	5.5/3000	5.5/1500
Time (min.)	1.0	1.0	1.0	1.0	1.0	1.0	1.0

[b]*mps = meters per second* [c]*based on 4-kg batch size*

Granules were screened (3/8") and dried to a moisture content of less than 2%. The dried granules were evaluated for particle size distribution before and after sizing through 18-mesh screen, and flow properties. Capsule-shaped tablets (800-mg, target weight) were manufactured under different compression forces (7.5 – 20 kN) and tableting speeds (30 – 60 rpm) and evaluated for physical properties and drug dissolution (USP Apparatus 2; media – pH 6.8 buffer and/or 0.1N HCl).

RESULTS

Granule Distribution

Formulations with low water or at high chopper speed produced fewer large particles (>850 microns) before sizing through 18-mesh screen. Processing conditions did not affect particle size distribution after sizing through 18-mesh screen (Figures 1 and 2).

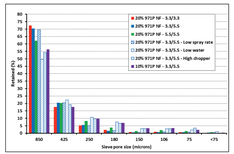

Fig. 1. Particle size distribution of guaifenesin granules – 10% and 20% CBP 971P NF formulations – before sizing through 18-mesh screen

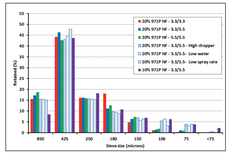

Fig. 2. Particle size distribution of guaifenesin granules – 10% and 20% CBP 971P NF – after sizing through 18-mesh screen

Granule Properties

All granules had good flow properties (Table 3).

Table 3. Granule properties of guaifenesin formulations

Formulation / Process Parameters	Critical orifice (mm)	Flow rate (g/sec)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Carr's Compressibility index
20% CBP 971P NF formulation:						
3.3/3.3	9	6.75	0.438	0.538	1.23	18.58
3.3/5.5	5	7.89	0.483	0.560	1.16	13.73
5.5/5.5	8	7.68	0.484	0.580	1.20	16.63
3.3/5.5 - Low spray rate	7	7.43	0.467	0.543	1.16	14.04
3.3/5.5 - Low water	9	7.05	0.478	0.567	1.19	15.66
3.3/5.5 - High chopper	10	7.90	0.497	0.593	1.19	16.13
10% CBP 971P NF formulation:						
3.3/5.5	9	7.76	0.510	0.604	1.18	15.58

Tablet Properties

All formulations (20% 971P NF and 10% 971P NF) compressed at 10 kN and 30 rpm gave acceptable tablet properties (Table 4).

Table 4. Physical properties of formulations manufactured under 10 kN compression force at 30 rpm

Formulation / Process Parameters	Weight (mg)	SD	Thickness (mm)	SD	Breaking force (KP)	SD	Friability 100 rot.	Friability 300 rot.
20% CBP 971P NF formulation:								
3.3/3.3	799.43	12.68	7.35	0.04	20.84	1.35	0.126	0.274
3.3/5.5	800.19	9.16	7.38	0.05	17.07	1.11	0.148	0.316
5.5/5.5	789.19	6.87	7.33	0.03	19.12	1.84	0.132	0.315
3.3/5.5 - High chopper	801.84	5.10	7.40	0.03	17.90	1.29	0.175	0.347
3.3/5.5 - Low impeller	799.43	12.68	7.35	0.04	20.84	1.35	0.126	0.274
3.3/5.5 - Low water	802.64	9.69	7.43	0.03	17.18	1.57	0.142	0.335
3.3/5.5 - Low spray rate	795.63	8.29	7.35	0.03	19.65	0.84	0.145	0.328
10% CBP 971P NF formulation:								
3.3/5.5	793.64	2.92	7.25	0.03	18.20	1.00	0.098	0.298

Formulations granulated under 3.3/5.5 impeller conditions were evaluated for effect of compression force/pre-compression force (7.5 – 20 kN), and tableting speed (30 – 60 rpm) on tablet properties (Table 5):

- Tableting speed (30 – 60 rpm) did not significantly affect tablet properties.
- Acceptable tablet properties were achieved at low compression force (10 kN). Increasing compression force did not provide significant benefit, but required addition of pre-compression.

