Manufacturing Scale Up of a Novel Drug Delivery System

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OBJECTIVE

To determine the suitability of manufacture of a novel solid oral delivery system at a scale intended for commercialization using operating parameters and conditions only from benchtop scale work.

General Background

Extension of drug product life cycles often involves modification of the drug delivery system. Modification of the release can be accomplished by either delaying or sustaining the release of the API, with many modern examples being the Cardizem CD[1] ® or Adderall XR[2] ® products. Other examples of life cycle extension are the rapid release Tylenol[3] ® product.

In this case study the client requested that Metrics develop and scale up prototype formulations and processes developed by a 3rd party that will change the dosage form from a hard gelatin capsule filled with two different multiparticulate formulations to a monolithic tablet. Due to requirements stipulated by the client, the prototype work was to be done at a benchtop scale with immediate conversion to a commercial scale with no pilot studies to be done whatsoever.

METHODOLOGY

Materials

Active Pharmaceutical Ingredient (API) X, supplied by client
Avicel ® Microcrystalline Cellulose, NF (Various PH grades supplied by FMC)
Partially Pregelatinized Starch, NF(Starch 1500® supplied by Colorcon)
Croscarmellose Sodium, NF (Ac-Di-Sol ® SD-711 supplied by FMC)
Magnesium Stearate, NF, (non-bovine), supplied by Mallinckrodt
Opadry® 03K19229 Clear, supplied by Colorcon
Acryl-EZE® 93F19255 Clear, supplied by Colorcon
Various reagent grade chemicals and solvents to execute required analytical testing

Manufacturing Equipment (Benchtop Scale/Commercial Scale)

20-mesh Hand Screen/ Vorti-Siv 15” sifter
Key KG-5 Vertical Shaft High-Shear Mixer/Fielder PMA-100 High Shear Mixer
GPCG-1 Fluid Bed Dryer/O’Hara Fluid Bed Dryer with 100 liter insert
Fitzpatrick Fitzmill L1A/ Fitzpatrick Fitzmill M
8 quart Twinshell Blender/15 Cubic Foot Tote Blender
Globe Pharma Mini-Press/Manesty Unipress
O’Hara M Coating Pan with 12” pan insert/ O’Hara Coating Pan with 48” pan

Analytical Equipment
Vankel Tap Density Tester
Hanson Flodex Flowability Tester
Key Hardness Tester
Standard USP Friabilator
Standard USP Disintegration Apparatus
HPLC system equipped with a UV detector, a column heater and a thermostated autosampler
Inertsil ODS-3 Column, 5 micron, 150 x 4.6 mm i.d.
USP Apparatus 2 Dissolution Bath
Olympus Model C2020Z Digital Camera

Background Formulation Information
The current drug product is supplied as a bead-filled hard gelatin capsule, delivering 30 mg of X immediately and the remaining 10 mg as delayed-release. The client supplied Metrics with formulation information for a new dosage form envisioned to be a single tablet with multiple layers of coatings in order to modify the release to make a new dosage form as a suitable candidate for *in vivo* bioequivalence studies. The client requested rapid turnaround of confirmation prototype batches followed by scale up batches and clinical trial batches for bioequivalence studies. See Table 1 below for a list of ingredients as supplied by the client and their functions in the new dosage form.

