CONCURRENT PROCESS VALIDATION OF VORICONAZOLE TABLETS

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Abstract- **Validation plays a important role in ensuring and maintaining quality of the final product consistently across different batches. It is an integral part of the manufacturing process, as it assures that each step is validated to produce a high-quality end product. This study focuses on the effectiveness of producing voriconazole tablets. The process validation of the three batches of voriconazole tablets involved observing various process variables such as shifting, dry mixing, granulation, drying, size reduction, compression, inspection, and packaging. Following the approved protocol for process validation, at different stages samples were taken. The analytical results demonstrated that all findings were satisfactory and well within the specified parameters, ensuring the quality of the manufactured voriconazole tablets.**

Keywords: **Validation, packaging and sampling.**

1. INTRODUCTION

Validation refers to the process of assessing the validity or effectiveness of something. It is a collaborative endeavor that involves individuals from different areas of the organization. In the context of the pharma industry, validation adheres to the FDA regulations outlined in 21 CFR parts 210 and 211, which establish (cGMP) for finished pharmaceuticals products.

1.1 VALIDATION SCOPE

Pharmaceutical validation encompasses a wide range of activities and accumulates various aspects of processing of pharmaceutical. Illustrating the scope of validation can be challenging due to its extensive coverage. Nevertheless, a systematic examination of pharmaceutical operations reveals several key areas that are typically addressed in pharmaceutical validation. Some of these areas include:

1. Equipment Validation: Ensuring that equipment used in manufacturing, testing, and packaging processes is properly calibrated, qualified, and validated to meet required specifications.
2. Process Validation: Validating the manufacturing processes to ensure consistent product quality and compliance with regulatory standards. This involves evaluating critical process parameters and establishing appropriate control strategies.
3. AMV: Validating different analytical methods used for testing the quality and identity of raw materials, in-process samples, and finished products. This ensures accurate and reliable analytical results.
4. Cleaning Validation: Verifying the effectiveness of cleaning procedures to remove any residues from equipment surfaces, ensuring product safety and preventing cross-contamination.
5. Computer System Validation: Validating computer systems used in pharmaceutical operations to ensure data integrity, security, and compliance with regulatory requirements.

1.2 VALIDATION TYPES/METHODS

Prospective Validation: Validation is the process of establishing documented evidence that a system performs its intended functions according to a predetermined protocol. It is typically conducted before the distribution of a new product or a product manufactured using a revised process. The validation is carried out on at least three consecutive production batches. Prospective Validation involves executing the validation protocol prior to the commercial use of the process. During the product development phase, the production process is divided into individual steps.

Concurrent Validation: It is a type of validation that shares similarities with both prospective and retrospective validation approaches. In this approach, the operating firm sells the product to the public at its accurate market price during the qualification runs.

In exceptional situations, it might be justifiable incompletion of a full validation program before initiating daily production. However, the action to pursue concurrent validation must be documented and approved by authorized personnel. The documentation requirements for concurrent validation are alike as those objectified for prospective validation.

Retrospective Validation: It is a type of validation that relies on the review and analysis of historical information to establish documented evidence that a system performs as intended. This approach involves examining the historical manufacturing and testing data to demonstrate that the process has consistently remained under control. It is typically employed for well-established processes and is not suitable when recent changes have been made to the product composition, operating procedures, or equipment.

Revalidation: Re-validation plays a important role in illustrating that modifications made to a process or its environment must not have an adverse effect on characteristics and quality of product. The requirements of documentation for re-validation are the alike as those for the starting validation of the process.

However, re-validation becomes important in certain situations when changes are introduced that may affect the process or product. Some examples of changes that require validation are:

- Changes in raw materials: Any alterations in the physical properties of raw materials, such as density, viscosity, particle size distribution, and moisture content, which have the potential to impact the process or product.

