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Research Article

PROCESS VALIDATION OF ANTI- MALARIAL DRUG: ARTEMETHER (20 MG) AND LUMEFANTRINE (120 MG) TABLET.

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ABSTRACT

Product quality is the primordial intention of any industries and is achieved by Process Validation. The thumb rule says "Quality should be built into the product, and testing alone cannot be relied onto ensure product quality", so to assure that the final product is of best quality Process Validation plays an integral role which is part of quality assurance program in industries. The main objective of my research is to study process validation of Artemether (20 mg) and Lumefantrine (120 mg) tablet which has anti- malarial properties. The entire study of process provides assurance that the manufacturing process (includes quality parts and materials) and the entire procedure is suitable for intended purpose and is consistently producing a product meeting the predetermined specifications and quality attributes as per specified master formula record. This review provides information of various steps involved in validation like sifting, mixing, granulation, sizing, compression, and analyses of final finished products. During process careful attention to critical process parameters is required which includes uniformity in blend, bulk density, tapped density, flow property, uniformity of content, uniformity of dosage unit, average weight, thickness, hardness, friability, disintegration time, dissolution test, and assay. A product/ process shall be considered validated when 3 consecutive commercial scale batches is meeting the acceptance criteria and then the process is said to be in a state of control and is capable of producing the product consistently.

KEYWORDS

Artemether, Lumefantrine, Validation, Critical Process Parameter, Process Capability.

INTRODUCTION Kaur et al. (2012)

The concept of Process Validation started in early 1970s associated with current good manufacturing practice (cGMP). Development of drug product starts from discovery of drug, to testing in laboratory, preclinical studies in animals, clinical trials in human, registration by the regulatory bodies and their approval. Hence to control entire processes during drug development is important because it will have a greater effect on the quality. To improve the efficacy and safety of the drug product, regulatory officials established that there was a legal basis for requiring process validation and to examine its drug product for identity, strength, quality, purity and stability before release the drug product for commercial use. The concept of validation appeared in United States in 1978 but the origin of validation in the healthcare industry is after the failure of the process in terminal sterilization in the early 1970s. FDA has the authority and responsibility to inspect and to evaluate process validation. Several reasons for validating a product or a process includes: First, By Law manufacturer are required to conform to cGMP regulations. Secondly to make a profitable business, a manufacturer should avoids the possibility of rejected or recalled batches. Third, validation helps to ensure that the product obtained is uniform, reproducible and with quality inputs.

In 2008, the definition of Process Validation by FDA "Guidelines on General Principles of Process Validation" defines process validation as "establishing documented evidence which provides a high degree of assurance that a process will consistently produce a product meeting a predetermined specifications and quality attributes.

In 2011, the definition of Process Validation modified as: "A process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products"

Systematic Approach: Manufacturing Process requires Identification, measurement, evaluating, Documenting and re-evaluating a series of critical steps in the manufacturing process that require control to ensure reproducible final product.

Objectives of Process Validation: Patel et al. (2011)

To understand the Process Validation Concepts based on regulatory & scientific reasons.
To learn how to determine the critical process parameters (CPP).
To learn about the Sampling Plan and Acceptance Criteria for Process Validation.
To ensure a robust product which is highly reproducible over time

Elements of validation: Sharma et al. (2013)

Design Qualification (DQ): It may be considered as total building and facility specifications which are approved by the authorized persons of the client. The DQ is the first element of validation intended to specify that the equipment, system or facility is designed in accordance with the necessities of the user and Good Manufacturing Practice (GMP) guidelines.

Installation Qualification (IQ): It should refer to the empty premises. Validation of the finished, but empty premises will clearly indicate if the building, facility and the environment is capable of meeting the predetermined specifications. It is first tested to ensure that the equipment is supplied as per the design requirements/technical terms. The Engineer confirms that the equipment and components are supplied in accordance with the terms mentioned in (DQ). Installation Qualification is considered completed only when all the above said parameters are confirmed and documented as per the approved IQ protocol.

