



# Lab-Scale to Full Production Scale Evaluation of a Controlled- Release Formulation Based on Hypromellose and Manufactured Using Roll Compaction Technology

*Paul Sheskey<sup>1</sup>, Kerry Pacholke<sup>1</sup>,  
Gary Sackett<sup>2</sup>, and Larry Maher<sup>2</sup>*

<sup>1</sup>*The Dow Chemical Company  
Larkin Laboratory  
Midland, MI 48674*

<sup>2</sup>*The Vector Corporation  
Marion, IA 52302*

# Purpose

Evaluate the impact of scale-up (lab-scale to pilot-scale to full production-scale) using Vector Corporation roller compaction granulation equipment on a matrix controlled-release (CR) tablet formulation based on METHOCEL\* K4M Premium CR Grade hypromellose<sup>†</sup> 2208, USP.

# Abstract

A theophylline CR formulation was dry-granulated using a Vector Corporation laboratory-scale (model TF-Mini) roller compactor. Roll pressure, screw speed, and roll speed were optimized and used to determine the direct scale-up equipment parameters. The tablet formulation was then scaled up to pilot-scale (model TF-156) and full production-scale (model TF-3012) roller compaction equipment. Direct scale-up involved the use of linear roll speed and compaction force per linear inch of roll width. Dry granulations were evaluated at 1X, 2X, and 4X the equipment variable settings established during the direct scale-up stage. Granulations and tablets prepared from the granulations were tested for physical properties and drug dissolution. Similarity in drug-release characteristics was determined using F2-Metric analysis. Accelerated and ambient stability tests were performed on prepared tablets.

# Materials and Methods

## Formulation:

- Model drug compound: Theophylline, USP, anhydrous powder (wt% = 50)
- CR polymer: METHOCEL K4M Premium CR Grade, USP 2208 (wt% = 30)
- Filler excipient: Fast Flo Lactose 316, NF (wt% = 19.75)
- Lubricant: Magnesium stearate, NF (wt% = 0.25)

## Mixing:

All mixes were performed in twin-shell blenders equipped with intensifier bars. Powders were mixed for a total of 10 minutes.

- lab-scale: 8-qt
- pilot-scale: 5 ft<sup>3</sup>
- full-scale: 20 ft<sup>3</sup>

## Tablet preparation:

- Manesty Beta Press (instrumented), 4000 lb (17.8 kN) applied upper punch force
- Tablet dimensions: 0.27 x 0.49 inches, oval (equivalent to NDA and ANDA products)
- Target tablet weight: 400 mg ± 3%

## Roll compaction and milling (Figures 1-3):

- Lab-scale: model TF-Mini/CoMil
- Pilot-scale: model TF-156/Vector rotary granulator
- Full-scale: model TF-3012/Colton 540 rotary granulator
- Roll compaction sequence for all trials is shown in Table I

## Drug dissolution:

- 6 tablets from each variable run and 3 tablet samples from each stability condition was performed using a dissolution system (model 2100, Distek, North Brunswick, NJ)
- Testing was performed in accordance with *USP 23/NF 18*, Official Monographs, Theophylline Extended-Release Capsules, Test 1 (for products labeled for dosing every 12 h). *USP Apparatus 2* (paddles), 50 rpm, three-prong clips, 900 mL of pH 1.2 simulated gastric fluid (without pepsin) for the first hour and pH 6.0 phosphate buffer thereafter, 37.5°C, with detection at 268 nm for theophylline
- Data were acquired via a diode array spectrophotometer (model 8452A, Agilent Technologies, Wilmington, DE)
- F2-Metric testing was performed on each variable run and stability sample. Comparisons were made using the TF-Mini (laboratory-scale) as the reference sample

## Stability conditions:

- Ambient condition 21°C/50% RH
- Accelerated conditions 40°C/75% RH
- Containers: 60-mL, translucent high-density polyethylene bottles. Polypropylene caps (33 mm) with polyethylene film foam liners were hand-tightened to activate pressure seals
- Testing intervals were: 0 (initial), 1, 2, 3, 6, 9, and 12 months