- Changes in the source of the active raw material manufacturer: Shifting to a new manufacturer for the active raw material necessitates re-validation to ensure consistent quality.
- Changes in packaging materials: Modifications to the primary container or closure system used for packaging the product require re-validation to ensure proper containment and preservation.
- Changes in the process: Alterations in process parameters, such as mixing time, drying temperatures, or batch size, necessitate re-validation to evaluate their impact on product quality.

1.3 STAGES OF PROCESS VALIDATION

The Three Stages of Process Validation are an important framework for ensuring the quality and consistency of a manufacturing process. Let's explore each stage in more detail:

Stage 1 – Process Design: This stage involves the development phase of defining a manufacturing process of the product. It includes creating a QTPP to outline the desired quality attributes, identifying CQAs that impact product quality, defining CPPs that need to be controlled, and conducting risk assessments.

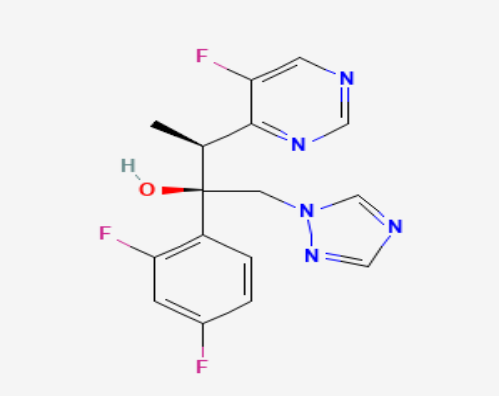
Stage 2 – Process Validation or Qualification of Process: In this stage, the process designed in Stage 1 is studied to ensure it can consistently produce products of the desired quality. Data is collected and analyzed at all stages of the manufacturing process, including building and facilities compliance, transportation and storage of raw materials, employee knowledge and practices, and every step involved in transforming raw materials into the finished product.

Stage 3 – Continued Verification of Process: This stage focuses on continued validation during commercial production to ensure the process maintains its quality standards. The aim is to detect and address process drift, ensuring consistent product quality. Product sampling, analysis, and verification are conducted at various points in the manufacturing process, involving employees with quality control training.

2. DRUG PROFILE

Voriconazole is an antifungal medication commonly used to treat aspergillosis in transplant patients, particularly those who have undergone lung transplantation. One notable side effect of voriconazole is its ability to cause photosensitivity, resulting in sunburn-like skin redness on areas exposed to sunlight. Voriconazole is an FDA-approved antifungal medication used to treat certain fungal infections, including esophageal candidiasis and invasive candidiasis. It acts by selectively inhibiting a specific enzyme involved in fungal cell membrane production, leading to fungal cell lysis. It is commonly used in the treatment of opportunistic infections associated with HIV.

Chemical StructureDepiction



IUPAC Name---(2*R*,3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoropyrimidin-4-yl)-1-(1,2,4-triazol-1-yl)butan-2-ol
Molecular Formula---$C_{16}H_{14}F_3N_5O$

1.9 CLINICAL PHARMACOLOGY

Mechanism of action

Voriconazole, like other azole agents, works by inhibiting the cytochrome P450-dependent 14α-lanosterol demethylation, a crucial step in the synthesis of ergosterol, the main component of fungal cell membranes. While it exhibits fungistatic (inhibiting fungal growth) effects for yeasts, it can be fungicidal (causing fungal cell death) for certain filamentous organisms.

Pharmacodynamics

Pharmacodynamics refers to the relation between drug exposure and its effects. Voriconazole exhibits high efficacy against most Candida species, including C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei. However, some strains of C. glabrata and C. krusei may develop resistance to all available azole antifungals.

Pharmacokinetics

Voriconazole exhibits non-linear pharmacokinetics, and its dose-response relationship shows wide interpatient variability. The therapeutic index is small, and serum concentrations are significantly influenced by various drug-drug interactions. It can be administered orally or intravenously.

