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High Shear Granulation of Extended Release Tablets Containing Carbopol® 971P NF Polymer in Top-Drive vs. Bottom-Drive Equipment

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PURPOSE

To evaluate aqueous granulation of guaifenesin formulations containing high level of Carbopol® 971P NF polymer (20% w/w) in pilot-scale top-drive vs. bottom-drive granulators, and compare the properties of the granules, tablets obtained by the two processes.

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 600-mg (75.0% w/w) extended release formulations containing 20% w/w Carbopol 971P NF polymer (Table 1) were granulated in pilot-scale high shear granulators: bottom-drive (Freund-Vector GMXB/Pilot/25L) or top-drive (Freund-Vector GMX-25L), at a 4-kg batch size, under different impeller speeds (3.3 – 5.5 m/s) – Table 2.

The resulting granules were dried in a fluid bed (Freund-Vector VFC-15M) to less than 2% moisture and evaluated for particle size distribution and flow properties. Granules were compressed into capsule-shaped tablets (800-mg target weight), under different compression forces (7.5 – 20 kN), and evaluated for physical properties and drug dissolution.

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

Ingredient	(% w/w)
Guaifenesin	75.00
Carbopol® 971P NF polymer	20.00
Emcocel® 50M microcrystalline cellulose	4.50
Magnesium stearate	0.50
Total	100.00

Table 2. Granulation conditions for guaifenesin formulations

Processing	Bottom-drive	Top-drive
Dry mixing		
Impeller speed (m/s)	3.3	
Chopper speed (rpm)	0	500
Mixing time (min.)	3.0	
Agglomeration I		
Impeller speed (m/s)	3.3 – 5.5	
Chopper speed (rpm)	750	0
Spray rate (% w/w/min.)	1.95	
Time (min.)	~3.6	~1.5
Water added (% w/w)*	7	3
Agglomeration II		
Impeller speed (m/s)	-	3.3 – 5.5
Chopper speed (rpm)	-	1500
Spray rate (% w/w/min.)	-	1.95
Time (min.)	-	~2.2
Water added (% w/w)*	-	4
Wet massing		
Impeller speed (m/s)/chopper speed (rpm)	-	5.5/1500
Time (min.)	-	1
Total time (min.)	**~ 3.6**	**~ 4.7**
Total water added (% w/w)*	**~ 7**	**~ 7**

**as weight percentage of the batch size*

RESULTS

Guaifenesin formulations containing Carbopol 971P NF polymer (20% w/w) were successfully granulated in pilot-scale top-drive and bottom-drive granulators. In both equipment types, the impeller speed had no significant effect on granule and tablet properties or on drug release. Larger granules (before and after sizing through 18-mesh screen) were produced in top-drive granulator compared to bottom drive – Figures 1 and 2.

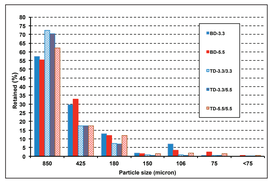

Fig. 1. Particle size distribution of guaifenesin granules produced in bottom-drive (BD) or top-drive (TD) before sizing through 18-mesh screen

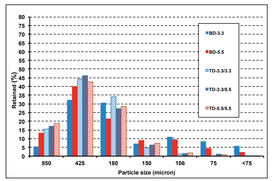

Fig. 2. Particle size distribution of guaifenesin granules produced in bottom-drive (BD) or top-drive (TD) after sizing through 18-mesh screen

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

Process Parameter	Flodex (mm)	Flow rate (g/s)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner ratio	Compressibility index
BD-3.3	16	5.53	0.428	0.571	1.33	24.93
BD-5.5	6	8.28	0.497	0.656	1.32	24.21
TD-3.3/3.3	9	6.75	0.438	0.538	1.23	18.58
TD-3.3/5.5	5	7.89	0.483	0.560	1.16	13.73
TD-5.5/5.5	8	7.68	0.484	0.580	1.20	16.63

While similar processing conditions could be used in both equipment designs, the preferred settings were:

- Bottom-Drive granulator — one-stage addition (impeller speed 3.3 m/s). This lower speed prevented powder segregation and provided mixing efficiency.
- Top-Drive granulator — two-stage water addition process (low impeller speed 3.3 m/s in first stage, followed by high speed 5.5 m/s in second stage). This assured adequate mixing (especially in the second stage) without causing powder segregation (in the first stage).
- High impeller speed (greater than 5.5 m/s) should be avoided to prevent powder segregation during granulation.

