Effect of Water Level Used in Granulation on the Performance of Extended Release Tablets Containing Carbopol® 971P NF Polymer

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OBJECTIVE

To evaluate Carbopol® 971P NF polymer as an extended release excipient for guaifenesin (high-solubility) or ketoprofen (low-solubility) tablets manufactured by high shear aqueous granulation; to determine the effect of the amount of water used in granulation on granule and tablet properties, and 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 (Sheffield Pharma Ingredients, Norwich, NY), Magnesium stearate (Ferro Corporation, Walton Hills, OH), Ketoprofen (Medisca Inc., Plattsburgh, NY), Talc (Acros Organics USA, Morris Plains, NJ), Cab-O-Sil® M5 fumed silica (Cabot Corporation, Billerica, MA)

Methods

Guaifenesin 600 mg (75.0% w/w; as a water-soluble model drug) or ketoprofen 200 mg (66.7% w/w; as a poorly water-soluble model drug) extended release (ER) tablets containing Carbopol® 971P NF polymer (15% w/w) were prepared by high shear granulation using water as the granulating liquid – Table 1. All formulations were granulated in a Glatt Tabletop Vertical Granulator TMG (Glatt GmbH) fitted with a 4-L vessel, under the same process parameters, except for the water amount and addition rate – Table 2.

Table 1. Composition (% w/w) of Guaifenesin 600 mg or Ketoprofen 200 mg ER Tablets

Ingredient (% w/w)	Guaifenesin	Ketoprofen
Guaifenesin	75.00	-
Ketoprofen	-	66.67
Carbopol® 971P NF polymer	15.00	15.00
Emcocel® 50M microcrystalline cellulose	4.50	5.44
Lactose monohydrate	5.00	10.89
Cab-O-Sil® M5 fumed silica	-	0.50
Talc	-	1.00
Magnesium stearate	0.50	0.50
Total	**100.0**	**100.0**
Target tablet weight (mg)	800.0	300.0
Dose (mg)	600.0	200.0

Table 2. Granulation Conditions for Guaifenesin 600 mg or Ketoprofen 200 mg ER Tablets

Formulation[a]	Guaifenesin	Ketoprofen
1. Dry mixing		
Speed (impeller/chopper) rpm	300/500	300/500
Mixing time (min.)	6.0	6.0
2. Spraying		
Spray rate (% w/w/min.)	1.28	3.62
Speed (impeller/chopper) rpm	400/750	400/750
3. Wet massing		
Speed (impeller/chopper) rpm	600/300	600/300
Time (min.)	1.0	1.0
Total water added (% w/w)	**5 ± 1**	**17.5 ± 3.5**

[a]*Batch size = 600 g*

The dried granules were sized, blended with magnesium stearate and compressed on an automated Korsch PH100/DMS Rotary Press, to target tablet weight (800 mg for guaifenesin and 300 mg for ketoprofen) and breaking force (10 kP). The resulting granules were evaluated for flow rate, critical orifice diameter (Flodex), bulk and tapped densities, and Carr's compressibility index. The tablets were evaluated for weight variation, breaking force, friability, and drug dissolution (in pH 6.8 phosphate buffer and/or 0.1N HCl).

RESULTS

Blend and Tablet Properties

All formulations were prepared under the same processing conditions except for the water amount and addition rate. 5 ± 1% of water was used for the guaifenesin formulations, and 17.5 ± 3.5% of water was used for the ketoprofen formulations. The range for the amount of water used to produce acceptable formulations was narrower for guaifenesin formulations (4 – 6%) than ketoprofen formulations (14 – 21%). However, percent variation (± 20%) from the mid-point was similar for both drug systems.

The blend properties are summarized in Table 3. All formulations had acceptable blend properties, except G-4% H2O which had inferior flow properties (large Flodex and compressibility index). Increasing the water level from the low-level to targeted mid-point resulted in greater improvement of the granules performance.

All formulations had acceptable tablet properties (Table 4).