Operational Qualification (OQ): It refers to validation of equipped but non-operational premises. This is important to determine the air flow pattern in the critical areas associated with the processing equipment, lighting and sound levels should also be carried out.

Performance Qualification (PQ): It refers to validation of the operational premises. It is the final stage of qualification, which shows, how the equipment/system will perform when tested under simulated or actual production conditions also the total environmental quality which influence factors present.

Development/ Pilot Batches

⇩

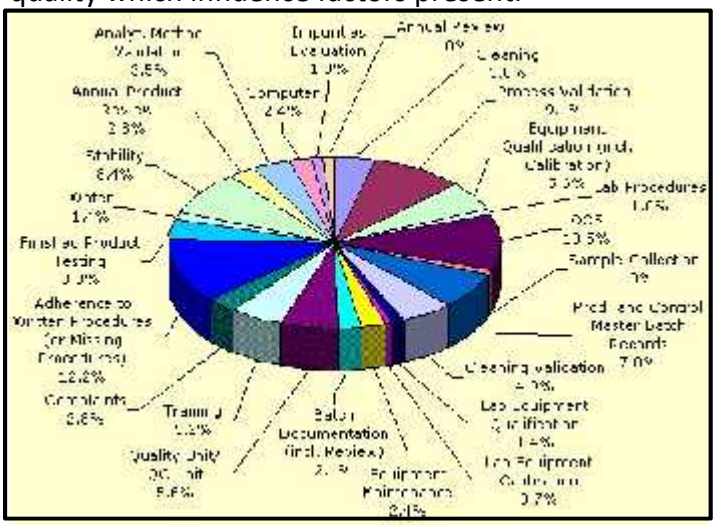
Identify critical parameters
Set Specifications
Establish Operating ranges

Full Scale Demo Batches

⇩

Validation Protocol

⇩



Validation Commercial Process

Figure. 1: Development of Process Validation

Figure. 2: Non-Compliance Issues

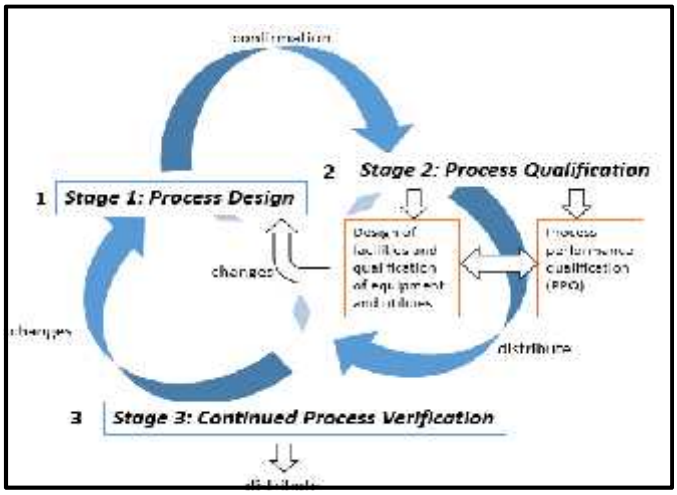


Figure. 3: Process Understanding

Figure. 4: Stages of Process Validation:

Stage 1 — Process Design
Stage 2 — Process Qualification
Stage 3 — Continued Process Verification

Advantages of Process Validation: **Verma et al. (2012)**

- Increase in product output
- Decrease in rejection and reworks
- Decrease in service costs
- Prevention of capital expenses
- Few complaints about process related failures
- Reduced inspection of in process and finished goods
- More abrupt and precise investigations into process nonconformities
- More abrupt and valid start-up of new equipment
- Easy to increase development work
- Easy to maintain the equipment
- Improved efficiency and productivity of process

Reason for Process Validation

The desirable reason of performing process validation may include:

- Existing products or new product as per SUPAC changes.
- Change in place of manufacturing.
- Change in batch size.
- Change in equipment/ Instruments.
- Change in raw material, packaging material.
- Change in composition or components.

