ROLLER COMPACTION METHOD FOR CARBOMER SUSTAINED RELEASE TABLET FORMULATIONS

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OBJECTIVE

To develop a roller compaction method for preparing carbomer-containing controlled-release tablets comprising water-soluble or water-insoluble model drugs (theophylline or ketoprofen), and to demonstrate the utility of carbomer in creating controlled-release formulations via the roller compaction process.

BACKGROUND

Carbomers have demonstrated useful controlled-release (CR) performance properties in tablet applications. However, when powdery-grade carbomer is employed, the scale-up of tablet production to pilot and manufacturing scale has been challenging. Generally, when a sufficient quantity of powdery carbomer is used as a CR excipient, the resulting formulation does not flow properly, and so a granulation step is needed to achieve adequate flow properties in formulations. Since carbomers are hydrophilic polymers, water addition can make the wet granulation process challenging. Therefore, a dry granulation method that creates good flowability and also improves the final physical characteristics and drug release performance of tablets is desirable.

This study evaluates the use of roller compaction for producing carbomer-containing CR formulations. Theophylline is used as a water-soluble model drug, and Carbopol® 971P NF polymer, dibasic calcium phosphate (DCP), and lactose are used as the primary excipients. In order to understand the effect of drug solubility on drug release in the roller-compacted formulation, ketoprofen is used as a water-insoluble model drug in a comparative study. The effect of polymer level on granulation, tablet physical properties, and drug release properties of tablets produced by roller compaction is determined and compared with the results obtained from tablets produced by direct-compression and wet-granulation processes.

METHODOLOGY

Materials

The drugs and excipients used for this study were: Theophylline anhydrous (Lot 200304037, Dastech), Ketoprofen (Lot QO 0754, Spectrum), Carbopol® 71G NF polymer (granular, Lot TW15GAJ022, Noveon, Inc.), Carbopol® 971P NF polymer (powdery, Lot CC118AJ106, Noveon, Inc.), #316 Fast-Flo® granulated lactose monohydrate (modified-spray dried) (Lot 850081463, Foremost), Emcompress® dibasic calcium phosphate dihydrate (Lot 7042, JRS Pharma LP), Magnesium stearate (Lot 6301123019802, Synpo), Talc USP (Lot A013574901, Acros)

Methods

Preparation of Formulation Blend:

For each formulation (Tables 1 – 3), the appropriate amounts of ingredients were weighed out (excluding magnesium stearate), passed through an 18-mesh screen, charged into a V-blender (Patterson-Kelly Company), and mixed for 30 minutes. Magnesium stearate was then added and mixed for two minutes. In the case of the roller compaction process, the talc and magnesium stearate were added post-granulation. For the wet granulation process, magnesium stearate was added post-granulation.

Roller Compaction:

Blends of theophylline or ketoprofen with various levels of 971P NF, Emcompress®, and lactose were compacted and granulated in an Alexanderwerk WP120X40 lab-scale roller compactor equipped with two grooved-surface rollers. The general operation conditions for the compaction process were as follows: screw feeder speed = 40 rpm, roller speed = 8 rpm, compaction pressure = 75 bar, granulator speed = 80 rpm, granulator screen size = 2 mm for the top screen and 1 mm for the bottom screen, vacuum pressure = 0.5 bar, and roller gap size = 1.5 mm.

Roller-Compacted Ribbon/Granule Testing:

The cross-sections of roller-compacted ribbons at different polymer levels were examined by the scanning electron microscopy (SEM). Milled granules were analyzed for density, compressibility index (CI), and particle size distribution. The particle size distribution was determined by Air-Jet Sieve (ASTM D1921- 96, Hosokawa Air-Jet Sieve Model II), using a fresh sample for each screen size.

Wet Granulation:

Carbomer 971P NF-containing granules for tableting were prepared using an all-aqueous granulation technique. The formulations were subjected to low-shear granulation using deionized water as the granulating fluid, sieved through a 6-mesh screen, dried, sized through an 18-mesh screen, lubricated, and then tableted.

Tablet Preparation:

The formulations were tableted on an automated Korsch PH100/DMS Rotary Press equipped with 0.375-inch round-concave dies and operating at 30 rpm. A 300-mg tablet weight and a 10-kP tablet hardness were targeted during tablet production.