Drug interactions

Co-administration of voriconazole with drugs that affect CYP2C19 activity can have significant effects on voriconazole plasma concentrations. Drugs such as rifampin, rifabutin, phenytoin, carbamazepine, and long-acting barbiturates can reduce voriconazole serum concentrations. Conversely, the levels of rifabutin and phenytoin may be increased when taken with voriconazole, necessitating monitoring of their serum levels.

MATERIALS AND METHODS:

1. INTRODUCTION

The process validation will be performed as concurrent validation. The complete documentation for the validation comprises several independent documents; reference to relevant documents will be given as part of this protocol. The results of the validation activities will be summarized in the validation protocol.

2. OBJECTIVE

To perform Process validation of **Voriconazole tablet 200mg (Batch size: 25,000 Tablets)**. Concurrent validation of tablet manufacturing process includes major manufacturing steps like sifting and mixing, kneading/wet passing, drying and rasping (dry screening), lubrication, and compression of three successive batches of **Voriconazole tablet.**

3. SCOPE

3.1. This validation protocol is applicable for the manufacturing of **Voriconazole tablet** and is limited to the manufacturing plant of Alive Pharmaceutical Pvt. Ltd. Dumraha, Duhabi Municipality, Sunsari, Nepal.

3.2. The Validation activities consists of:

3.2.1. Documentation of the process
3.2.2. Sampling Plan
3.2.3. Review of Data
3.2.4. Evaluation of Data

3.3. This protocol consists of the process of testing of different manufacturing steps.

4. LIST OF RAW MATERIALS

List of Raw materials to be used in the manufacturing of **Voriconazole tablet** are as follows:

S. No.	Name of the Ingredients	Specification	Label Claimed/Tab.	Overages (%)	Std. Quantity	UOM
1.	Voriconazole	IP	200.0mg	-	5.000	Kg
2.	Cross Car. Sodium	IP	15.00 mg	-	0.375	Kg
3.	MCCP-101	IP	63.20 mg	-	1.580	Kg
4.	PVPK-30	IP	6. 000 mg	-	0.150	Kg
5.	IPA	IP	-	-	3.000	Ltrs.
For Lubrication						
6.	Aerosil	IP	1.400 mg	-	0.035	Kg
7.	Magnesium Stearate	IP	1.400 mg	-	0.035	Kg
8.	Sodium Starch Glycolate	IP	13.00 mg	-	0.325	Kg
For Coating						
9.	White Insta coat Film Coating Solution	INH	13.60 mg	-	0.340	Kg
10.	Quinoline Yellow Lake	INH	0.720 mg	-	0.018	Kg
11.	Indigo Carmine Lake	INH	0.720 mg	-	0.018	Kg
12.	IPA	IP	-	-	2.6	Ltrs.
13.	Methylene Chloride	USP	-	-	3.9	Ltrs.

5. LIST OF MACHINES/ EQUIPMENTS

List of equipments used in the manufacturing and packing of **Voriconazole tablet** are described in table below:

S. No.	Name of Equipments	Capacity

1.	Dispensing Booth	Nil
2.	S.S. Scoops and Spoons	Nil
3.	Dehumidifier	7.5 HP
4.	SS Container	50 Liters
5.	16 Station Rotary Compression Machine	14,400-40,300Tabs/Hr.
6.	Colloid Mill	Nil
7.	Conventional Coating Machine	36'' Dia.
8.	Tablet Inspection Machine	Nil
9.	IR Moisture Analyzer	Nil
10.	Leak Test Apparatus	Nil
11.	Disintegration Test Apparatus	Nil
12.	Friability Test Apparatus	Nil
13.	Digital Hardness Tester	Nil
14.	Digital Vernier Caliper	Nil
15.	Electronic Balance	210 gm
16.	Automatic Batch Coding Machine	Nil
17.	Blister Pack Machine	120 Blisters/Min
18.	Conveyor Belt	0.5 HP
19.	HSAJET MICRON Printer	-
20.	De-Blistering Machine	---

6. PROCESS DESCRIPTION AND FLOW CHART DIAGRAM

6.1. **Cross verification of weights and AR No:** received materials was cross checked for weights.