- Change in the critical control parameters.
- Change in vendor of API or excipient.
- Change in standards on input material.

- Abnormality in quality parameters of product through review during Annual Product Review (APR).
- Aim of Out of Specification (OOS) or Out of Trend (OOT) in consecutive batches.

DR. CHAO: FOUR KEYS Alam (2012)

1 Definition---desirable attributes & undesired
2 Establishment of limitations or constraints for attributes
3 Determination of the controls or testing parameters used for measuring or testing
4 Initiation of studies to establish control or boundary limits for key attributes that influence product, process, quality and performance.

Subpart	Section of CGMPs	Qualification and control documentation
A	General provisions	
B	Organization and personnel	Responsibilities of the quality control unit
C	Buildings and facilities	Plant and facility installation and qualification Maintenance and sanitation Microbial and pest control
D	Equipment	Installation and qualification of equipment and cleaning methods
E	Control of components, containers and closures	Incoming component testing procedures
F	Production and process controls	Process control systems, reprocessing control of microbial contamination
G	Packaging and labeling controls	Depyrogenation, sterile packaging, filling and closing, expire dating
H	Holding and distribution	Warehousing and distribution procedures
I	Laboratory controls	Analytical methods, testing for release component testing and stability testing
J	Records and reports	Computer systems and information systems
K	Return and salvaged drug products	Batch reprocessing

Figure. 5: Checklist of Qualification and Control Documentation

MATERIALS AND METHODS

Manufacturing process in brief:

1. Raw Material sifting:

Mix and sift required Quantities of Artemether, Lumefantrine, MCC (B.P), maize starch (B.P) through 100# for 10 min. Sift lactose monohydrate and sodium starch glycolate through 40# using vibratory sifter.

2. Binder Solution preparation:

Take purified water in paste kettle. Add and dissolve in it Polysorbate 80. Take Purified water in SS tank. Disperse slowly HPMC 15 CPS. Keep dispersed aside for 60 min. Add Polysorbate 80 solution to HPMC 15 CPS under slow stirring for 15 min. take purified water in other RMG and boil. Disperse maize starch 1.140 Kg in 3L of purified water and make slurry. Add above slurry to boiling water with continuous stirring to

form a smooth translucent paste. Cool paste to 40˚C- 45 ˚C. Add additional purified water (1-5 L) and impeller and fast speed chopper. Mix the mass for about 1 min. at fast speed impeller and fast speed chopper to reach the end point.

2. Dry Mixing:

Load the sifted raw materials into RMG and Mix for 10 min. at slow speed for (50±2 RPM) with chopper off.

3. Wet mixing:

Add binder solution into RMG first and then add starch paste to dry mix in RMG. Mix till proper dough like consistency mass is obtained. Continue mixing till granulation end point is reached. If required purified water can be added to achieve granulation end point.

DETERMINATION OF GRANULATION END POINT:

A. Banana breaking test:

Precaution: Use hand gloves for this test.

Procedure: Take one handful of wet mass in the palm and press to form a lump. Open the palm and break the lump by pressing the thumb at the centre of the lump.

Observation: The lump shall break into small pieces.

At the end point of granulation,

a. Impeller: 29 Ampere
b. Chopper: 7 Ampere

B. Kneading Ampere Reading.

4. Drying:

Dry the wet granules in FBD at 55-65^{o}C inlet air temperature till the loss on drying (LOD) of the granules is achieved between 0.50- 1.50% (w/w) at 65^{o}C for 5 min.

5. Milling

Dried granules are milled in oscillating granulator using 20# sieve. Mill the retained granules on sifter through Multi mill using 1.00 mm/ 1.50 mm perforated screen.

6. Premixing

Milled granules are premixed for 5 min. using the bin blender.

7. Lubricants sifting:

Transfer the milled and sieved granules to octagonal blender. Sift lubricants through 40# using vibratory sifter, sift Cross Povidone, Purified Talc, Colloidal Anhydrous Silica, and Maize Starch separately and collect in a separate polybag.

