Evaluation of Pilot Scale High Shear Granulation for Extended Release Tablets Containing Carbopol® 971P NF Polymer

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PURPOSE

To evaluate the pilot scale 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 conditions on the granule and tablet properties, and drug release.

INTRODUCTION

Carbopol® 971P NF polymer is an efficient controlled-release tablet excipient due to its crosslinked nature and high molecular weight. Manufacture of tablets containing high level of Carbopol® 971P NF polymer by aqueous high shear granulation may pose challenges due to the hydrophilic nature and fast swelling behavior of the polymer in the presence of water. Formulations containing Carbopol® polymers have been investigated in various lab studies, however no pilot scale aqueous granulation has been previously conducted.

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).

Equipment

Pilot-scale bottom-drive high shear granulator (Freund-Vector GMXB-Pilot equipped with a 25-L vessel by Freund-Vector Corp.), CoMill® (Model U10 by Quadro Engineering Corp.), fluidized bed dryer (Freund-Vector VFC-15M equipped with a 20-L bowl by Freund-Vector Corp.), and automated tablet press (Piccola 469 Tablet Press by SMI).

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 – Table 2.

Table 2. Granulation conditions for guaifenesin formulations

Processing/Formulation	20% 971P NF -2.2	20% 971P NF -3.3	20% 971P NF -4.4	20% 971P NF -5.5	10% 971P NF -3.3
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	3.3	4.4	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 batch size*

The granulated material was wet-screened (⅞"), and 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). Additionally, the formulations (20% 971P NF- 3.3 and 10% 971P NF-3.3) were evaluated under different compression forces (7.5 – 20 kN) and tableting speeds (30 and 45 rpm).

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

RESULTS

Granule distribution

The granules manufactured under different impeller speeds had similar particle size distribution. The particle size distributions of granules before and after sizing through an 18-mesh screen are summarized in Fig. 1-2.

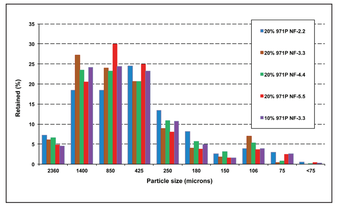

Fig. 1. Particle size distribution of Guaifenesin granules before sizing through 18-mesh screen

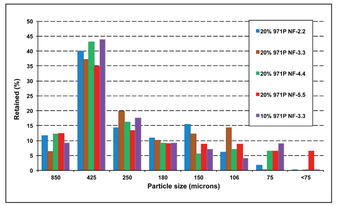

Fig. 2. Particle size distribution of Guaifenesin granules after sizing through 18-mesh screen

Granule Properties

All formulations had good flow properties (Table 3), and high impeller speeds produced slightly denser granules than low impeller speed.

Table 3. 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	9	5.68	0.430	0.555	1.29	22.48
20% 971P NF- 3.3	16	5.53	0.428	0.571	1.33	24.93
20% 971P NF-4.4	5	7.77	0.459	0.565	1.23	18.73
20% 971P NF-5.5	6	8.28	0.497	0.656	1.32	24.21
10% CBP 971P NF formulation:						
10% 971P NF-3.3	12	5.67	0.424	0.557	1.31	23.86

Tablet Properties

All formulations tableted under 10 kN compression force of 30 rpm had acceptable tablet properties (Table 4).

Table 4. 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	804.43	6.21	7.42	0.02	17.40	0.92	0.187	0.400
20% 971P NF- 3.3	804.92	3.77	7.38	0.03	16.71	0.81	0.164	0.359
20% 971P NF-4.4	806.75	4.40	7.54	0.05	13.36	0.90	0.264	0.483
20% 971P NF-5.5	803.44	8.29	7.40	0.03	15.27	1.86	0.302	0.609
10% CBP 971P NF formulation:								
10% 971P NF-3.3	799.77	5.04	7.21	0.03	20.38	1.20	0.322	0.355

Two formulations (10% or 20% CBP 971P NF) granulated under an impeller speed at 3.3 m/s were further evaluated for the effect of compression forces (7.5 – 20 kN), tableting speeds (30 and 45 rpm), and pre-compression force on tablet properties (Table 5):

- Tableting speeds (i.e., 30 rpm and 45 rpm) did not have any impact on the tablet properties (i.e., weight, thickness, breaking force, and friability).
- High compression force (i.e., 20 kN) had a detrimental effect on tablet friability at 300-rotation. Addition of a pre-compression force (PCF up to 750 N) significantly improved the friability (at 300 rotations) of the tablets.