Tablet Property Testing:

Tablets randomly chosen from each formulation were tested for weight variation (n=20), crushing strength (n=10), thickness (n=10), and friability (n=20).

Dissolution Testing:

Drug dissolution for each formulation was conducted according to the USP method for modified release products:
- Apparatus: Type-II (paddles, Model Total Solution VK7010, Vankel), 50 rpm.
- Medium: 750 mL of 0.1N HCl for the first two hours and 1000 mL of pH 6.8 phosphate buffer thereafter.
- Method: UV-vis spectrophotometer (model Cary 50 UV-Vis, Vankel), with detection wavelength at 270 nm for theophylline and 260 nm for ketoprofen.

Some of the theophylline formulations were also tested according to the USP 27 *Drug Release Test 8* (Apparatus I, 100 rpm) for Theophylline Extended-Release Capsules.

Table 1. **Roller-Compaction Formulation**

Excipients	Function	Weight (%)
Carbopol® 971P NF polymer	Controlled-release polymer	2.5-20
Theophylline or ketoprofen	Model drug	16.67
Dibasic calcium phosphate	Diluent	31.16-39.92
Lactose	Diluent	31.16-39.92
Talc	Glidant	0.5
Magnesium stearate	Lubricant	0.5

Table 2. **Direct-Compression Formulation**

Excipients	Function	Weight (%)
Carbopol® 71G NF polymer	Controlled-release polymer	10-25
Theophylline	Model drug	16.67
Dibasic calcium phosphate	Diluent	28.66-36.16
Lactose	Diluent	28.66-36.16
Talc	Glidant	0.5
Magnesium stearate	Lubricant	0.5

Table 3. **Wet-Granulation Formulation**

Excipients	Function	Weight (%)
Carbopol® 971P NF polymer	Controlled-release polymer	10
Theophylline or ketoprofen	Model drug	16.67
Dibasic calcium phosphate	Diluent	36.16
Lactose	Diluent	36.16
Talc	Glidant	0.5
Magnesium stearate	Lubricant	0.5

RESULTS

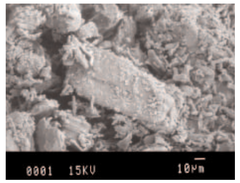
Physical Properties of Roller-Compacted Ribbons/Granules:

Figure 1 shows SEM photographs (500X) of the cross-sections of roller-compacted theophylline ribbons with various levels of Carbopol® 971P NF polymer. Samples containing higher levels of 971P NF are denser and have less voids.

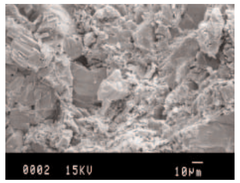
Figures 2 and 3 show the effect of 971P NF levels on the particle size distribution of roller-compacted theophylline and ketoprofen granules, respectively. In both cases, increasing the 971P NF level causes an increase in the amount of coarse granules (> 150 mm) accompanied by a decrease in the amount of fines (<150 mm). Because 971P NF has unique thermoplastic and binding properties for granulation applications, a higher polymer level generates a ribbon that is more resistant to the milling process and thus produces a coarser particle-size distribution.

Tables 4 and 5 list the physical properties of roller-compacted, direct-compressed, and wet-granulated formulations. When formulations containing the same level of carbomer are compared, the bulk and tap densities fall in the following order: roller compaction > direct compression > wet granulation. The compressibility index (CI), which indirectly measures the flowability of a powder mass, is calculated from bulk and tap density values. In general, a lower CI value indicates a higher flowabilty. All of the granulation formulations give improved flowability compared to the powder blends.

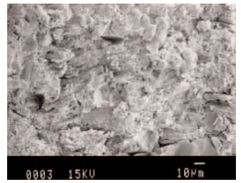
Figure 1. SEM photographs of the cross-sections of roller-compacted ribbons.