Tablet Properties

All formulations tableted under 10 kN compression force of 30 rpm had acceptable tablet properties (Table 4). 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 and/or tableting speed (Table 5).

Table 4. Physical properties of guaifenesin tablets manufactured under 10 kN compression force

Process Parameter	Weight (mg)	SD	Thickness (mm)	SD	Breaking force (KP)	SD	Friability 100 rot.	Friability 300 rot.
BD-3.3	804.92	3.77	7.38	0.03	16.71	0.81	0.164	0.359
BD-5.5	803.44	8.29	7.40	0.03	15.27	1.86	0.302	0.609
TD-3.3/3.3	799.43	12.68	7.35	0.04	20.84	1.35	0.126	0.274
TD-3.3/5.5	800.19	9.16	7.38	0.05	17.07	1.11	0.148	0.316
TD-5.5/5.5	789.19	6.87	7.33	0.03	19.12	1.84	0.132	0.315

Table 5. Physical properties of guaifenesin tablets manufactured under 20 kN compression force at 30 rpm, without or with pre-compression force (750 N)

Process Parameter	Weight (mg)	SD	Thickness (mm)	SD	Breaking force (KP)	SD	Friability 100 rot.	Friability 300 rot.
BD-3.3 without pre-compression	805.78	4.08	6.97	0.05	18.51	1.48	0.190	Failed
BD-3.3 with pre-compression	794.18	7.03	6.85	0.05	21.65	2.88	0.137	0.306
TD-3.3/5.5 without pre-compression	800.11	7.61	6.95	0.04	22.46	3.28	0.087	Failed
TD-3.3/5.5 with pre-compression	800.05	8.85	6.90	0.05	28.58	1.83	0.098	0.155

Drug Release

In both dissolution media, the type of granulator equipment did not result in significant difference in drug release (f2>50). Drug release from tablets processed in bottom-drive granulator was not affected by the impeller speed, while in the case of top-drive granulator, lower speed resulted in slightly slower release (Figures 3 and 4).

Increasing the compression force did not have a major impact on the drug release – Figure 5.

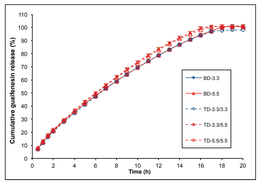

Fig. 3. Effect of granulation (granulator type and impeller speed) on drug release in pH 6.8 phosphate buffer from guaifenesin tablets compressed at 10 kN (n=6 ± SD)

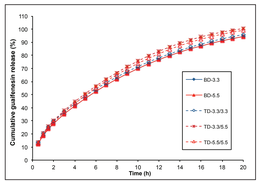

Fig. 4. Effect of granulation (granulator type and impeller speed) on drug release in 0.1N HCl from guaifenesin tablets compressed at 10 kN (n=6 ± SD)

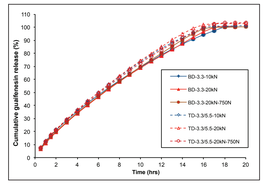

Fig. 5. Effect of compression/pre-compression force on guaifenesin release in pH 6.8 phosphate buffer (n=6 ± SD)

CONCLUSION

In this study, high shear aqueous granulation of extended release guaifenesin tablets containing high level of Carbopol 971P NF polymer (20%) was accomplished in both top-drive and bottom-drive pilot-scale granulators.

While similar processing conditions could be used in both equipment designs, the preferred settings were:

- Bottom-Drive granulator — one-stage addition (impeller speed 3.3 m/s) provided mixing efficiency and prevented powder segregation.
- Top-Drive granulator — two-stage water addition process (impeller speed 3.3 m/s followed by 5.5 m/s) to assure adequate mixing and avoid powder segregation.

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

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