

SCALE UP AND TECHNOLOGY TRANSFER OF ATORVASTATIN AND EZETIMIBE TABLETS

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Summary

The present study involves scale up and technology transfer for manufacture of atorvastatin and ezetimibe tablets. Study is conducted for critical steps, variables of manufacturing process and feasibility of manufacturing process. In the present study, it is found that considering worst case study, standardization, scale up and test batch for atorvastatin and ezetimibe, there was no significant difference in quality from laboratory scale to production scale.

Key Words: Scale up, Technology transfer, Atorvastatin, Ezetimibe

Introduction

Scale up is generally defined as the process of increasing the batch size. The American association of pharmaceutical scientists (AAPS) offered to assist the food and drug administration (FDA) in compiling the information necessary to support scale up/scale down of solid oral dosage forms¹. The SUPAC (scale up and post approval changes) task force was able to develop the SUPACIR (immediate release oral solid dosage forms) guidance, which was issued in November of 1995². The November 1999 guidance clearly states that the recommended reporting categories for component and composition changes provided in previously published guidances, such as the SUPAC guidances, still apply³. A study was conducted for multivariate modeling of wet granulation process and tableting optimization⁴. It is reported for need of optimization for the design and development of novel drug delivery system⁵. A study is performed on granulation and scale up. In the study, additional factors considered are specific surface area, moisture content, liquid saturation, intragranulator porosity, heating and apparent viscosity⁶. Pertaining to all these studies and guidances, present study is undertaken for scale up and technology transfer of atorvastatin and ezetimibe tablets.

Materials and Methods

Materials: Atorvastatin calcium trihydrate, ezetimibe (Dr. Reddy's lab, Hyderabad), calcium carbonate (J.J. Chemicals, Goa), lactose (Sun Chemicals, Mumbai), microcrystalline cellulose grade 114C TVR Pharmaceuticals, Pune), Croscarmellose sodium (Tel labs, Mumbai), hydroxy propyl cellulose (MSN laboratories, Hyderabad), sodium lauryl sulphate (Devi's laboratories, Uppal), magnesium stearate (Sun chemicals, Mumbai) and opadry YS-1-7040 white (Colorcon pvt. Htd., Mumbai) were obtained from commercial sources and used as received.

Methods: The methods include worst case studies, scale up studies, standardization and monitoring of test batches.

Worst Case Study

Table 1

Sampling Plan for Worst Case Studies

Stage	Time	Test to be performed	Sample size	Acceptance criteria
Blending (Trial 1,2& 4)	Final blending (lubrication)	Uniformity of content & RSD. Assay, Bulk Density, Angle of Repose and Sieve analysis	Each sample between 210 to 630mg. 100g from the blender	100 ±10% RSD, NMT6% -
	Over lubrication	Uniformity of content and RSD	210 to 630mg	-
Compression Lubricated blend (over & under granulated)	Tablet compressed at lower, higher and optimum thickness	Dissolution and disintegration	Trial 1: 40 tab Trial 2 : 40 tab Trial 4 : 40 tab	-
Over lubricated blend (trial 1 & 2) and trial 4 blend	Tablet compressed at optimum thickness after optimum blending tablet	Content uniformity	Trial 1 : 60 tab Trial 4 : 60 tab	100±10%, RSD, NMT 6%
	Compressed at over lubrication	Content uniformity	Trial 1 : 60 tab Trial 2: 60 tab	
Coating	At the end of 6mg, 7mg & 8mg of coating build up	Dissolution	Trial 5: 40 tab	

RSD = Relative Standard Deviation; NMT = Not More than; tab = tablets

Scale up Studies

Table 2
Sampling Plan for Scale –up Study

Stage	Process variable	Sampling Frequency	Test to be performed	Approx Sample size	Acceptance criteria
Dry mixing (Atorvastatin)	Mixing time	6,8& 10min interval	Content uniformity	Atorvastatin (100.84-302.52)	100 ±10% RSD, NMT 6%
		Final mixing interval	Bulk density, LOD, sieve analysis	Ezetimibe (82mg-246mg pool sample approx 100g)	
Granulation (Atorvastatin & Ezetimibe)	Mixing time impeller amperage	Granulation end point	Appearance of granules	NA	Granules formation evaluation (impeller amperage to be recorded)
Drying (Atorvastatin & Ezetimibe)	Inlet temperature out let temperature drying time	At every ten minutes interval till desired LOD is obtained at the end of the drying after achieving desired LOD	LOD at 60°C	Pooled of 10g from the different place of the bowl	LOD, NMT 3% w/w at 60°C
			LOD at 60°C	5 g from 5 different location of the bowl	NMT 3% w/w at 60°C
Blending	Blending time	20, 25min intervals (Pre-lubrication)	Content uniformity & RSD	210 mg to 630mg	100±10% RSD, NMT 6%
		Final blending (Lubrication)	Content uniformity & RSD assay & LOD Bulk density sieve analysis compressibility index, angle of response	130mg to 390mg Pooled sample Approximate 100gm pooled sample	100±10% RSD, NMT 6%
Compression	Machine speed	Pre-compression initially at different speed and then complete compression at optimum speed	Dissolution	6 tablets	As per current Specification
			Group weight, Individual	20 tablets	4.2g ± 3 % 210mg±5%
			Weight	30 tablets	NLT3kg/cm ²