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

Formulation	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								
20% 971P NF-3.3 (7.5 KN)	814.58	8.79	7.63	0.03	14.63	1.04	0.230	0.520
20% 971P NF-3.3 (10 KN)	804.92	3.77	7.38	0.03	16.71	0.81	0.164	0.359
20% 971P NF-3.3 (15 KN)	793.80	5.00	7.04	0.03	21.35	1.13	0.141	0.310
20% 971P NF-3.3 (20 KN)	805.78	4.08	6.97	0.05	18.51	1.48	0.190	failed
20% 971P NF-3.3 (20 KN - 750 PCF)	794.18	7.03	6.85	0.05	21.65	2.88	0.137	0.306
Effect of tableting speed								
20% 971P NF-3.3 (10 KN – 30 RPM)	804.92	3.77	7.38	0.03	16.71	0.81	0.164	0.359
20% 971P NF-3.3 (10 KN - 45 RPM)	801.19	6.37	7.46	0.06	15.80	0.94	0.230	0.284
10% CBP 971P NF formulation:								
Effect of compression and pre-compression force								
10% 971P NF-3.3 (7.5 KN)	805.87	4.88	7.50	0.04	15.27	0.84	0.321	0.613
10% 971P NF-3.3 (10 KN)	799.77	5.04	7.21	0.03	20.38	1.20	0.322	0.355
10% 971P NF-3.3 (15 KN)	805.58	10.20	6.97	0.06	23.52	1.96	0.143	failed
10% 971P NF-3.3 (15 KN - 750 PCF)	793.85	9.98	6.85	0.03	25.15	1.51	0.127	0.300
10% 971P NF-3.3 (20 KN)	806.76	5.20	6.86	0.04	22.33	1.51	0.236	failed
10% 971P NF-3.3 (20 KN - 750 PCF)	803.07	4.50	6.84	0.04	26.43	2.24	0.272	0.353
Effect of tableting speed								
10% 971P NF-3.3 (10 KN – 30 RPM)	799.77	5.04	7.21	0.03	20.38	1.20	0.322	0.355
10% 971P NF-3.3 (10 KN - 45 RPM)	792.54	4.60	7.13	0.04	18.89	1.01	0.196	0.271

Drug Release

All 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). In both dissolution media, a similar release profile was observed for the tablets manufactured under different impeller speeds (Fig. 3-4).

The formulation containing 20% Carbopol® 971P NF polymer resulted in longer and less variable release than the 10% CBP formulation (Fig. 5). The drug release was not affected by compression force, tableting speed, and pre-compression force (Fig. 6).

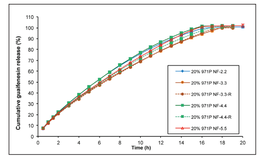

Fig. 3. Effect of impeller speed on drug release in pH 6.8 phosphate buffer from Guaifenesin tablets with 20% CBP 971P NF compressed at 10 kN (n=6 ± SD; R-replicate batch)

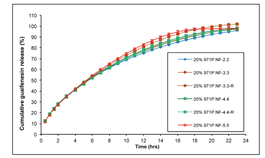

Fig. 4. Effect of impeller speed on drug release in 0.1N HCl from Guaifenesin tablets with 20% CBP 971P NF compressed at 10 kN (n=6 ± SD; R-replicate batch)

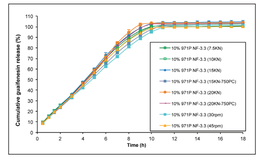

Fig. 5. Effect of compression parameters on guaifenesin release in pH 6.8 phosphate buffer from formulation with 10% 971P NF granulated at 3.3 m/s impeller speed (n=6 ± SD)

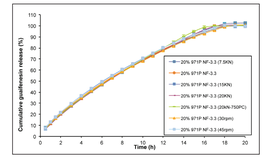

Fig. 6. Effect of compression parameters on guaifenesin release in pH 6.8 phosphate buffer from formulation with 20% 971P NF granulated at 3.3 m/s impeller speed (n=6 ± SD)

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 aqueous high shear granulation in a pilot-scale granulator. The polymer imparted binding properties to the formulation, thus no additional binder was necessary.

The granulation could be conducted with low amount of water (7% w/w). This should be beneficial during granulation (avoid over-wetting) and drying (shorter time needed).

The robustness of the formulations in terms of physical properties and drug release was demonstrated under different processing (granulation and compression) conditions:

- The impeller speeds evaluated had no significant effect on granule performance, tablet physical properties, and drug release.
- Similar granulation conditions could be used for the two polymer levels.
- Increasing the compression force or tableting speed did not have a major impact on the drug release.
- Addition of a pre-compression force (up to 750 N) significantly improved tablet properties (friability and weight variation) in the case of high compression force.