# Results

## Particle size distribution (PSD) (Figure 4 and Table II):

- Production-scale trials showed 28% of the granulation passing through a 100-mesh screen
- Pilot-scale trials showed 25%
- Laboratory-scale trials showed 18%
- Production-scale and pilot-scale milling used similar rotating bar operations
- Laboratory-scale milling used a rotating impeller operation
- PSD appeared to be a result of the type of mechanical operation of the mill and not the scale of the roll compactor equipment

## Tablet crushing strength:

- Direct compression of the original mix: 36 scu
- TF-Mini: 24 scu (lab-scale)
- TF-156: 25-30 scu (pilot-scale)
- TF-3012: 28-31 scu (production-scale)

## Tablet thickness:

- All tablet thickness values for all scales of roll compaction equipment tested were 0.227-inch, ± 0.005-inch

## Density:

- Ribbons generated from each scale of roller compactor equipment are shown in Figure 5
- Product density increased with roll compaction (Table II)
- Slightly higher tap density values for TF-3012 samples

## Tablet friability:

- The friability of all samples was less than 1% weight loss after 6 minutes of testing

## Drug dissolution:

- F2-Metric values for TF-Mini (laboratory) and TF-156 (pilot-scale) were greater than 80 (Figure 6)
- F2-Metric values for drug release from TF-Mini (laboratory) and TF-3012 (production-scale) formulations were greater than 50 (Figure 7)

## Stability testing:

- All F2-Metric values for all stability conditions were greater than 70
- Stability testing showed no major changes in tablet physical properties and drug release (Table III)

\*Trademark of The Dow Chemical Company

<sup>†</sup>Previously referred to as hydroxypropyl methylcellulose or HPMC.

## Scaling observations and resolutions:

- TF-Mini to TF-156
  - Roll force and roll speed scaled directly
  - TF-156 screw speed not directly scaled from the TF-Mini
  - Reduced screw speed on TF-156 to eliminate excessive powder feed to roll pair
  - Adjusted TF-156 screw speed to obtain quality ribbon
  - Established new roll speed as 1X setting on TF-156
  - Screw speed to roll speed ratio adjusted from 3:1 (TF-Mini) to 1.3:1 (TF-156)
- TF-156 to TF-3012
  - Roll force and roll speed scaled directly
  - Screw speed: used 2X TF-156 settings as 1X speed on TF-3012 due to minimal speed requirements in order to provide sufficient rate of powder feed to rolls
  - Used 1.3:1 screw-to-roll ratio (same as that used for the TF-Mini)

## Conclusions

- Results show that scale-up of a theophylline controlled-release formulation using roll compaction granulation equipment and containing METHOCEL K4M Premium had minimal problems.
- All tablets, regardless of equipment scale, exhibited acceptable physical characteristics.
- Dissolution profiles from ambient and accelerated stability for all formulations were essentially unchanged (F2 values all greater than 70).

## References

1. P. Sheskey, G. Sackett, L. Maher, K. Lentz, S. Tolle, and J. Polli, "Roll Compaction Granulation of a Controlled-Release Matrix Tablet Formulation Containing HPMC-Effect of Process Scale-Up on Robustness of Tablets and Predicted In Vivo Performance," *Pharmaceutical Technology-Yearbook 1999*. October p6-21.
2. Guidance for Industry SUPAC-MR: Modified-Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (September 1997).
3. Guidance for Industry SUPAC-IR/MR: Immediate-Release and Modified-Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum (draft guidance, April 1998).

Table I. Processing Parameters Used for Laboratory, Pilot-Plant, and Manufacturing Equipment