8. Lubrication:

Mixing of Cross Povidone, Colloidal Anhydrous Silica, with premixed granules for 10 min. and mixing with Purified Talc for 2 min in bin blender.

9. Compression:

Compress the tablets using tablet compression machine. Compress the tablets at the average weight 105 mg ± 3.0 % double rotary compression machine 45 station D/B tooling.

MACHINERIES USED

Vibratory Sifter (300-500 per hours) (Pharm Tab), Rapid Mixer Granulator (Bowmen and Archer), Binder preparation vessel (Pharma Tab), Fluid bed dryer (Bowmen and Archer), Granulator (Kanath Eng.), Octagonal blender (Macwell Pharma), Tablet Compression Machine (Samdevang), Tablet Deduster machine (Omega Pharma), Metal Detector (Technofore electronic).

UTILITIES

HVAC System (ABB), HVAC System (ABB), Compressed air System (Ingersoll-Rand), Purified water System (Christnisotec).

INSTRUMENTS USED FOR ANALYSIS

HPLC (Shimandzu), Weighing Balance (LCGC Radwag), Disintegration Apparatus (Electro-Lab), Disintegration Apparatus (Electro-Lab), UV Spectrophotometer (Perkin Elmer), Sieve Shaker (Elactron Pharma), Tap Density Tester (Electro-Lab), Friability Apparatus (Electro-Lab), Hardness Tester (Pharmatron), Moisture Balance (Sartorins), Vernier Caliper (Mitntoyo).

PROCESS STAGES, CONTROL VARIABLES AND MEASURING RESPONSE / JUSTIFICATIONS [21-23]

Following process parameters will be monitored during the manufacturing process

Table no. 1: Critical Control Parameter

Stage	Step	Control Variables	Measuring Response/Justifications
Granulation	**Dry mixing**	Time	Uniform distribution of active ingredients with excipients
	Wet mixing	Mixer speed	Proper mixer speed is required so that mixing and binding is completed in optimal mixing time
		Mixing time	Over mixing / under-mixing will greatly affect the granular composition and characteristic of the granules. Checked by Ampere reading at end point consistency of wet mass.
	Drying	Inlet and outlet temperature	Control of inlet air temperature is greatly essential for drying of the granules.
		Drying time	Over or under drying of the granules leads to compression problem.
			Check by LOD of dried granules.
	Sizing	Speed of the blade	More or less fines leads to compression problem & flow property of the granules.
	Lubrication	Mixing time	Control over mixing time and speed of mixer determines the distribution of lubricants in overall mix, which is very essential to achieve blend uniformity and trouble free compression. **Check by** Description, content uniformity, sieve analysis, untapped and tapped density and LOD
		Sequence of the addition of the lubricants (Premixing, before addition of magnesium stearate, after addition of magnesium stearate)	Yield of lubricated granules.

Table no 2: List of Raw Materials and their Functions

Item code	Ingredients	Quantity/ Tablet (mg)	Quantity/Batch (Kg)	Use
DRY MIXING				
1ARTE02	Artemether	20	36.00	Active pharmaceutical ingredient
1LUM101	Lumefantrine	120	216.00	Active pharmaceutical ingredient
1STAR01	Maize starch BP	20.00	36.00	Diluent/ Binder/ Disintegrant
1MICRO3	Microcrystalline cellulose	62.90	113.220	Emulsifier/Bulking agent
WET GRANULATION				
1HYDR14	Hydroxyl Propyl Methyl Cellulose 15 CPC BP	7.50	13.500	Lubricant/ Thickening agent/ Viscocity enhancer
1TWEE01	Polysorbate 80 (Tween 80 BP)	1.00	1.800	Emulsifier
1STAR01	Maize starch BP (paste preparation)	2.140	4.320	Binder
RE410	Purified water	q.s	q.s	Vehicle
BLENDING/ LUBRICATION				
1CROSO1	Cross Povidone	10.00	18.00	Disintegrant/dissolution enhancer
1COLL01	Colloidal anhydrous silica BP	1.20	2.160	Adsorbent/Disintegrant/Binder/anti-caking agent
1TALC03	Purified Talc	3.00	5.400	Glidant
1MAGN13	Magnesium Stearate	2.00	3.600	Glidant
1STAR01	Maize starch	4.032	5.094	Binder

SAMPLING PLAN:-

During the manufacturing process of Artemether (20 mg) and Lumefantrine (120 mg) tablet various samples were collected to perform various tests.