			Hardness Thickness Disintegration Friability	6 tablets 30 tablets 6 tablets 20 tablets	3.6±0.2mm NMT 15 min NMT 1% w/w
	Hopper study	Full, middle, end hopper Initial, middle, end cycles	Dissolution Group weight, Individual weight Hardness Thickness Disintegration Friability Content uniformity	6 tablets 20 tablets 30 tablets 6 tablets 30 tablets 6 tablets 20 tablets 30 tablets	As per specification 4.2g± 3% 210mg ±5% NLT 3 kg/cm ² 3.6± 0.2mm NMT 15 min NMT 1% w/w As per specification
Coating	Inlet temperature, Exhaust temperature, Bed Temperature, Pan Speed, Atomization pressure, Spray rate, Gun distance, Peristaltic pump RPM	At the end of the process	Content uniformity Dissolution profile of tablets at 10, 20, 30, 45,60 min	50 tablet 75 tablet	As per current product release specifications

LOD = Loss on drying, NLT = Not less than, NMT = Not more than,
min = minute (s), RPM = Revolutions per minute

Process Standardization

Table 3

Sampling Plan for Process Standardization

Stage	Process variable	Sampling Frequency	Test to be performed	Approx Sample size	Acceptance criteria
Dry mixing (Atorvastatin & Ezetimibe)	Mixing time	10min interval 6 min interval Final mixing interval	Content uniformity Bulk density, LOD, sieve analysis	Atorvastatin (100.84 – 302.52) Ezetimibe (82mg-24mg) Pool sample approx 100g	100±10% RSD= NMT 6 %
Granulation (Atorvastatin & Ezetimibe)	Mixing time impeller amperage	Granulation end point	Appearance of granules	NA	Granules formation evaluation (impeller amperage to be recorded)
DRYING (Atorvastatin & Ezetimibe)	Inlet temperature out let temperature drying time	At every ten minutes interval till desired LOD is obtained at the end of the drying after achieving desired LOD	LOD at 60°C LOD at 60°C	Pooled of 10g from the different place of the bowl 5g from 5 different locations of the bowl	LOD, NMT 3% w/w at 60°C NMT is 3% w/w at 60°C
Blending	Blending time	25 min intervals (Pre-lubrication) 30 min intervals (Lubrication)	Content uniformity & RSD Content uniformity & RSD assay & LOD Bulk density sieve analysis compressibility index, angle of response	210mg to 630mg 130mg to 390mg Pooled sample Approximate 100g pooled sample	100± 10% RSD NMT 6% 100± 10% RSD NMT 6%

Continued Table 3

Compression	Machine speed	Pre-compression	Dissolution	6 tablet	As per current specification
	Machine speed (18 to 22 RPM)	At different speed and during compression optimum speed at regular interval	Group weight	20 tablets	4.2g ± 3%
			Individual weight	30 tablets	210mg±5%
			Hardness	6 tablets	NLT 3kg./cm ²
			Thickness	30 tablets	3.6±0.2 mm
			Disintegration	6 tablets	NMT 15min
			Friability	20 tablets	NMT 1% w/w
			Dissolution at	2*6 tablets	As per specification
	Hopper study	Full, middle, end hopper	Group weight	20 tablets	4.2g± 3%
			Individual weight	30 tablets	210mg ± 5%
			hardness	6 tablets	NLT 3kg/ cm ²
			Thickness	30 tablets	3.6 ± 0.2 mm
			Disintegration	6 tablets	NMT 15 min
			Friability	20 tablets	NMT 1% w/w
	Optimum speed	Initial, middle, end cycles	Content uniformity	30 tablet	As per specification
Coating	Inlet temperature, Exhaust temperature, Bed temperature, pan speed, atomization pressure, Spray rate, gun distance peristaltic pump RPM	At the end of the process	Content uniformity	50 tablets	As per current product release specifications
			Dissolution profile of tablets at 10, 20, 30, 45, 60 min	75 tablets	-

NA = Not applicable

Monitoring of Test Batches

Table 4

Sampling Plan for Monitoring of Test Batches

Stage	Process variable	Sampling Frequency	Test to be performed	Approx Sample size	Acceptance criteria
Dry mixing (Atorvastatin & Ezetimibe)	Mixing time	10 min interval 6 min interval Final mixing interval	Content uniformity Bulk density LOD, sieve analysis	Atorvastatin (100.84-02.52mg) Ezetimibe (82mg-246mg) Pooled sample approx 100 g	100±10%, RSD NMT 6%
Granulation (Atorvastatin & Ezetimibe)	Mixing time out let temperature drying time	Granulation end point	Appearance of granules	NA	Granules formation evaluation (impeller amperage to be recorded)
Drying (Atorvastatin & Ezetimibe)	Inlet temperature out let temperature drying time	At every ten minutes interval till desired LOD is obtained at the end of the drying after achieving desired LOD	LOD at 60c LOD at 60°C	Pooled of 10g from the different place of the bowl 5g from 5 different locations of the bowl	LOD, NMT 3% w/w At 60°C NMT 3% w/w at 60°C
Blending	Blending time	25 min intervals (Pre-lubrication) 30min intervals (Lubrication)	Content uniformity & RSD Content uniformity & RSD assay & LOD Bulk density sieve analysis compressibility index, angle of repose	210 mg to 630mg 130mg to 390mg Pooled sample Approximate 100gm pooled sample	100± 10% RSD=NMT 6% 100± 10% RSD NMT 6%