6.2. **Sifting and Mixing:** Voriconazole, MCCP-101 and Cross Carmellose sodium was sifted through a 40-mesh sieve.The materials were mixed manually for 5 minutes in a double polybag.

6.3. **Preparation of Binder:**

(i) 3 Liters of IPA was passed through Super Fine Nylon Fab No. 16.
(ii) PVPK-30 was dispersed slowly in 3 Liters of IPA with constant stirring.
(iii) Stirring was continued until a clear solution was obtained.

6.4. **Kneading:** The binder solution was added slowly in small lots to the dry mix while mixing manually to get proper dough mass. The dough mass so obtained was discharged and collected in a SS Vessel.

6.5. **Wet Passing:** The dough mass was sifted through 14 mesh. The wet granules was collected in the trays of Tray Dryer.

6.6. **Drying and Rasping (Dry screening):** The granules was dried in Tray Dryer, initially without application of heat with air circulation only, until the wet granules gets air dried, followed by drying at temperature set at 40±2ºC till the Moisture Content is between 2-3 % at 105 ºC by IR Moisture Analyzer.
The dried granules was passed through 16 # sieve. The wet granules was collected in SS drums.

6.7. **Lubrication:** Magnesium Stearate was sifted through 60 # Sieve and collected in double lined poly bag and kept separately. Aerosil & Sodium Starch Glycolate was sifted through 60 # sieve and blended with the rasped granules manually for 4 minutes. Pre-sieved Magnesium Stearate was added and all the materials were lubricated manually for further 2 minutes.

6.8. **Compression:** The lubricated granules from above steps are then compressed according to the specification for the product.

6.9. **Coating:** The compressed tablet was then subjected for film coating according to the specification for the product.

6.10. **Inspection:** The compressed tablet was then inspected for the defect specified.

6.11. **Blister Packing:** The inspected tablet was then subjected to Blister Packing.
6.12.