(a) with 2.5% of 971P NF



(b) with 10% of 971P NF



(c) with 20% of 971P NF

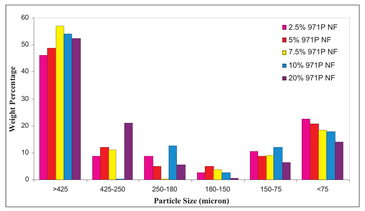


Figure 2. Particle size distribution of roller-compacted theophylline granules. Each point shows the mean of three independent measurements.

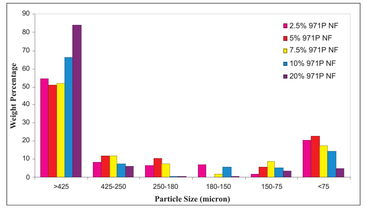


Figure 3. Particle size distribution of roller-compacted ketoprofen granules. Each point shows the mean of three independent measurements.

Table 4
Properties of Theophylline Formulations

Formulation Description	Bulk Density (g/cc)	Tap Density (g/cc)	Compressibility Index (%)
Roller-Compacted			
With 2.5% of 971P NF	0.801	1.018	21.31
With 5% of 971P NF	0.750	0.927	19.15
With 7.5% of 971P NF	0.748	0.906	17.40
With 10% of 971P NF	0.739	0.899	17.75
With 20% of 971P NF	0.707	0.849	16.68
Directly-Compressible			
With 10% of 71G NF	0.641	0.780	17.91
With 20% of 71G NF	0.597	0.716	16.54
With 25% of 71G NF	0.557	0.668	16.64
Wet-Granulated			
With 10% of 971P NF	0.593	0.697	14.92

Table 5
Properties of Ketoprofen Formulations

Formulation Description	Bulk Density (g/cc)	Tap Density (g/cc)	Compressibility Index (%)
Roller-Compacted			
With 2.5% of 971P NF	0.749	0.953	21.47
With 5% of 971P NF	0.747	0.916	18.53
With 7.5% of 971P NF	0.740	0.901	17.88
With 10% of 971P NF	0.725	0.880	17.62
With 20% of 971P NF	0.683	0.842	18.83
Wet-Granulated			
With 10% of 971P NF	0.592	0.726	18.41

Physical Properties of Tablets

Tables 6 and 7 summarize the physical properties of the tablets produced from roller-compaction, direct-compression, and wet-granulation. All tablets show acceptable physical properties. They have low weight variation and acceptable hardness. The friability of all tablets is less than 0.3%.

Table 6:
Properties of Theophylline Tablets

Formulation Description	Weight (mg, SD)	Hardness (kP, SD)	Thickness (mm, SD)	Friability (%)
Roller-Compacted				
With 2.5% of 971P NF	297.5, 4.7	12.0, 0.8	3.60, 0.05	0.19
With 5% of 971P NF	300.4, 3.2	12.1, 0.6	3.68, 0.03	0.17
With 7.5% of 971P NF	301.0, 1.7	12.3, 0.6	3.68, 0.03	0.09
With 10% of 971P NF	300.7, 3.7	12.5, 0.4	3.70, 0.03	0.16
With 20% of 971P NF	300.1, 2.6	11.5, 1.0	3.90, 0.02	0.15
Directly-Compressible				
With 10% of 71G NF	300.6, 1.5	9.4, 0.2	3.70, 0.01	0.26
With 20% of 71G NF	300.1, 2.7	9.8, 0.5	3.90, 0.02	0.18
With 25% of 71G NF	300.0, 2.6	10.2, 0.6	3.98, 0.01	0.22
Wet-Granulated				
With 10% of 971P NF	302.6, 3.4	10.3, 0.7	3.71, 0.01	0.25

Table 7:
Properties of Ketoprofen Tablets

Formulation Description	Weight (mg, SD)	Hardness (kP, SD)	Thickness (mm, SD)	Friability (%)
Roller-Compacted				
With 2.5% of 971P NF	300.9, 2.9	11.1, 1.2	3.63, 0.03	0.19
With 5% of 971P NF	299.5, 2.9	12.6, 0.7	3.65, 0.03	0.17
With 7.5% of 971P NF	301.2, 3.2	12.3, 1.2	3.69, 0.02	0.17
With 10% of 971P NF	301.0, 2.8	11.9, 0.8	3.74, 0.03	0.16
With 20% of 971P NF	299.8, 2.5	10.1, 0.6	3.89, 0.02	0.13
Wet-Granulated				
With 10% of 971P NF	302.1, 2.9	9.7, 0.7	3.93, 0.02	0.10

Theophylline Release:

Figure 4 shows the theophylline release profiles of roller-compaction tablets containing various 971P NF levels. The tablets containing 2.5% of 971P NF give faster drug release with larger error bars than tablets containing 5% of 971P NF. When the level of 971P NF is increased beyond 5%, the drug release profile is little changed. Therefore, the minimum carbomer level required for sustained drug release is about 5%.