Table no. 3: Sampling plan

Process step	Equipment	Sampling plan	Monitoring/ evaluation parameter
Dry mixing	RMG	From total 11 locations sample quantity is taken: at least equivalent	Content of active ingredients in dry mix

		to 1-3 times the dosage unit. Average weight of single dosage unit: 250 mg Composite samples 3 gm. 4 samples from Top,3 samples from middle and 3 samples from bottom	
Wet mixing	RMG	-	Appearance of wet mass
			Ampere reading at the end of granulation end point
Wet milling	Multi mill		Size of screen used
Drying	FBD	Collect 5 gm of sample from 3 different locations of FBD as mentioned in the sampling plan	Loss of drying
			Inlet and outlet temperature
			Total drying time
Sifting & sizing	Vibratory sifter & multi mill		Size of sieve used
			Total sizing time
Lubrication	Octagonal blender	Collect approximately 3 times of unit dose sample quantity required for analysis from octagonal blender using sampling device.	Content of active ingredients in lubricated granules.
		Composite sample of approximately 20g from all the 10 sampling points.	LOD/sieve analysis, bulk density, granules flow properties.
Compression	Compression machine	Composite tablets for challenge study of low and high operational range	(test carried out by IPQA)
		3 tablets each at initial, middle and end stage of compression	Assay and dissolution rate in QC
		4 tablets each at initial, middle and end stage of compression	Thickness
Compression	Compression machine	*10 tablets each at initial, middle and end stage of compression	Friability
		4 tablets each at initial, middle and end stage of compression	Hardness
		3 tablets each at initial, middle and end stage of compression	Average weight
		#80 tablets each at initial, middle and end stage of compression	Uniformity of weight
		4 tablets each at initial, middle and end stage of compression	Disintegration test
		$ approximately 100 tablets (composite sample)	Complete analysis in QC

RESULTS AND DISCUSSION

Table no. 4: Observations and Acceptance Criteria for Hardness Challenge Study

BATCH-1				
Test	Acceptance criteria	Observation		
		Min speed	Optimum speed	Max speed
Machine speed	Minimum speed	15 RPM	20 RPM	25 RPM
	Turret speed	15 RPM	20 RPM	25 RPM
Compression force	Pre compression force	-	-	-
	Main compression force	4.63 k N	6.43 k N	5.21 K N
Appearance	Yellow colored, circular, uncoated, flat, beveled edges tablet, having break line on one side and plain on other side.	Complies	Complies	Complies
Average weight	231.3 mg- 268.7 mg ± 5 %	251.1 mg	250.9 mg	250.8 mg
Uniformity of weight	Within ± 5 % of average weight	Min:247 mg Max:252 mg	Min: 246 mg Max:254 mg	Min:247 mg Max:252 mg
Diameter	9.10 mm- 9.50 mm ± 0.2 mm	Max:9.31 mm Min: 9.36 mm	Max:9.32 mm Min: 9.35 mm	Max: 9.32 mm Min: 9.34 mm
Thickness	2.80mm-3.20 mm ± 0.3 mm	Max: 2.98 mm Min: 3.04 mm	Max: 2.95 mm Min: 3.02 mm	Max: 2.97 mm Min: 3.041mm
Hardness	NLT 30.0 N	Max: 57.0 N Min: 68.5 N	Max: 54.5 N Min: 63.1 N	Max: 55.3 N Min: 65.5 N
Friability	NMT 1.0 % w/w after 100 drops	0.01 % w/w	Nil	Nil
Disintegration time	NMT 15 minutes	2min 23 sec.	2min 56 sec.	2min 43 sec.
Dissolution	NLT 60% dissolved in 45 min			
Content Uniformity	More than 15 for first 10 dosage unit. % RSD= NMT 3%			