Table 1 – Formulation Information for Tablet Dosage Form

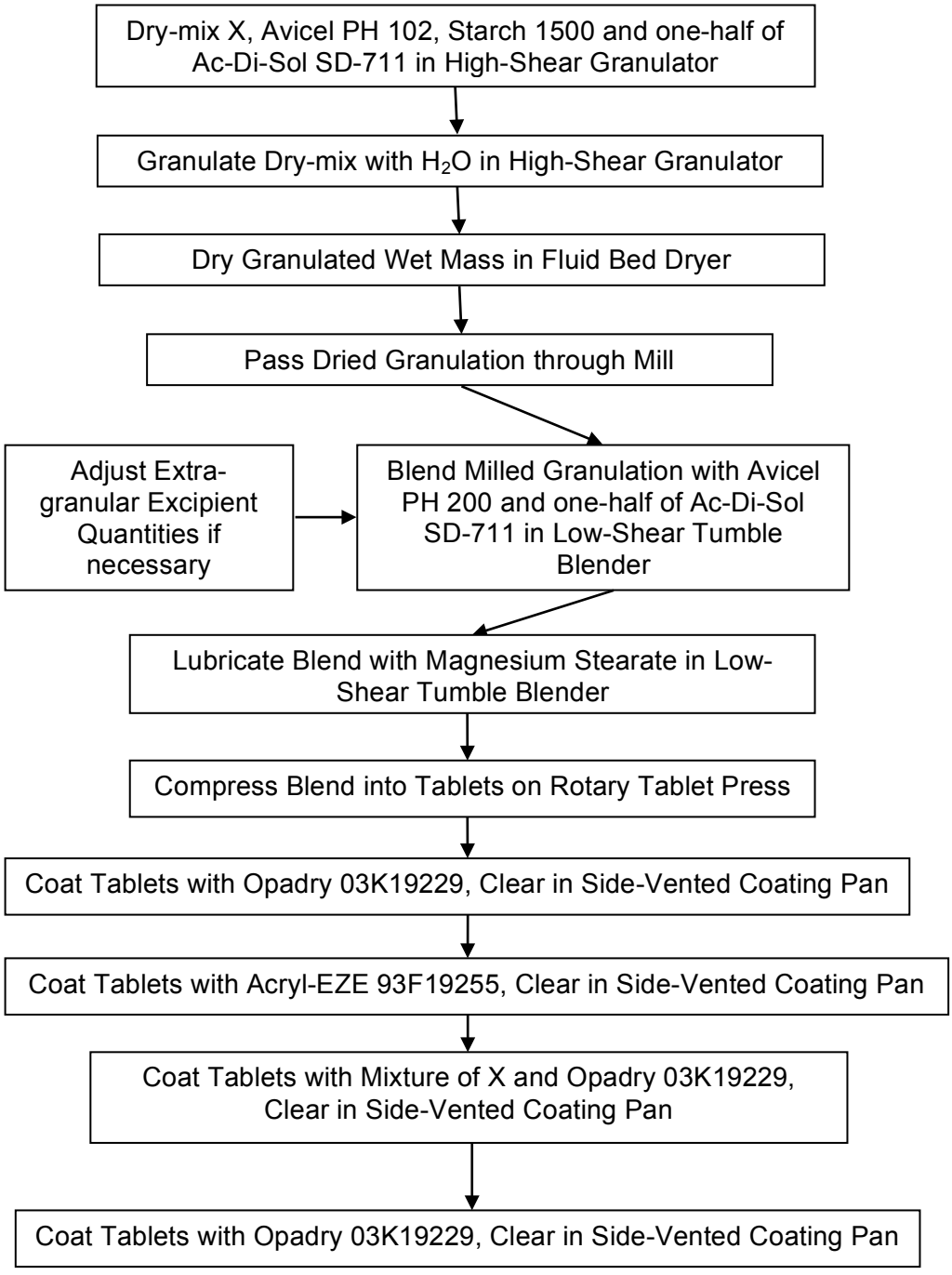
	Core Tablet	
Ingredient	**Typical Functionality**	**Amount per Tablet (mg)**
X	API (in Core Tablet)	10.00
Avicel PH 102	Diluent, Compressing Aid	53.00
Starch 1500	Diluent, Binder	20.00
Avicel PH 200	Diluent, Compressing Aid	12.50
Ac-Di-Sol SD-711	Super-disintegrant	4.000
Magnesium Stearate	Lubricant	0.5000
	Coating	
Ingredient	**Typical Functionality**	**Amount per Tablet (mg)**
X	API (in Outer Coating)	30.00
Opadry 03K19229, Clear	Coating	40.30
Acryl-EZE 93F19255, Clear	Delayed Release Coating Agent	12.50

The formulation information presented above reflects total per tablet quantities, the actual per batch quantities dispensed were dependent upon equipment size and multiple applications of coating ingredients. Dispensing of extragranular excipients was factored based on yield from final milling step compared to a theoretical yield of 100% in order to maintain per tablet quantities of these ingredients as listed above.

Manufacturing Procedures

A flowchart showing general operations for the manufacture of the tablets is given below in Figure 1.

Figure 1 – Flowchart for Manufacture of 40 mg Tablets



Manufacturing Specifics for Prototype Scale Manufacture
Using the flowchart above, Metrics chose the following equipment train for prototype scale batch manufacture. See Table 2 below for the individual pieces of manufacturing equipment used.