Figure 5 shows the theophylline release profiles of direct-compression and wet-granulation tablets containing 71G NF or 971P NF. The data indicated that wet-granulation tablets give slower drug release than direct-compression tablets, and that a higher level of 71G NF is required in direct compression in order to achieve drug release equivalent to that of the wet granulation method.

Figure 6 compares the theophylline release profiles of tablets produced by different manufacturing processes. The results indicate that roller compaction method requires a lower level of carbomer to achieve the sustained theophylline release than wet granulation or direct compression method. In addition, the roller compaction method gives a more uniform distribution of the ingredients in the matrix, which is evidenced by the fact that the tablets maintain their integrity even after 24-hr dissolution. In contrast the tablets produced by direct compression and wet granulation erode during dissolution.

Figure 7 shows the drug release profile *(USP Drug Release Test 8)* of roller-compaction tablet containing 5% of 971P NF. The result indicates that the roller-compaction tablet releases theophylline within the guidelines of the USP "Theophylline Extended-Release Capsules" Monograph.

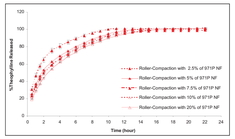


Figure 4. Theophylline release from roller-compaction tablets.

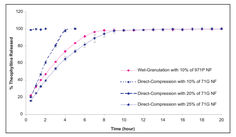


Figure 5. Theophylline release profiles from direct-compression and wet-granulation tablets.

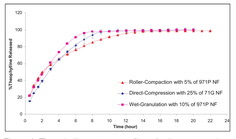


Figure 6. Theophylline release profiles of roller-compaction, direct-compression and wet-granulation tablets.

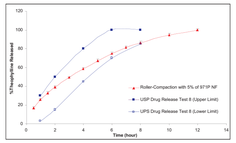


Figure 7. Theophylline release from roller-compaction tables (USP Test 8 methodology).

Ketoprofen Release:

Figure 8 shows the ketoprofen release profiles of roller-compaction tablets at various 971P NF levels. Increasing 971P NF level causes a slower drug release. When the 971P NF level is increased to 10% or above, the drug release cannot reach 100% even after 24 hours. The drug release rate of ketoprofen tablets is slower than that of theophylline tablets. This could be attributed to the lower solubility of ketoprofen as compared to theophylline.

Figure 9 compares the drug release properties of ketoprofen tablets produced by roller compaction and wet granulation with those of the commercial 200-mg ketoprofen capsule. The roller-compaction tablets containing 2.5% of 971P NF give slower drug release than the wet-granulated tablets containing 10% of 971P NF and the commercial ketoprofen capsules.

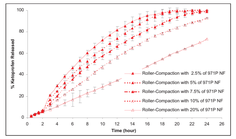


Figure 8. Ketoprofen release from roller-compaction tablets.

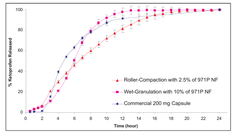


Figure 9. Ketoprofen release profiles of roller-compaction, wet-granulation tablets, and commercial capsules.

Conclusions

This work demonstrates that Carbopol® polymer-based, sustained-release tablets can be prepared by the roller compaction process. The roller compaction formulations exhibit good processability both during roller compaction and tablet manufacturing. A relatively low polymer loading (ca. 5% in theophylline formulation and 2.5% in ketoprofen formulation) is needed for roller-compaction tablets to achieve sustained drug release. The drug release profile *(USP Drug Release Test 8)* of the roller-compaction theophylline tablet is in conformance with the specifications of the USP "Theophylline Extended-Release Capsules" Monograph.