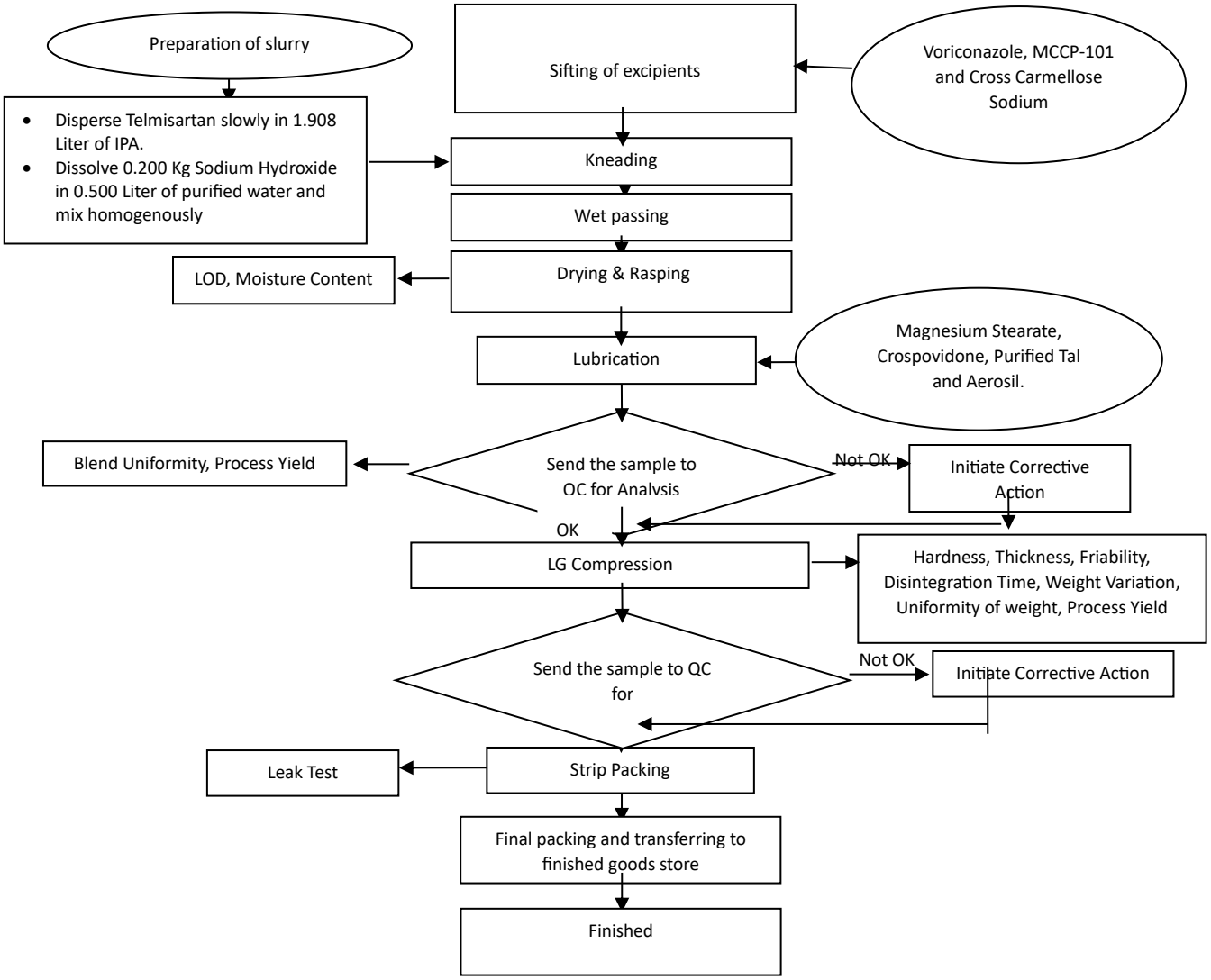


Fig: Process Flow Diagram

7. CRITICAL PROCESS PARAMETER

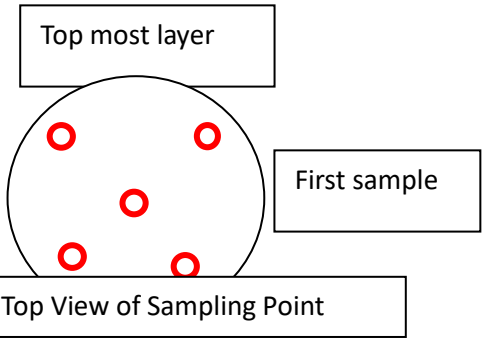
Following critical stages required to be validated to provide a high degree of assurance for the manufacturing of tablets.

S. No.	Stage	Parameters
1.	Sifting	Sieve Size
		Speed of machine
2.	Dry mixing	RPM
		Load size
3.	Kneading and Wet Passing	Binder addition time
		Mixing time after binder addition/Total granulation time
		Uniformity of granulated mass (Visual Checking)
4.	Drying	Dryer outlet temperature
		Dryer inlet temperature
		Drying load
		Total drying time
		Weight of the dried granules

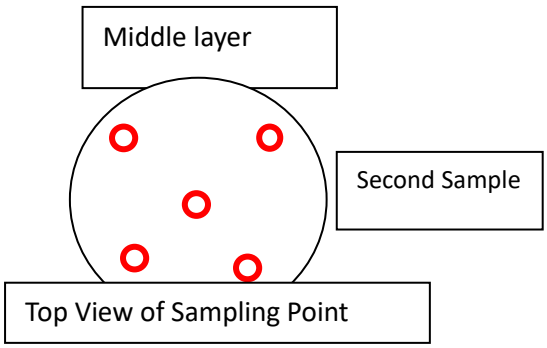
5.	Lubrication	Load size
		Speed of equipment (RPM)
		Total time of mixing
		Assay- (individual sample)
6.	Compression	Temperature of area
		Humidity of area
		Machine Details
		Weight variation of 20 tablets
		Average weight of tablet
		Disintegration time
		Friability
		Thickness
		Hardness
		Assay
7.	Packaging	Compressed Air Pressure
		Sealing Roller Temperature
		Forming Roller Temperature
		Speed of Machine