Table 2 – Equipment Train for Prototype Batch Manufacture
Scale = 15,000 Tablets (1.500 kg of Core Tablets)

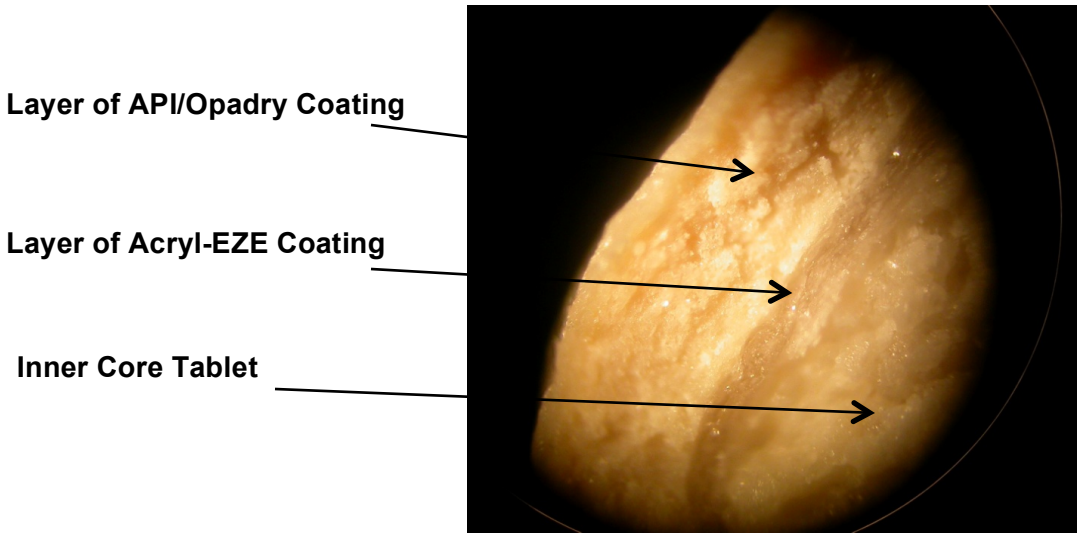
Unit Operation	Equipment	Select Parameters
High-Shear Granulation	KG-5 (~5 liter) – Two Portions	Impeller = 250 RPM Chopper = 1500 RPM
Fluid Bed Drying	GPCG-1 (~8 liter) – Two Portions	Inlet Temp = 60°C Target LOD = 2.5-4.5%
Milling	Fitzmill L1A	Screen = 0.033”
Low-Shear Tumble Blending	8-Quart	EG blend time = 12 mins Lubrication time = 2 mins
Compression	10-Station Mini-Press 0.25” Round Standard Concave Tooling	Speed = ~30 RPM Target Hardness = 4-8 kP
Tablet Coating	O’Hara 12” Coating Pan	Air Flow = 65-70 cfm Inlet Temperature for Opadry = 57-60°C Inlet Temperature for Acry-EZE = 45°C Pan Speed = 18-20 RPM Spray Rate = 8-14 mL/min

Manufacturing Specifics for Commercial Scale Manufacture
Metrics was able to convert the processes from the Prototype Scale to the envisioned Commercial Scale using similar pieces of manufacturing equipment at a substantially larger scale, with only minor differences in processing based on equipment restrictions. See Table 3 below for the individual pieces of manufacturing equipment used. See Figure 2 below for a cross-sectional view of a final coated tablet, with individual layers labeled.

Table 3 – Equipment Train for Commercial Scale Batch Manufacture
Scale = 1,300,000 Tablets (130.0 kg of Core Tablets)

Unit Operation	Equipment	Select Parameters
High-Shear Granulation	PMA-100 (~100 liter) – Five Portions	Impeller = II (High) Chopper = II (High)
Fluid Bed Drying	O'Hara (~100 liter) – Five Portions	Inlet Temp = 60°C Target LOD = 2.5-4.5%
Milling	Fitzmill M	Screen = 0.033" Speed Low/High
Low-Shear Tumble Blending	15 cubic foot Tote	EG blend time = 30 mins Lubrication time = 7 mins
Compression	27 Station Manesty Unipress 0.25" Round Standard Concave Tooling	Speed = ~93 RPM Target Hardness = 3-8 kP
Tablet Coating	O'Hara 48" Pan	Air Flow = 2300 cfm Inlet Temperature for Opadry = 57-60°C Inlet Temperature for Acry-EZE = 50-55°C Pan Speed = ~7 RPM Spray Rate = 300-475 mL/min