Table 5. Physical properties of formulations obtained at 3.3/5.5 impeller conditions (effect of compression force/pre-compression, tableting speed)

Formulation / Process Parameters	Weight (mg)	SD	Thickness (mm)	SD	Breaking force (KP)	SD	Friability 100 rot.	Friability 300 rot.
20% CBP 971P NF formulation:								
Effect of compression and pre-compression force								
7.5 kN	803.49	5.05	7.64	0.06	13.35	0.99	0.214	0.495
10 kN	800.19	9.16	7.38	0.05	17.07	1.11	0.148	0.316
20 kN	800.11	7.61	6.95	0.04	22.46	3.28	0.087	Failed
20 kN – 750 N	800.05	8.85	6.90	0.05	28.58	1.83	0.098	0.155
Effect of tableting speed								
10 kN – 30 RPM	800.19	9.16	7.38	0.05	17.07	1.11	0.148	0.316
10 kN – 60 RPM	797.30	15.36	7.37	0.03	15.46	1.71	0.137	0.298
10% CBP 971P NF formulation:								
Effect of compression and pre-compression force								
7.5 kN	794.28	3.52	7.49	0.04	13.87	0.91	0.184	0.404
10 kN	793.64	2.92	7.25	0.03	18.20	1.00	0.098	0.298
20 kN	788.55	6.99	6.77	0.05	26.00	2.12	0.116	0.208
20 kN – 750 N	801.73	4.05	6.82	0.02	28.72	1.02	0.081	0.195
Effect of tableting speed								
10 kN – 30 RPM	793.64	2.92	7.25	0.03	18.20	1.00	0.098	0.298
10 kN – 60 RPM	807.19	7.57	7.30	0.05	18.47	1.93	0.067	0.286

Drug Release

Similar release profiles were observed in pH 6.8 buffer and 0.1N HCl for tablets compressed at 10 kN compression force and 30 rpm irrespective of granulation conditions (Figures 3 and 4).
Tableting parameters (compression/pre-compression, tableting speed) did not have a major impact on release (Figures 5 and 6).

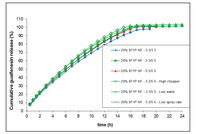

Fig. 3. Effect of granulation conditions (impeller speed, spray rate, chopper) on drug release in pH=6.8 phosphate buffer from guaifenesin tablets with 20% CBP 971P NF compressed at 10 kN (n=6).

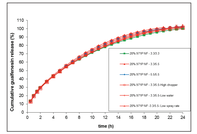

Fig. 4. Effect of granulation conditions (impeller speed, spray rate, and chopper) on drug release in 0.1N HCl from guaifenesin tablets with 20% CBP 971P NF compressed at 10 kN (n=6).

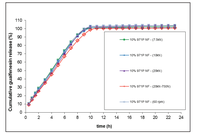

Fig. 5. Effect of compression parameters on guaifenesin release in pH=6.8 phosphate buffer from formulation with 10% 971P NF granulated at 3.3/5.5/1500 m/s-rpm impeller-chopper speed (n=6).

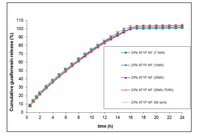

Fig. 6. Effect of compression parameters on guaifenesin release in pH=6.8 phosphate buffer from formulation with 20% 971P NF granulated at 3.3/5.5/1500 m/s-rpm impeller-chopper speed (n=6).

CONCLUSIONS

In this study, guaifenesin tablets with Carbopol 971P NF polymer (10% or 20%) were successfully produced by aqueous high shear granulation in a top-drive pilot-scale granulator.

Changes in processing conditions (granulation and compression) had no major impact on granule, tablet properties, and drug release.

- Similar granulation conditions could be used for the 10% and 20% Carbopol 971P NF polymer formulations.
- Granulation condition of two-stage water addition (impeller speed: first stage 3.3 m/sec, second stage 5.5 m/sec) produced robust granules and tablets.

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