Trial #	1	2	3	4	5	6	7	8	9	10
Compactor model	TF-Mini	TF-156	TF-156	TF-156	TF-156	TF-156	TF-156	TF-156	TF-156	TF-156
Throughput (kg/h)	2	12	12	11	11	11	19	23	45	40
Roll speed (rpm)	6	4	4	4	4	4	8	8	16	16
Linear roll velocity (in./min)	74.2	74.2	74.2	74.2	74.2	74.2	148.4	148.4	296.8	296.8
Screw speed (rpm)	17.9	5.2	5.2	5.2	5.2	5.2	10.4	10.4	20.8	20.8
Screw speed to roll speed ratio	3:01	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1
Roll force (tons)	3	5.6	5.6	5.6	6.6	4.6	5.6	6.6	5.6	6.6
Force per linear inch (tons/in.)	3.1	3.1	3.2	3.2	3.8	2.7	3.2	3.8	3.2	3.8
Milling method	Rotating impeller	Rotating impeller	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar
Granulator screen (mesh, US Standard)	12	12	16	14	14	14	14	14	14	14
Granulator speed (rpm)	500	500	117	117	117	117	117	117	117	117
Trial #	11	12	13	14	15	16	17	18	19A	19B
Compactor model	TF-3012	TF-3012	TF-3012	TF-3012	TF-3012	TF-3012	TF-3012	TF-3012	TF-3012	TF-3012
Throughput (kg/h)	75	75	75	130	130	135	242	228	228	228
Roll speed (rpm)	4	4	4	8	8	8	18.4	18.4	18.4	18.4
Linear roll velocity (in./min)	148.5	148.5	148.5	297	297	297	683	683	683	683
Screw speed (rpm)	5.2	5.2	5.2	10.4	10.4	10.4	23.4	23.4	23.4	23.4
Screw speed to roll speed ratio	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1	1.3:1
Roll force (tons)	10.8	9.8	11.9	10.8	9.8	11.9	10.8	9.8	11.9	11.9
Force per linear inch (tons/in.)	3.1	2.8	3.4	3.1	2.8	3.4	3.1	2.8	3.4	3.4
Milling method	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar	Rotating bar
Granulator screen (mesh, US Standard)	14	14	14	14	14	14	14	14	14	14
Granulator speed (rpm)	87	87	87	87	87	87	87	87	87	87

Table II. Summary of Physical Testing of Original Mix and Granulations

Trial Description	Bulk Density (g/cm <sup>3</sup> )	Tap Density (g/cm <sup>3</sup> )	Compressibility Index (%)
ANDA Rx product	na	na	na
Original Mix	0.420	0.645	36
Trial 1, TF-Mini	0.610	0.802	24
Trial 2, TF-156	0.617	0.730	15
Trial 3, TF-156	0.516	0.697	26
Trial 4, TF-156	0.536	0.705	24
Trial 5, TF-156	0.546	0.683	20
Trial 6, TF-156	0.528	0.695	24
Trial 7, TF-156	0.539	0.690	22
Trial 8, TF-156	0.558	0.735	24
Trial 9, TF-156	0.558	0.715	22
Trial 10, TF-156	0.556	0.713	22
Trial 11, TF-3012	0.539	0.745	28
Trial 12, TF-3012	0.535	0.746	28
Trial 13, TF-3012	0.531	0.757	30
Trial 14, TF-3012	0.525	0.748	30
Trial 15, TF-3012	0.517	0.727	29
Trial 16, TF-3012	0.533	0.741	28
Trial 17, TF-3012	0.525	0.735	29
Trial 18, TF-3012	0.531	0.743	28
Trial 19A, TF-3012	0.526	0.741	29
Trial 19B, TF-3012	0.534	0.751	28

**Table III.** Summary of Stability Testing Results of Tablet Crushing Strength of Laboratory (TF-Mini), Pilot-Scale (TF-156), and Full-Scale (TF-3012) Tablets

