Design of Experiments: Critical Process Parameters Confirmation for the Scale-up Manufacturing of Solithromycin 200 mg Capsules

W4344

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ABSTRACT

Purpose: In the course of development, solithromycin 200 mg capsules were manufactured for use in clinical studies. To continue product development, a Design of Experiments (DOE) was used to establish the range of operation for critical process parameters (CPP) of the manufacturing process and the design space. It was of interest to confirm the operation ranges for the CPP by manufacturing a confirmation batch at the same scale as the planned registration batches.

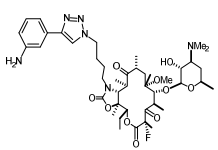
Methods: The manufacturing process of the solithromycin 200 mg capsules involves wet granulation, fluid bed drying, milling, blending (lubrication) and encapsulation. From the analysis of the DOE results, the optimal target and operational ranges for producing capsules that met the critical quality attributes (CQA) were established. Since the DOE batches were manufactured at the 5 kg-scale, the quantitative formula was scaled-up to the registration batch scale of 52 kg. The equipment and equipment parameters were scaled-up appropriately. The confirmation and registration batches were manufactured with intervals of sample testing and bulk samples were collected for release testing. Samples were analyzed for assay, blend uniformity, uniformity of dosage units and dissolution profile.

Results: Physical properties (bulk and tapped densities, particle size distribution), blend uniformity, uniformity of dosage units (by weight variation), assay, and dissolution profile were evaluated. The obtained tapped densities were comparable to those of the DOE batch used to generate the scale-up parameters and to the predicted values from the regression equation obtained from the DOE. For the confirmation batch, at least 99.73% of the in-process fill weight of the capsules were within the control limits, blend uniformity testing had a %CV of NMT 5% and the uniformity of dosage units across all the intervals had an Acceptance Value of NMT 15. The dissolution profiles were consistent with those of the clinical batches. All other in-process and finished drug product analytical results were also within the specifications.

Conclusions: The confirmation and registration batches confirm that the CPP and operational ranges identified from the DOE batches were scalable. The DOE batches identified operating ranges for CPP that are necessary to consistently produce capsules with predefined CQA.

INTRODUCTION

Solithromycin (Figure 1) is a fourth generation macrolide, the first fluoroketolide, which is in Phase 3 clinical trials for Community Acquired Bacterial Pneumonia (CABP). One of the dosage forms under development is an immediate release 200 mg hard gelatin capsule for oral administration. The formulation contains 200 mg solithromycin per capsule with the excipients Microcrystalline Cellulose, Croscarmellose Sodium, Sodium Lauryl Sulfate, Povidone, and Magnesium Stearate. As part of the capsule development work, the process for manufacturing solithromycin capsules 200 mg was optimized, and the operating ranges for the critical process parameters identified at the 5-kg scale, using a Design of Experiments (DOE) approach, consistent with Quality by Design (QbD) principles. In preparation for registration batches manufacture, it was essential to demonstrate that the process optimized at the 5-kg scale was scalable to the 52-kg scale.



Molecular Formula: $C_{43}H_{65}FN_6O_{10}$
Molecular weight: 845.02

Figure 1. Molecular Structure of Solithromycin

The purpose of these studies was to demonstrate that when scaled to the registration batch size of 52 kg, the manufacturing process produced drug product that met the pre-determined drug product specifications.

MATERIALS AND METHODS

The manufacturing process and the process equipment used is shown in Figure 2.

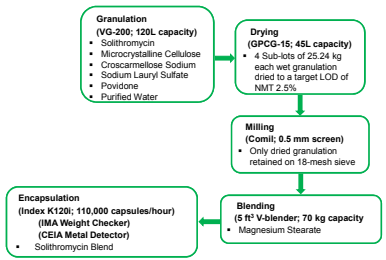


Figure 2. Manufacturing Process Flow Chart and Equipment Used

The parameters used for the manufacture of the scale-up batch were obtained through a DOE study. For the scale-up and ensuing registration batches, the amount of water used for granulation was approximately 99.4% w/w relative to the dry weight of the batch and the total kneading time was NMT 10 minutes. The process parameters for wet granulation are listed in Table 1. For the registration batches, however, all the water for a given batch was added at one time instead of two separate additions.

The wet granulation was divided into four sub-lots for drying in a fluidized bed dryer to NMT 2.5% moisture and sieved through an 18-mesh screen. The dried granulation retains were milled using a Comil equipped with a 0.5 mm screen. The four sub-lots of dried milled granulation were pooled and blended with the required amount of magnesium stearate for 3 minutes. The resulting blend was encapsulated into size 0 Capsugel hard gelatin capsules shells. This was followed by weight sorting and visual inspection. The process parameters for each of the processes (granulation through encapsulation) for the scale-up batch are listed in Table 1.