Figure 2 – Cross-sectional Photomicrograph of Finished Coated Tablet



RESULTS

Physical testing of the final lubricated blends was performed for the prototype scale and the commercial scale batches. A comparison of the data is shown in Table 4 below

Table 4 – Comparison of Physical Testing Done on Blends

	Prototype Scale	Commercial Scale
Bulk Density (g/mL)	0.453	0.486
Tapped Density (g/mL)	0.581	0.609
Carr Index (%)	22.0 % (Good Flow)	20.2% (Good Flow)
Flow by Minimum Orifice – Flodex (mm)	5 (Excellent)	4 (Excellent)

Data from core tablet physical testing comparing the prototype scale and the commercial scale batches are shown in Table 5 below.

Table 5 – Comparison of Physical Testing Done on Core Tablets

	Prototype Scale	Commercial Scale
Average Tablet Weight (mg) / RSD	102.2 / 0.73%	101.0 / 1.73%
Average Hardness (kP)	6.7	3.2
Standard USP Friability (%)	0.00	0.05
Gauge Thickness (mm)	3.86	3.22
Mean Disintegration Time in H_2O (sec)	36	112

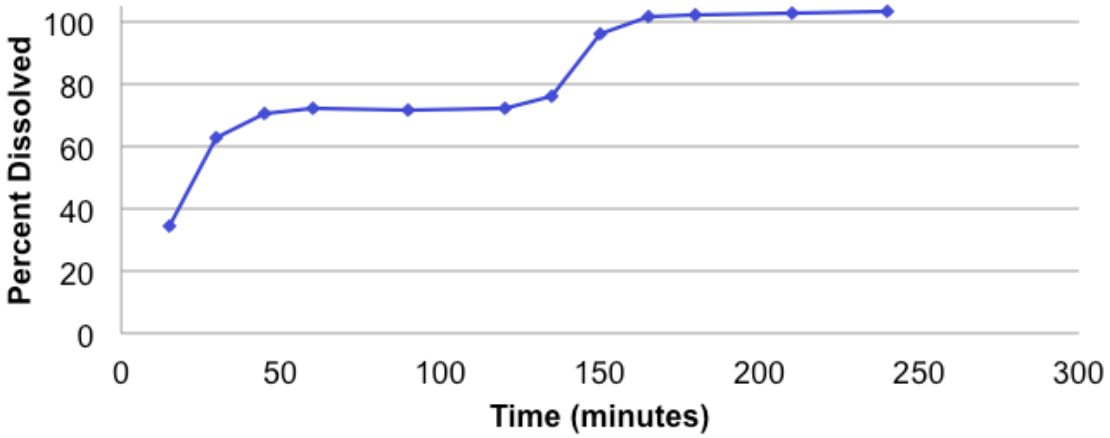
Chemical testing was performed on the prototype completed 40 mg modified release tablet product. See Table 6 below for a summary.

Table 6 – Testing and Results of 40 mg Prototype Scale Drug Product

Test	Result
Assay by HPLC	Prep 1 = 99.8% l.c., Prep 2 = 99.7% l.c.
Total Impurities by HPLC	Prep 1 = 0.45% l.c., Prep 2 = 0.46% l.c.
Uniformity of Dosage Units by Current USP <905>	Average = 99.3% l.c. Acceptance Value = 10.4%

Because the drug product is considered to be modified release, a dissolution method consisting of a pH adjustment from 0.1 N HCl to pH 6.0 buffer after two hours was developed by a 3rd party testing laboratory and transferred to Metrics. Specifications for the test were 60-85% dissolved at 2 hours and not less than 80% dissolved at 4 hours. See Figure 3 below for results of dissolution testing done on the prototype batch.

Figure 3 - Dissolution Profile of 40 mg Prototype Tablet



Chemical testing on the commercial scale core tablet batch consisted of an abbreviated blend uniformity profile and then a modification of a stratified sampling protocol per FDA draft Guidance[4]. See Table 7 below for blend uniformity profile test results from the 15 cubic foot tote blender and see Table 8 for stratified core tablet sampling in-process from the Manesty Unipress.