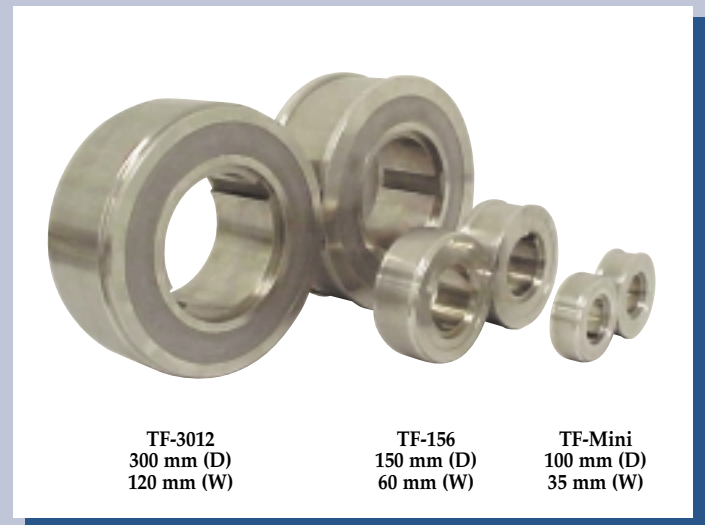
Stability Sample (Time, Condition)	TF-Mini Trial 1 (Laboratory-scale)	TF-156 Trial 4 (Pilot scale-1X)	TF-3012 Trial 12 (Full scale-1X)
Initial	24.3, 2.6	29.8, 2.0	30.6, 1.4
<i>Ambient</i>			
1-month	24.2, 1.2	31.0, 1.4	29.1, 3.0
2-months	24.7, 2.1	31.5, 2.1	27.1, 2.5
3-months	26.5, 1.7	30.2, 1.3	25.9, 1.4
6-months	26.3, 1.6	31.1, 1.3	23.8, 1.4
9-months	25.3, 2.9	28.6, 2.4	†
12-months	23.3, 2.1	30.7, 1.8	†
<i>Accelerated</i>			
1-month	24.9, 1.5	30.8, 1.9	26.2, 2.1
2-months	23.1, 2.0	30.5, 2.1	24.4, 1.5
3-months	24.8, 1.4	26.5, 2.1	24.4, 1.2
6-months	23.0, 1.6	27.3, 2.0	23.1, 1.2
9-months	22.3, 2.0	25.6, 1.5	†
12-months	21.8, 1.5	25.3, 2.3	†

†Ongoing

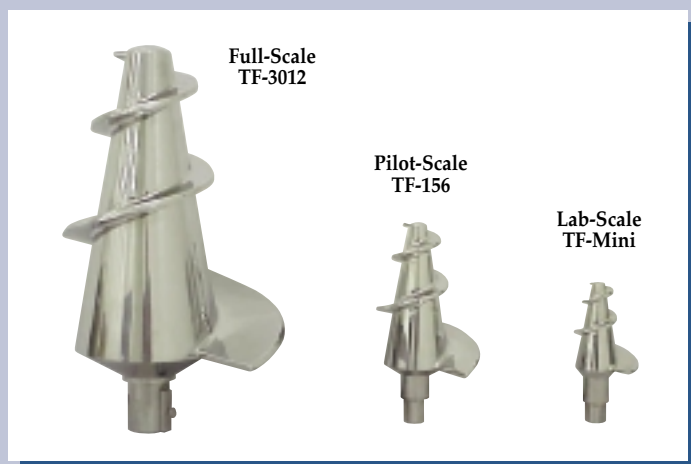
**Figure 1:** Comparison of Lab-Scale Roll Compaction Equipment (TF-Mini), Pilot-Scale Roll Compaction Equipment (TF-156), and Full-Scale Roll Compaction Equipment (TF-3012)



**Figure 2:** Comparison of Roll Size of Lab-Scale Roll Compaction Equipment (TF-Mini), Pilot-Scale Roll Compaction Equipment (TF-156), and Full-Scale Roll Compaction Equipment (TF-3012)



**Figure 3:** Comparison of Screw Size of Lab-Scale Roll Compaction Equipment (TF-Mini), Pilot-Scale Roll Compaction Equipment (TF-156), and Full-Scale Roll Compaction Equipment (TF-3012)



**Figure 4:** Particle Size Distribution of Granulations Prepared at Laboratory (TF-Mini), Pilot-Plant (TF-156), and Full-Scale (TF-3012) Conditions