During the manufacture, extensive in-process, stratified and bulk capsules sampling was performed for moisture, bulk and tapped density, particle size distribution, blend uniformity, assay, uniformity of dosage units, polymorphism by XRPD, optical rotation and dissolution testing. The dissolution profiles for capsule samples collected at predefined intervals (Stratified sampling) and bulk release samples were obtained using USP Apparatus I (baskets) in 50 mM acetate buffer at pH 4.5, 50rpm, at 5, 10, 15, 20, 30, 45, 60 and 75 (∞ pull) minutes.

Sampling during the manufacture of the registration batches was similar to the sampling plan of the scale-up batch, with the following additions to the sampling plan:

i. Optical rotation testing of the blends
ii. Optical rotation testing of the bulk capsules
iii. Additional dissolution profile testing for the beginning (B), middle (M) and end (E) intervals of the stratified sampling

MATERIALS AND METHODS (cont'd.....)

Table 1. Manufacturing Process Parameters for the 52-kg Scale-up Batch

Process	Steps/Target	Recommended Parameters	Range	Actual Readings
Granulation (High Shear Granulator)	Screening (API and excipients) Target: Material Passes Through	20-mesh screen	NA	Materials passed through
	Dry mixing (VG 200); Target: 5 minutes	Impeller = 50 RPM	30 - 70 RPM	5 minutes
		Cross Screw off	NA	
	Main water addition (VG 200); Target: 4.1 minutes	Impeller = 125 RPM	100 - 160 RPM	4 minutes
		Cross Screw = 2500 RPM	2000 - 3000 RPM	
	Reserve Water addition to Pressure Pot; Target: N/A (not a typical step; kneading continued during this step)	Impeller = 125 RPM	100 - 160 RPM	2 minutes
		Cross Screw = 2500 RPM	2000 - 3000 RPM	
	Reserve Water addition (VG 200); Target: 2.2 minutes	Impeller = 125 RPM	100 - 160 RPM	2 minutes
		Cross Screw = 2500 RPM	2000 - 3000 RPM	
	Additional Kneading time after Reserve Water Addition; Target: 2 minutes	Impeller = 125 RPM	100 - 160 RPM	~1.3 minutes
		Cross Screw = 2500 RPM	2000 - 3000 RPM	
Drying in four sub-lots (Fluidized Bed Dryer)	Inlet air temperature	65 °C	60 - 70 °C	63.1-67.2 °C
	Process air volume	600 – 900 cfm	600 - 900 cfm	600-743 cfm
	Dew point	NMT 12 °C	NMT 12 °C	8.6-12.4 °C
	Product Temperature	48 °C	NLT 48 °C	52.1-58.8 °C
	Screening of dry granules	18-mesh sieve	NA	3-4 kg retained per sub-lot
Milling (Comil)	Milling of Dried Granulation Retains; Target: Material Passes Through	0.5 mm screen, 1500 RPM	NA, 1200 - 1800 RPM	Material passed through
Blending (V-blender)	Magnesium stearate Screening; Target: Material Passes Through	40-mesh screen	NA	Material passed through
	Blending; Target: 3 minutes	25 rpm	20-30 rpm	22 rpm, 3 minutes
Encapsulation (Capsule filler, Weight checker, Metal detector)	Empty Capsule shells	Size 0 hard gelatin capsules	NA	Size 0 hard gelatin capsules
	Average capsule shell weight	Average of 10 capsules	NA	93 mg
	Target Gross Filled Capsule Weight (GFW)	325 mg + empty capsule shell	NA	418 mg
	Filled capsule weight control	UCL = GFW x 1.05 LCL = GFW x 0.95	LCL - UCL	397-439 mg
	Weighting sorting			

RESULTS AND DISCUSSION

The results for the in-process testing, stratified samples testing, and bulk drug product testing for the scale-up and registration batches is listed in Table 2 and in Figures 3-7.

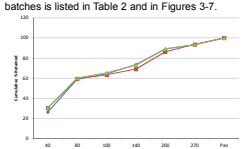


Figure 3. Trend Plot of Cumulative PSD Results for the Blend

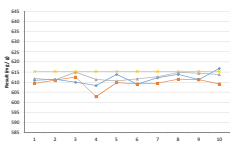


Figure 4. Trend Plot of Blend Uniformity Results for the Blend

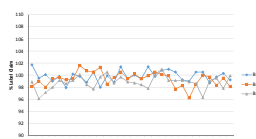


Figure 5. Uniformity of Dosage units for the Stratified Bulk Samples

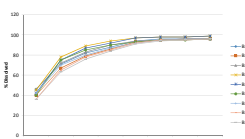


Figure 6. Dissolution Profiles for the Stratified Bulk Samples

RESULTS AND DISCUSSION (cont'd.....)