8. SAMPLING PLAN

Mixing and Lubrication stage

- The sampling was done by taking two samples from the container.
- These two samples were taken from two different layers of the container i.e. top most layers and the middle layer.
- The first sample was drawn from the mixture of the samples from five different sampling points which includes east, west, north, south and center of the top most layer of the container.
- 

- The second sample was drawn from the mixture of the samples from five different sampling points which includes east, west, north, south and center of the Middle layer of the container.



Drying Stage

The sampling was done by taking one sample from the container. This one sample was taken from the middle layer of the container. The sample was drawn from the mixture of the samples from five different sampling points, which includes the east, west, north, south, and centre of the middle layer of the container.

Tray Dryer: Sample to be drawn from every tray of the dryer.

Sample	1 Tray	2 Tray	3 Tray	4 Tray	5 Tray	6 Tray	7 Tray	8 Tray	9 Tray	10 Tray	11 Tray	12 Tray	Avg.
%Moisture Content													

9. AMPLE QUANTITY AND SAMPLING TIME

Sampling Quantity: Depends on quantity required for analysis (should not be less than thrice the sample required for single analysis).

Sampling Time: Bracketing the time between 3 to 4 intervals of total mixing/blending time during dry mixing and lubrication.

Stage	Time Interval (minutes)			Location
Dry Mixing	5	10	15	Layer as defined in sampling plan
Lubrication	2	4	6	Layer as defined in sampling plan

10. SAMPLING STAGE

S. No.	Process/Variable	Equipment setting (Control Variables)	Acceptance Criteria
1.	**Manufacturing**		
	Sifting	Visual Inspection	No visible foreign particulate matter should be observed.
2.	**Granulation**		
	Granulation	Finely divided material without free powder and excessive wetted lumps.	Finely divided material without free powder and excessive wetted lumps.
	Wet passing and Screening	Nature of granules	Granules should be finely divided.
	Drying	Moisture Content (sample to be tested at 105^0C).	Inlet Temperature: 50 °C Outlet Temperature: 45 °C Final Moisture Content: 2.5-3.5 % Determine the drying time for the moisture content specified.
	Dry screening	Nature of granules	Granules should be finely divided.
	Lubrication	Time	Fix the mixing time and speed with less RSD variation between the batches.
3.	Tablet compression	Compression Speed Compression force	Average Weight: 315 mg Thickness: 4.20 mm-4.40 mm Hardness: NLT 2.0 kg/cm^2 Friability: NMT 1% Disintegration time: NMT 30 min Assay: 90%-110%
4.	Blister packing	Compressed air pressure/Sealing Temperature/ Forming Temperature/ Leak test	Packing must Pass the leak test. Fix the forming/sealing temperature as per the leak test report.

11. TEST FAILURE

If any test does not meet the limits specified for that test, then the cause should be analyzed or sorted for and the validation team should propose the solution for the problem.

12. REVALIDATION

Revalidation is required after:

13.1Change in batch size.
13.2Change of vendor/manufacturer of any raw materials.
13.3Installation of new machine.
13.4Change in manufacturing or other process.
13.5Transfer of process to another site.
13.6Problems are encountered in a validated procedure.