Table no. 5: Batch yield of compressed tablets

Batch No.	A	B	C
Yield	97.75 %	96.56 %	97.64 %

MIXING:-

Table no. 6: Results of Dry Mixing (Blend uniformity)

Sr. no	Sampling point	Batch 1		Batch 2		Batch 3	
		LOT A	LOT B	LOT A	LOT B	LOT A	LOT B
1.	Top Left Back	99.0%	100.0%	97.0%	98.3%	99.6%	100.7%
2.	Top Left Front	101.2%	100.9%	98.3%	98.2%	98.1%	98.3%
3.	Top Right Back	101.1%	100.5%	98.5%	98.3%	97.5%	97.3%
4.	Top Right Front	101.4%	99.6%	98.3%	97.5%	97.5%	98.5%
5.	Top Middle	101.0%	100.9%	96.8%	98.0%	99.4%	1000.0%

6.	Middle Middle	101.3%	102.3%	98.2%	99.1%	102.7%	102.3%
7.	Middle Right Back	101.4%	99.6%	97.4%	97.4%	101.4%	101.8%
8.	Middle Right Front	101.6%	100.4%	98.1%	98.6%	96.4%	98.3%
9.	Middle Left Back	102.0%	101.7%	97.5%	99.3%	100.0%	101.0%
10.	Middle Left Front	101.3%	101.3%	97.0%	98.0%	100.8%	101.5%
11.	Bottom Middle	101.1%	99.6%	97.6%	97.6%	98.9%	100.8%
	Average	101.1%	100.6%	97.77%	98.97%	99.30%	100.09%
	SD	1.38439718	1.18958	1.32837	1.38327	1.0478	1.17988
	% RSD	0.75%	0.89%	0.62%	0.63%	1.89%	1.68%

Limit: (% Content uniformity) (by HPLC) 90.0 % - 110.0 % of label amount, RSD: NMT 5.0 %
Mean of individual test result: 97.0 % - 101.0 %.
Hence 5 min dry mixing time at slow speed (50±2 RPM) with chopper off shall remain validated.

DRYING:-

Table no. 7: Results of LOD

Sr. no.	Sampling location	Batch 1		Batch 2		Batch 3	
		LOT A	LOT B	LOT A	LOT B	LOT A	LOT B
1.	Left	0.98	0.90	0.92	0.97	0.88	0.94
2.	Right	0.96	0.92	0.94	0.98	0.90	0.92
3.	Centre	0.97	0.90	0.98	0.97	0.92	0.93
4.	Front	0.98	0.92	0.99	0.96	0.98	0.92
5.	Back	0.99	0.94	0.98	0.97	0.92	0.94
6.	Composite	0.92	0.92	0.94	0.95	0.94	0.92

Limit: 0.5-1.5 % w/w at 65°C for 60 min.
The drying time observed in the range of 50-72 min (limit: 20-60 min) for each lot manufactured.
Hence drying parameter within the inlet temperature 55-65^{o}C remain validated. Outlet temperature of 45-55^{o}C.

SIZING:-

Stage	Results								
	Batch no: AR6051			Batch no: AR6052			Batch no: AR6053		
	Lot-I	Lot-II	Lot-III	Lot-I	Lot-II	Lot-III	Lot-I	Lot-II	Lot-III
Wet mixing Add quantity of purified water.	NA	NA	NA	NA	NA	NA	NA	NA	NA
Total quantity of purified water added	85.0 kg	85.0 kg	85.0 kg	85.0 kg	85.0 kg	85.0 kg	85.0 kg	85.0 kg	85.0 kg
Duration of wet mixing									