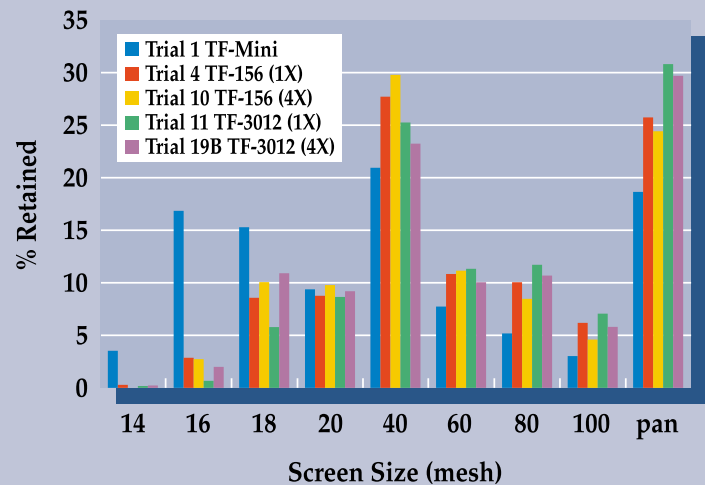


Figure 5: Comparison of Compacted Ribbon Size



Figure 6: Drug-Release From TF-Mini and TF-156 Formulations

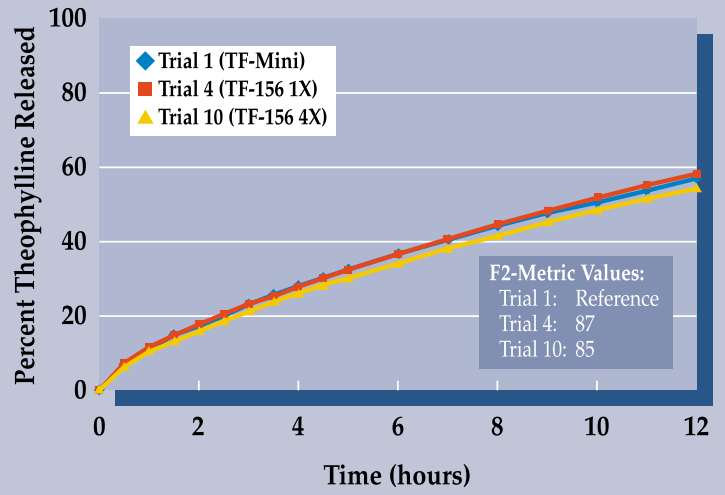
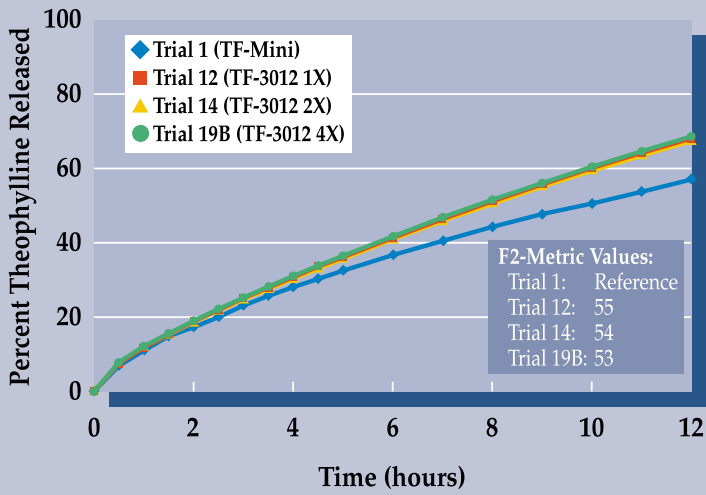


Figure 7: Drug-Release From TF-Mini and TF-3012 Formulations



**For more information, complete literature, and product samples,  
you can reach a Dow representative at the following numbers:**

From the United States and Canada: .....call 1-800-447-4369  
.....fax 1-989-832-1465

In Europe: .....call toll-free +800 3 694 6367†  
.....call +32 3 450 2240  
.....fax +32 3 450 2815

From Latin America and Other Global Areas: .....call 1-989-832-1560  
.....fax 1-989-832-1465

†Toll free from Austria (00), Belgium (00), Denmark (00), Finland (990), France (00), Germany (00), Hungary (00), Ireland (00), Italy (00), The Netherlands (00), Norway (00), Portugal (00), Spain (00), Sweden (00), Switzerland (00), and the United Kingdom (00).

**Or you can contact us on the Internet at [www.methocel.com](http://www.methocel.com)**

**NOTICE:** No freedom from any patent owned by Seller or others is to be inferred. Because use conditions and applicable laws may differ from one location to another and may change with time, Customer is responsible for determining whether products and the information in this document are appropriate for Customer's use and for ensuring that Customer's workplace and disposal practices are in compliance with applicable laws and other governmental enactments. Seller assumes no obligation or liability for the information in this document. **NO WARRANTIES ARE GIVEN; ALL IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE ARE EXPRESSLY EXCLUDED.**

