Carbopol® Polymers for Extended Release Tablets Manufactured by High Shear Granulation

Elena Draganoiu, Hong Luo, Andrew Stansbrey

Lubrizol Advanced Materials, Inc., Cleveland, OH

OBJECTIVE

To evaluate the use of Carbopol® 971P NF polymer as a matrix forming excipient for Guaifenesin 600 mg extended release tablets manufactured by aqueous high shear granulation and to determine the effect of processing variables on granules, tablet properties and drug release.

METHODOLOGY

Materials

Guaifenesin (Tianjin Xin Xin Pharmaceutical Corporation, China), Carbopol® 971P NF polymer (Lubrizol Advanced Materials, Inc., Cleveland, OH) – 971P NF, Avicel® PH 101 microcrystalline celullose (FMC Biopolymer, Philadelphia, PA), Synpro® Magnesium Stearate NF (Ferro Corporation, Walton Hills, OH)

Methods

Guaifenesin, a non-ionic water soluble drug (solubility1:33), was chosen as a model drug. The dose used for this study was 600 mg/tablet, representing 84.5% w/w of the tablet weight. Carbopol® 971P NF polymer was investigated at a 10% w/w inclusion level – Table 1.

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

Ingredient (% w/w)	% w/w
Guaifenesin	84.50
Carbopol® 971P NF Polymer	10.00
Avicel® PH-101 Microcrystalline Cellulose	5.00
Magnesium Stearate	0.50
Total	**100.0**

The drug and excipients were added to a high-shear granulator (Glatt TMG) and granulated with deionized water, under different processing conditions: impeller and chopper speed, spraying rate – Table 2. The dried granules were sized, blended with magnesium stearate and compressed on an automated Korsch PH100/DMS Rotary Press, using 0.32x0.67-inch capsule shape punches, to tablet target weight (710 mg) and hardness (10 kP).

Table 2. Processing conditions for Guaifenesin 600 mg tablet experimental runs

Processing/Run	#1 (#1-R[a])	#2 (#2-R[a])	#3	#4	#5	#6	#7
1. Dry mixing Speed (impeller/ chopper) rpm	300/500	300/500	300/500	300/500	300/500	300/500	300/500
Mixing time (min.)	4	4	4	4	4	4	4
2. Spraying Spray rate (%w/w /min.)	0.68	1.59	2.42	2.42	1.59	0.68	0.68
Speed (impeller/ chopper) rpm	400/750	600/900	600/900	600/900	400/750	400/750	600/900
3. Wet massing Speed (impeller/ chopper) rpm	600/900	600/900	600/900	-	600/900	600/900	600/900
Time (min.)	2.0[b]	1.0	1.0	-	1.0	1.0	1.0
Total water added (%w/w)[c]	6.9	7.1	7.1	3.5	7.1	6.8	6.9

[a] *#1-R and #2-R were replicates of #1 and #2, respectively.*
[b] *#1 - wet massing: 1 min. at 600/900 rpm and 1 min. at and 400/750 rpm.*
[c] *Batch size = 900 g*

The properties of the resulting granules and tablets were evaluated as a function of processing variables: impeller and chopper mixing speeds, and water spraying rate and amount. The impact of these factors was determined on the Guaifenesin release from tablets in 0.1N HCl or pH=6.8 USP phosphate buffer media (USP apparatus 2, 50 rpm).

RESULTS

Granule distribution

The runs resulted in granules with similar size, except for runs #4 and #7, which had larger amount of fines – Fig. 1. Run #4 was granulated with lower amount of water, while #7 was processed under high agitation speed and low spray rate.

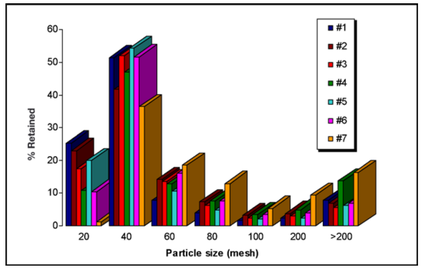

Fig. 1. Particle size distribution of Guaifenesin granules

Blend properties

The blends had similar properties, except for run #4, which had lower bulk density, tapped density, flow rate and higher compressibility index and Flodex – Table 3. This could be correlated with the particle size distribution (finer in the case of #4) and it was attributed to the lower amount of water used for granulation.