➢ Impeller slow without chopper ➢ Impeller slow with chopper ➢ Additional mixing with addition of water	05 min 02 min NA	05 min 02 min NA	05 min 02 min NA	05 min 02 min NA	05 min 02 min NA	05 min 02 min NA	05 min 02 min NA	05 min 02 min NA	05 min 02 min NA
Endpoint value (Ampere)	30˚A	30˚A	30˚A	30˚A	30˚A	30˚A	30˚A	30˚A	30˚A

LUBRICATION:-

Table no. 8: Results of Blend Uniformity of Lubrication Stage

Sr. No	Sampling location	Batch 1	Batch 2	Batch 3
1.	Top (Left)	98.9 %	99.7 %	99.3 %
2.	Middle (Left)	97.9 %	98.1 %	100.1 %
3.	Bottom (Left)	98.3 %	100.2 %	97.7 %
4.	Top (Rear)	98.5 %	99.9 %	98.4 %
5.	Bottom (Rear)	99.8 %	98.5 %	100.5 %
6.	Top (Front)	101.5 %	99.7 %	98.2 %
7.	Bottom (Front)	99.1 %	101.7 %	98.7 %
8.	Top (Right)	99.2 %	98.4 %	100.2 %
9.	Middle (Right)	100.8 %	100.8 %	98.4 %
10.	Bottom (Right)	98.2 %	99.9 %	98.8 %
	AVERAGE	99.22	99.69	99.03
	SD	1.16886	1.11699	0.95225
	% RSD (NMT 5.0 %)	1.17804	1.12046	0.96158

Limit: (%LC) (by HPLC) 90.0%-110.0 % of label amount, RSD: NMT 5.0 %
Mean of individual test result: 99.0 %-105.0 %.

COMPRESSION:

Run	Test to be performed
IPQA	
Minimum, optimum, maximum speed	Appearance, average weight, uniformity of weight, hardness, thickness, friability, diameter, DT
QC Lab	
Optimum speed Start	Appearance, average weight, uniformity of weight, hardness, thickness, friability, diameter, DT **(SAMPLE QUANTITY: 150)**

Middle	Appearance, average weight, uniformity of weight, hardness, thickness, friability, diameter, DT
End	Appearance, average weight, uniformity of weight, hardness, thickness, friability, diameter, DT
During compression test	3 Tablet (initial)+ 4 Tablet (middle)+ 3 Tablet (end) for QC analysis
For Dissolution	2 Tablet (initial)+ 2 Tablet (middle)+ 2 Tablet (end) during compression and send for QC analysis

Table no. 9: Sieve Analysis on Composite Sample

Sieve Analysis	**% Passed through**		
	Batch 1	Batch 2	Batch 3
Mesh 20 (425 µ)	78.34 %	77.87 %	78.98 %
Mesh 40 (250 µ)	72.19 %	74.78 %	73.86 %
Mesh 80 (180 µ)	68.71 %	67.93 %	69.85 %
Mesh 100 (150 µ)	64.74 %	65.64 %	64.94 %
Sieve Analysis	**% Retained**		
	Batch 1	Batch 2	Batch 3
Mesh 60 (250 µ)	27.81 %	27.96 %	28.81 %
Mesh 100 (150 µ)	36.56 %	35.67 %	34.26 %

Table no. 10: Bulk density and LOD

Batch No.	**A**	**B**	**C**
P – bulk density g/ml (untapped)	0.67 gm/cc	0.67 gm/cc	0.63 gm/cc
Pt – bulk density g/ml (tapped)	0.78 gm/cc	0.78 gm/cc	0.73 gm/cc
LOD (0.5- 1.5 % w/ w) at 65˚C	0.88 %	0.81 %	0.86%

Table no. 11: Angle of Repose

Batch No.	A	B	C
Angle of repose	26.28 ˚	26.00 ˚	24.44˚

Table no. 12: % Compressibility

Batch No.	**A**	**B**	**C**
% Compressibility = $\left(\frac{\quad}{\quad}\right)$ 100	18.04	19.86	16.27