Table 7 – Blend Uniformity Data from Commercial Scale Batch
Spec from Guidance, n=10 samples, RSD < 5.0%, all units within 10% of mean

Test	Result
Blend uniformity – 30 minutes	
Top right	106% l.c.
Top left	103% l.c.
Middle right	100% l.c.
Middle left	102% l.c.
Bottom	102% l.c.
Blend uniformity – Lubricated Blend	
Top right	105% l.c.
Top left	100% l.c.
Middle right	101% l.c.
Middle left	102% l.c.
Bottom	103% l.c.

Table 8 – Core Tablet Stratified Sampling Data from Commercial Scale Batch
Specs from Guidance, Readily Pass (n=60 units) = RSD < 4.0%, each location mean within 10% of target, all samples between 75-125% of target
Specs from Guidance, Marginally Pass (n=140 units) = RSD < 6.0%, each location mean within 10% of target, all samples between 75-125% of target

Test	Result	Test	Result	Test	Result
Tablet 1	99% l.c.	Tablet 1	100% l.c.	Tablet 1	100% l.c.
Beginning – Tablet 2	100% l.c.	160 minutes– Tablet 2	101% l.c.	300 minutes – Tablet 2	101% l.c.
Tablet 3	101% l.c.	Tablet 3	101% l.c.	Tablet 3	101% l.c.
Tablet 1	99% l.c.	Tablet 1	99% l.c.	Tablet 1	99% l.c.
40 minutes – Tablet 2	100% l.c.	180 minutes – Tablet 2	100% l.c.	320 minutes – Tablet 2	99% l.c.
Tablet 3	101% l.c.	Tablet 3	100% l.c.	Tablet 3	101% l.c.
Tablet 1	101% l.c.	Tablet 1	100% l.c.	Tablet 1	101% l.c.
80 minutes – Tablet 2	99% l.c.	200 minutes – Tablet 2	101% l.c.	340 minutes – Tablet 2	100% l.c.
Tablet 3	100 % l.c.	Tablet 3	99% l.c.	Tablet 3	101% l.c.
Tablet 1	100% l.c.	Tablet 1	101% l.c.	Tablet 1	100% l.c.
100 minutes – Tablet 2	100% l.c.	220 minutes – Tablet 2	101% l.c.	360 minutes – Tablet 2	101% l.c.
Tablet 3	100% l.c.	Tablet 3	101% l.c.	Tablet 3	102% l.c.
Tablet 1	101% l.c.	Tablet 1	101% l.c.	Tablet 1	101% l.c.
120 minutes – Tablet 2	102% l.c.	240 minutes – Tablet 2	100% l.c.	380 minutes – Tablet 2	101% l.c.
Tablet 3	101% l.c.	Tablet 3	100% l.c.	Tablet 3	101% l.c.
Tablet 1	100% l.c.	Tablet 1	100% l.c.	Tablet 1	99% l.c.
140 minutes – Tablet 2	101% l.c.	260 minutes – Tablet 2	101% l.c.	400 minutes – Tablet 2	98% l.c.
Tablet 3	100% l.c.	Tablet 3	102% l.c.	Tablet 3	99% l.c.
		Tablet 1	101% l.c.	Tablet 1	101% l.c.
		280 minutes – Tablet 2	102% l.c.	End – Tablet 2	100% l.c.
		Tablet 3	99% l.c.	Tablet 3	101% l.c.

Discussion of Results
Physical testing data generated during both prototype and commercial scale data satisfied requirements of flowability and compressibility for the core tablet formulations. Chemical testing of the finished product at the prototype scale showed acceptable potency and dissolution. In-process chemical testing of the commercial scale product was conforming according to the modified testing program taken from guidance.

CONCLUSIONS

Using the scale up factors for key operating parameters taken from major unit operations resulted in a successful single-step scale up from benchtop to commercial scale manufacturing for a novel drug delivery system.

References:
1 – www.drugs.com/pdr/cardizem-cd.html
2 – www.adderallxr.com
3 – www.tylenol.com
4 – www.fda.gov/CDER/GUIDANCE/5831dft.htm