5. RESULT AND DISCUSSION:

DRYING STAGE:

Manufacturing Step: **Dry Mixing**			
CRITICAL PARAMETERS		**VALIDATION TESTING POINTS (Voriconazole)**	
Batch No.	Mixing time (Minutes)	Sample Code	% Assay
A	5 minutes	1T1	97.47
		1T2	99.56
	10 minutes	2T1	100.74
		2T2	100.14
	15 minutes	**3T1**	**97.91**
		3T2	98.07
B	5 minutes	1T1	97.02
		1T2	96.91
	10 minutes	2T1	98.57
		2T2	99.88
	15 minutes	3T1	98.24
		3T2	98.75
C	5 minutes	1T1	98.07
		1T2	97.44
	10 minutes	2T1	99.46
		2T2	99.51
	15 minutes	**3T1**	**99.53**
		3T2	98.55
Range of Experience	15 minutes	**3T1(A) – 3T1 (C)**	**97.91-99.53**
COMMENT: -The dry mixing time around 15 minutes was found to be suitable time for the mixing of ingredients of Voriconazole tablets.			

Calculation for Standard Deviation

Mixing Time: At 05 Minutes

Batch No.	*Sample Name*	*Assay (X)*	$\overline{X}$	$(X-\overline{X})$	$(X-\overline{X})^2$
A	*1T1*	97.47	97.74	*-0.27*	*0.0729*
	1T2	99.56		*1.82*	*3.3124*
B	*1T1*	97.02		*0.72*	*0.5184*
	1T2	96.91		*0.83*	*0.6889*
C	*1T1*	98.07		*0.33*	*0.1089*
	1T2	97.44		*0.3*	*0.09*
				$\sum(X-\overline{X})^2$	4.7915

Standard Deviation = $\sqrt{\frac{\sum(X-\overline{X})^2}{n-1}}$ = $\sqrt{\frac{4.7915}{6-1}}$ = *0.9789*

Mixing Time: At 10 Minutes

Batch No.	*Sample Name*	*Assay (X)*	$\overline{X}$	$(X-\overline{X})$	$(X-\overline{X})^2$
A	*1T1*	100.74	99.71	*1.03*	*1.06*
	1T2	100.14		*0.43*	*0.185*
B	*1T1*	98.57		*-1.14*	*1.29*
	1T2	99.88		*0.17*	*0.028*
C	*1T1*	99.46		*-0.25*	*0.062*
	1T2	99.51		*-0.2*	*0.04*
				$\sum(X-\overline{X})^2$	2.665

Standard Deviation = $\sqrt{\frac{\sum(X-\overline{X})^2}{n-1}}$ = $\sqrt{\frac{2.665}{6-1}}$ = *0.73006*

Mixing Time: At 15 Minutes

Batch No.	*Sample Name*	*Assay (X)*	$\overline{X}$	$(X-\overline{X})$	$(X-\overline{X})^2$
A	*1T1*	97.91	98.50	*-0.59*	*0.3481*
	1T2	98.07		*-0.43*	*0.185*
B	*1T1*	98.24		*-0.26*	*0.067*
	1T2	98.75		*0.25*	*0.0625*
C	*1T1*	99.53		*1.03*	*1.0609*
	1T2	98.55		*0.05*	*0.0025*
				$\sum(X-\overline{X})^2$	1.726

Standard Deviation = $\sqrt{\frac{\sum(X-\overline{X})^2}{n-1}}$ = $\sqrt{\frac{1.726}{6-1}}$ = *0.58753*

STANDARD DEVIATION COMPARISION TABLE

S.No.	Time (Minutes)	Standard Deviation
1.	05	*0.9789*
2.	10	*0.73006*
3.	15	*0.58753*

COMMENTS: After calculation of standard deviation for the determination of dry mixing time for Voriconazole tablet, taking three consecutive batches, Standard deviation values from 15 minutes dry mixing time was found to be lesser than 5 &10 minutes mixing time. Hence, the suitable time for the dry mixing of ingredients of Voriconazole tablet is 15 minutes.