Table no. 13: Observations and Acceptance Criteria for in process test (QC)

Test	**Observation**			**Acceptance criteria**
Batch	**A**	**B**	**C**	
Assay	99.3 %	98.8 %	100.9 %	90.0-110.0 % of the labelled amount
Dissolution	Min: 98.2 % Max: 100.8 %	Min: 99.8 % Max: 101.8 %	Min: 99.2 % Max: 104.6 %	NLT 60% (Qty. of the labeled amount of Artemether and Lumefantrine is dissolved in 45 min)

Table No. 14: For initial, middle, end samples for dissolution

Test	**Acceptance criteria**		**Observation**

Dissolution of Artemeter for 60 min	NLT 60% dissolved in 60min	Initial	Tablet-1	98.0%
			Tablet-2	98.0%
		Middle	Tablet-3	96.2%
			Tablet-4	94.4%
		End	Tablet-5	98.1%
			Tablet-6	94.4%
		Minimum		94.4%
		maximum		98.1%
Dissolution for 45min Lumefantrine	NLT 45% in dissolved 45min	Initial	Tablet-1	72.5%
			Tablet-2	69.4%
		Middle	Tablet-3	71.4%
			Tablet-4	74.5%
		End	Tablet-5	72.2%
			Tablet-6	72.8%
		Minimum		69.4%
		Maximum		74.5%

Table no. 15: Observations and Acceptance Criteria for in process test (QC) for tablet

Test	**Observation**			**Acceptance Criteria**
Batch	**A**	**B**	**C**	Yellow colored, circular, uncoated, flat, beveled edges tablet, having break line on one side and plain on other side.
Appearance	Confirms	Confirms	Confirms	
Average weight	251.1 mg	250.9 mg	250.8 mg	250 ± 5%
Uniformity of weight	Min:247 mg Max:252 mg	Min: 246 mg Max:254 mg	Min:247 mg Max:252 mg	Within ± 5 % of average weight
Diameter	Max:9.31 mm Min: 9.36 mm	Max:9.32 mm Min: 9.35 mm	Max: 9.32 mm Min: 9.34 mm	9.5 ± 0.2 mm
Thickness	Max: 2.98 mm Min: 3.04 mm	Max: 2.95 mm Min: 3.02 mm	Max: 2.97 mm Min: 3.07 mm	3.0 ± 0.3 mm
Hardness	57.0 N	63.1 N	65.5 N	NLT 30 N
Friability	0.23 % w/w	0.22 % w/w	0.21 % w/w	NMT 1.0 % w/w
Disintegration time	1min 50 sec.	1 min 51 sec.	1min 45 sec.	NMT 15 min
Assay	99.3 %	99.8 %	100.9 %	90.0-110.0 % of the labelled amount
Dissolution	Min: 98.2 % Max: 100.8 %	Min: 99.8 % Max: 101.8 %	Min: 99.2 % Max: 104.6 %	NLT 60% (Qty. of the labeled amount of Artemether and Lumefantrine is dissolved in 45 min)

SUMMARY

The Process Validation for the product Artemether20 mg and Lumefantrine 120 mg was performed with 3 consecutive commercial batches with batch size 30 Lac each. The protocol for Process Validation was prepared and executed. All manufacturing equipment, analytical instrument, utility supply was verified for their qualification status and was found to be qualified and satisfactory batches were manufactured as per batch manufacturing record. The environmental condition like temperature, Relative Humidity and Differential Pressure were monitored and documented. The sample was performed as per the sampling plan and all the test were performed as per the standard testing procedure and test result obtained were meeting predetermined specification limit. No deviation was observed from laid down procedure as mentioned in this protocol.

CONCLUSION

Based on the result obtained from the regrous study performed during process validation of three batches of Artemether 20 mg + Lumefantrine 120 mg tablet it is concluded that process used during manufacturing of said product is robust to produce quality product consistently and reproducibly hence process standards is validated.

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