Continued Table 4

Compression	Machine speed	Pre-compression	Dissolution	6 tablets	As per current specification
	Machine speed (18 to 22 RPM)	At different speed and during compression optimum speed at regular interval	Group weight	20 tablets	4.2gm ± 3%
	Hopper study	Full, middle, end hopper	Individual weight Hardness Thickness Disintegration Friability	30 tablets 6 tablets 30 tablets 6 tablets 20 tablets	210mg±5% NLT 3kg./cm ² 3.6±0.2 mm NMT 15min NMT 1% w/w
	Optimum speed	Initial, middle, end cycles	Dissolution Group weight Individual weight hardness Thickness Disintegration Friability Content uniformity	6 tablets 20 tablets 30 tablets 6 tablets 30 tablets 6 tablets 20 tablets 30 tablets	As per specification 4.2g± 3% 210mg ± 5% NLT 3kg/ cm ² 3.6 ± 0.2 mm NMT 15 min NMT 1% w/w As per specification
Coating	Inlet temperature Exhaust temperature Bed temperature, pan speed, atomization pressure, Spray rate, gun distance peristaltic pump RPM	At the end of the process	Content uniformity	50 tablets	As per current product release specifications
			Dissolution profile of tablets at 10, 20, 30, 45, 60 min	75 tablets	-
Blister packing	Machine speed forming and sealing temperature	At different speed and during packing at every 2 hrs interval	Leak tests blister quality	-	As per BPR
		At the end of packing	Impurities	30 tablets	As per PRS

BPR = Batch packing record, hrs = hours, PRS = Product release specification

Results and Discussion

In worst case study, it is found that there is no impact on the content uniformity, disintegration and dissolution of the compressed tablets for all the trials.

Table 5

Summary of scale up, standardization and test batch parameters

Parameters		Scale up		Standardization		Test batches	
Dry mixing	API	Atorvastatin	Ezetimibe	Atorvastatin	Ezetimibe	Atorvastatin	Ezetimibe
	Mixing time	10 min	6 min	10 min	6 min	10 min	6 min
	Impeller speed	Fast	Fast	Fast	Fast	Fast	Fast
	RSD	1.89	1.58	0.8	1.1	0.9	1.7
	Equipment	RMG	RMG	RMG	RMG	RMG	RMG
	Capacity	40 Ltrs	40 Ltrs	40 Ltrs	40 Ltrs	40 Ltrs	40 Ltrs
Granulation	Amperage	5	3	-	-	-	-
	Impeller speed	Fast	Fast	Slow	Slow	Slow	Slow
	Chopper speed	Fast	Fast	Slow	Slow	Slow	Slow
	Equipment	RMG	RMG	RMG	RMG	RMG	RMG
	Capacity	40 Ltrs	40 Ltrs	40 Ltrs	40 Ltrs	40 Ltrs	40 Ltrs
Drying	Outlet	35 to 37°C	35 to 37°C	35 to 37°C	35 to 37°C	36 to 38°C	33 to 35°C
	Equipment	FBD	FBD	FBD	FBD	FBD	FBD
	Capacity	20 Ltrs	20 Ltrs	20 Ltrs	20 Ltrs	20 Ltrs	20 Ltrs
Blending	Blending time	25 min, 30 min		25 min, 30 min		25 min, 30 min	
	Blender RPM	21		20		20	
	Equipment	OCB		DCB		DCB	
	Capacity	120 Ltrs		125 Ltrs		125 Ltrs	
Compression	Machine type	20 station single rotary machine		20 station single rotary machine		20 station single rotary machine	
	Machine speed	18 to 24 RPM		18 to 24 RPM		18 to 24 RPM	
	Tooling type	D-type		D-type		D-type	
	Physical parameters of tablets	Comply with the specifications		Comply with the specifications		Comply with the specifications	

Coating	Equipment Name	Perforated auto coating	Perforated auto coating	Perforated auto coating
	Capacity	30 kg	36kg	36 kg
	Coating parameters	Comply with product release specifications	Comply with product release specifications	Comply with product release specifications
Packing	Type of packing	-	-	Blister packing
	Machine speed	-	-	40 to 70 cuts/min
	Packing parameters	-	-	Comply with as BPR

RMG = Rapid Mixer Granulator

FBD = Fluid Bed Drier

OCB = Octagonal Blender

DCB = Double Cone Blender

During scale up study, process standardization and test batch monitoring studies, all critical parameters are well established. It may be concluded that there is no significant difference in quality from laboratory scale to production scale in manufacturing of atorvastatin and ezetimibe tablets.

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