Table 2. In-process, Stratified and Bulk Drug Product Test Results for the Scale-up and Registration Batches

Process	Test	Specification	Results			
			Scale-up batch	Registration # 1	Registration # 2	Registration # 3
Granulation (Dried in 4 sub-lots)	Moisture (LOD)	NMT 2.5%	1.24 – 2.32%	1.64 - 2.32%	1.48 – 1.96%	1.60 – 1.76%
Blend (Pooled dry milled granulation)	Moisture (LOD)	For Information Only (FIO)	2.70%	2.72%	2.99%	2.44%
	Bulk Density	FIO	0.50 g/mL	0.50 g/mL	0.52 g/mL	0.51 g/mL
	Tapped Density	>0.58 g/mL	0.61 g/mL	0.63 g/mL	0.63 g/mL	0.65 g/mL
	Cumulative Particle Size Distribution (PSD) (See Figure 3)	FIO	40-mesh: 22.5% 80-mesh: 51.3% 100-mesh: 59.5% 140-mesh: 71.0% 200-mesh: 91.5% 270-mesh: 95.5% Pan: 99.7%	40-mesh: 26.2% 80-mesh: 59.0% 100-mesh: 64.4% 140-mesh: 73.6% 200-mesh: 89.1% 270-mesh: 93.3% Pan: 100.0%	40-mesh: 30.2% 80-mesh: 59.4% 100-mesh: 63.4% 140-mesh: 69.1% 200-mesh: 86.3% 270-mesh: 93.6% Pan: 100.0%	40-mesh: 30.4% 80-mesh: 60.2% 100-mesh: 65.4% 140-mesh: 72.9% 200-mesh: 89.3% 270-mesh: 93.4% Pan: 100.0%
	Blend Uniformity by HPLC (See Figure 4)	RSDs≤5.0%, and all individuals are within ± 10% of target (target: 615.4 mg/g)	(i) 618.9 (RSD = 0.81%) (ii) 618.1 (RSD = 0.28%) (in duplicate)	611.8 (RSD = 0.4%)	609.6 (RSD = 0.4%)	612.7 (RSD = 0.3%)
	XRPD	No Form II observed in the Qualitative powder pattern	Form II was not observed	Form II was not observed	Form II was not observed	Form II was not observed
	Optical Rotation	Report results	Not Performed	+0.345°	+0.343°	+0.349°
Encapsulation (Stratified)	Uniformity of Dosage Units (n=30) (See Figure 5)	Complies with USP <905> Acceptance Value (AV) ≤ 15.0	AV was between 2.0 -7.4 across the intervals	AV = 1.9	AV = 2.3	AV = 2.2
	Dissolution Profiles at Begin (B), Mid (M), and End (E) intervals (See Figure 6)	NLT 75% (Q) of the label is dissolved at 45 minutes (for single point dissolution)	Not Performed	96% (B) 95% (M) 95% (E)	98% (B) 98% (M) 95% (E)	95% (B) 95% (M) 94% (E)
Encapsulation (Bulk) (Release Testing)	Assay by HPLC	NLT 90.0% and NMT 110.0% of the label	100.8%	100.1%	97.9%	99.1%
	XRPD	No Form II observed in the Qualitative powder pattern	Form II was not observed	Form II was not observed	Form II was not observed	Form II was not observed
	Optical Rotation	Report results	Not Performed	+0.341°	+0.340°	+0.341°
	Dissolution Profiles (See Figure 7)	NLT 75% (Q) of the label is dissolved at 45 minutes (for single point dissolution)	97% (RSD = 1.3%)	96% (RSD = 1.0%)	95% (RSD = 1.5%)	94% (RSD = 1.1%)
	Moisture (LOD)	NMT 6% w/w	3.0%	3.3%	3.3%	3.3%
	Uniformity of Dosage Units	Complies with USP <905> Acceptance Value (AV) ≤ 15.0	AV = 3.1	AV = 2.4	AV = 3.4	AV = 2.1

All three registration batches met the acceptance criteria for Related Substances and the Microbial Limits Test per the drug product specification during release testing.

The encapsulation yield for the scale-up and registration batches is shown in Table 3.

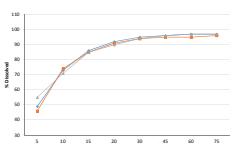


Figure 7. Dissolution Profiles for the Bulk Samples (Release Testing)

Table 3. Encapsulation Yield

Batch (Capsule Strength)	Accountable Yield (Specification: 95 - 105%)	Useable Yield (Report)	Production Report Results		
			Total Capsules	Good Capsules	Rejected Capsules
Scale-up (200 mg)	95%	74%	121,618	119,586	2,032 (1.7%)
Registration #1 (200 mg)	99%	93%	145,236	143,807	1,429 (1.0%)
Registration #2 (200 mg)	99%	87%	130,046	128,064	1,982 (1.5%)
Registration #3 (200 mg)	99%	94%	149,164	148,402	762 (0.5%)

CONCLUSION

The physical and analytical data for solithromycin capsules 200 mg, from the 52-kg scale-up batch and the three registration batches met the acceptance criteria of the drug product specification, thereby demonstrating that the manufacturing process is able to produce drug product that meets specifications and quality standards. Since these batches met all specifications, they were deemed successful.