Table 3. Properties of Guaifenesin or Ketoprofen Blends

Active	Guaifenesin			Ketoprofen		
Formulation	**G-4% H_2O**	**G-5% H_2O**	**G-6% H_2O**	**K-14% H_2O**	**K-17.5% H_2O**	**K-21% H_2O**
FloDex (mm)	20	6	6	16	8	6
Flow Rate (g/sec)	5.16	7.42	6.80	3.13	5.96	6.49
Bulk Density (g/cc)	0.40	0.42	0.42	0.38	0.38	0.41
Tap Density (g/cc)	0.54	0.52	0.51	0.47	0.46	0.50
Compressibility Index	25.29	18.69	18.93	18.91	16.45	17.33

Table 4. Physical Properties of Guaifenesin 600 mg or Ketoprofen 200 mg ER Tablets

Active	Guaifenesin			Ketoprofen		
Formulation	**G-4% H_2O**	**G-5% H_2O**	**G-6% H_2O**	**K-14% H_2O**	**K-17.5% H_2O**	**K-21% H_2O**
Weight (mg) ± SD	798.00 ± 4.42	798.07 ± 2.63	800.24 ± 5.95	299.08 ± 2.23	299.07 ± 2.36	301.82 ± 3.03
Thickness (mm) ± SD	7.50 ± 0.01	7.50 ± 0.01	7.47 ± 0.02	4.89 ± 0.01	4.88 ± 0.01	4.85 ± 0.01
Breaking force (kP) ± SD	11.79 ± 0.50	11.39 ± 0.60	12.17 ± 0.50	10.65 ± 0.54	10.76 ± 0.56	11.48 ± 0.88
Friability (%) @ 100 rot	0.214	0.187	0.186	0.163	0.125	0.081
Friability (%) @ 300 rot	0.498	0.494	0.370	0.512	0.379	0.283

Drug Release

Guaifenesin release (USP apparatus 2, 50 rpm in pH 6.8 phosphate buffer and 0.1N HCl) is plotted in Figures 1-2. The release in acid medium was slightly faster than in buffer. Varying the water level used for granulation had no major effect on drug release in both dissolution media.

The release profiles of ketoprofen 200 mg tablets in pH 6.8 phosphate buffer (USP apparatus 2, 75 rpm) are compared in Figure 3. Varying the water level used for granulation had no major effect on drug release.

Change in the amount of water used during granulation (± 20% from the target amount) did not affect drug release from guaifenesin or ketoprofen tablets formulated with Carbopol® 971P NF polymer.

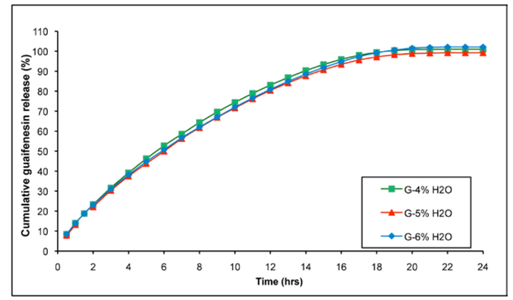

Figure 1. Guaifenesin release in pH 6.8 phosphate buffer (n=6 ± SD)

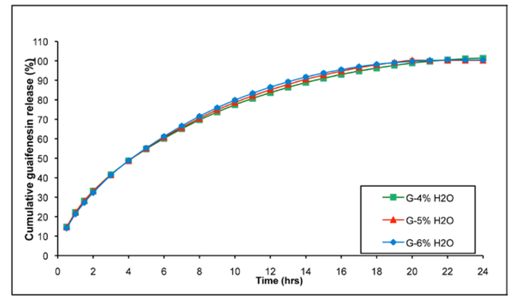

Figure 2. Guaifenesin release in 0.1N HCl (n=6 ± SD)

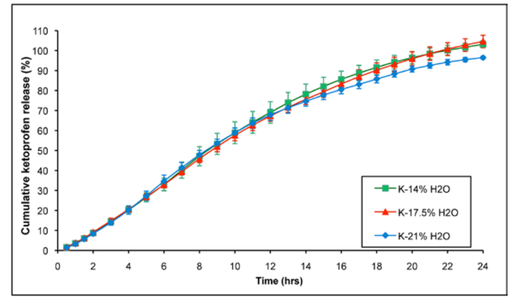

Figure 3. Ketoprofen release in pH 6.8 phosphate buffer (n=6 ± SD)

CONCLUSION

Extended release tablets containing Carbopol® 971P NF polymer could be successfully manufactured by high shear granulation using relatively low amounts of water. A lower water level was necessary for the water-soluble guaifenesin (5 ± 1% w/w), whereas a higher water level was required for the poorly water-soluble ketoprofen (17.5 ± 3.5% w/w). For guaifenesin or ketoprofen formulations, a ± 20% variation from the target water level affected granule properties, but had no significant effect on tablet properties or drug release.