Table 3. Properties of Guaifenesin blends

Run	Flodex (mm)	Flow rate (g/sec)	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility index
#1	6	6.67	0.409	0.488	16.03
#2	6	7.36	0.444	0.541	17.92
#3	6	7.21	0.443	0.521	14.99
#4	12	5.17	0.349	0.448	22.07
#5	6	6.58	0.431	0.521	17.16
#6	5	7.16	0.444	0.531	16.45
#7	5	7.70	0.467	0.566	17.48

Tablet Properties

All tablets had acceptable properties: weight, thickness, and hardness – Table 4. The tablets from run #4 had higher friability, which correlated with granule properties and lower amount of water used for processing.

Table 4. Physical properties of Guaifenesin 600 mg tablets

Run	Weight (mg)	SD	Thickness (mm)	SD	Hardness (kP)	SD	Friability @100 rot.	Friability @300 rot.
#1	715.64	5.25	6.74	0.03	14.08	1.16	0.081	0.212
#2	708.16	8.21	6.59	0.02	15.24	1.42	0.221	0.463
#3	710.28	4.79	6.77	0.03	13.27	0.50	0.323	0.504
#4	709.87	6.26	6.87	0.02	12.84	0.62	0.530	0.624
#5	709.71	4.99	6.84	0.01	12.25	0.60	0.194	0.335
#6	710.91	3.66	6.65	0.03	14.33	0.43	0.174	0.256
#7	710.44	3.85	6.74	0.03	12.61	0.35	0.188	0.349

Compression force: 5.3 – 7.5 kN; ejection force: 58.3 – 97.6 N

Drug release

The dissolution profiles are shown in Fig. 2 and 3.

The tablets from run #4, granulated with low amount of water (~3.5%), had the slowest release in both acid and buffer media. The amount of water also affected the granule and tablet properties, which were different compared to the other runs.

Mixing speed did not affect drug release. Batches run at the same spray rate and different speeds (400/750 rpm vs. 600/900 rpm) had similar dissolution profiles:
#1 vs. #7; #2 vs. #5

Spraying rate did not influence the dissolution rate. The release from batches processed at the same speed (600/900 rpm) was consistent, except for the release from G10 (slower). As previously discussed, this can be correlated with the lower amount of water used for granulation.
#2, #3, #4, #7

No effect of the **processing conditions** was observed in the case of batches granulated with ~7% water, thus proving the **robustness** of the formula.

Processed under the same conditions, the batches showed good **reproducibility** and **low intra-batch variability** (Fig. 4). No significant effect of the dissolution medium on the release was observed (F2>50).

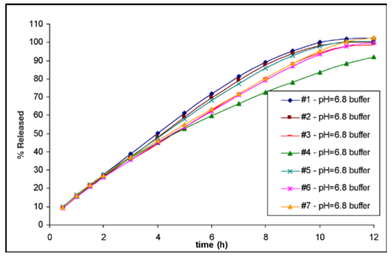

Fig. 2. Guaifenesin release in pH=6.8 buffer

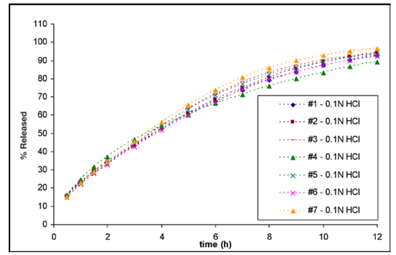

Fig. 3. Guaifenesin release in 0.1N HCl

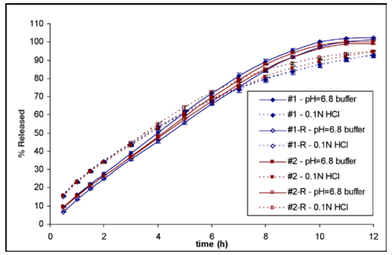

Fig. 4. Reproducibility of Guaifenesin release - average ± std dev (n=6)

CONCLUSIONS

- Carbopol® 971P NF polymer could be efficiently used at 10% inclusion level as matrix forming excipient for Guaifenesin 600 mg extended release tablets manufactured by aqueous high shear granulation.
- The polymer imparted binding properties to the formulation, thus no additional binder was necessary. This was beneficial given the high dose (600 mg)/high load (84.5 % w/w) of the formulation.
- The granulation could be conducted with low amount of water (<10% w/w). This should be considered during processing (in order to avoid overwetting) and drying (shorter drying time being advantageous).
- A sufficient amount of granulation liquid should be used to assure good granule formation (less fines) and consistent drug release.
- High agitation speed may lead to powder segregation, more difficult control of the granule formation, thus they are not recommended.
- When processed under the same conditions, the batches showed good reproducibility.
- The robustness of the formulation (physical properties, drug release) was demonstrated under different processing conditions (mixing speeds and spraying rates).