LUBRICATION STAGE:

Manufacturing Step: **Lubrication**			
CRITICAL PARAMETERS		**VALIDATION TESTING POINTS (Voriconazole-200)**	
Batch No.	Mixing time (Minutes)	Sample Code	% Assay
A	2 minutes	1T1	100.15
		1T2	100.18
	4 minutes	2T1	98.17
		2T2	98.56
	6 minutes	3T1	97.81
		3T2	**97.69**
B	2 minutes	1T1	102.65

		1T2	104
	4 minutes	2T1	100.47
		2T2	102.88
	6 minutes	3T1	98.50
		3T2	98.12
C	2 minutes	1T1	98.06
		1T2	98.66
	4 minutes	2T1	97.39
		2T2	97.80
	6 minutes	3T1	98.09
		3T2	**98.79**
Range of Experience	**6 minutes**	**3T2 (A) - 3T2 (C)**	**97.69-98.79**
COMMENT: The lubrication time around **6** minutes was found to be suitable for the lubrication of ingredients of Voriconazole. The Contents (% Assay) for Voriconazole was found uniform at **6** minutes mixing time.			

Calculation for Standard Deviation

Mixing Time: At 2 Minutes

Batch No.	*Sample Name*	*Assay (X)*	$\overline{X}$	$(X-\overline{X})$	$(X-\overline{X})^2$
A	*1T1*	100.15	100.61	*-0.46*	*0.2116*
	1T2	100.18		*-0.43*	*0.1849*
B	*1T1*	102.65		*2.04*	*4.1616*
	1T2	104		*3.39*	*11.45*
C	*1T1*	98.06		*-2.55*	*6.50*
	1T2	98.66		*-1.95*	*3.80*
				$\sum(X-\overline{X})^2$	26.30

Standard Deviation = $\sqrt{\frac{\sum(X-\overline{X})^2}{n-1}} = \sqrt{\frac{26.30}{6-1}} = 2.2934$

Mixing Time: At 4 Minutes

Batch No.	*Sample Name*	*Assay (X)*	$\overline{X}$	$(X-\overline{X})$	$(X-\overline{X})^2$
A	*2T1*	98.17	99.21	*-1.04*	*1.081*
	2T2	98.56		*-0.65*	*0.422*
B	*2T1*	100.47		*1.26*	*1.58*
	2T2	102.88		*3.67*	*13.47*
C	*2T1*	97.39		*-1.82*	*3.31*
	2T2	97.80		*-1.41*	*1.99*
				$\sum(X-\overline{X})^2$	21.851

Standard Deviation = $\sqrt{\frac{\sum(X-\overline{X})^2}{n-1}} = \sqrt{\frac{21.851}{6-1}} = 2.0904$

Mixing Time: At 6 Minutes

Batch No.	*Sample Name*	*Assay (X)*	$\overline{X}$	$(X-\overline{X})$	$(X-\overline{X})^2$
A	*3T1*	97.81	98.17	*-0.36*	*0.1296*
	3T2	97.69		*-0.48*	*0.2304*
B	*3T1*	98.50		*-0.33*	*0.1089*
	3T2	98.12		*-0.05*	*0.0025*
C	*3T1*	98.09		*-0.08*	*0.0064*
	3T2	98.79		*0.62*	*0.3844*
				$\sum(X-\overline{X})^2$	0.8622

$$\textit{Standard Deviation} = \sqrt{\frac{\sum (X - \overline{X})^2}{n-1}} = \sqrt{\frac{0.8622}{6-1}} = 0.415$$

STANDARD DEVIATION COMPARISION TABLE

S.N.	Time (Minutes)	Standard Deviation
1.	02	2.2934
2.	04	2.0904
3.	06	0.415

COMMENT: After calculation of standard deviation for the determination of lubrication time for **Voriconazole**, taking three consecutive batches, standard deviation values from **6** minutes were found to be lesser than **2** & **4** minutes. Hence, the suitable time for the lubrication of **Voriconazole** is **6** minutes.

PACKAGING STAGE DATA RECORDING

Manufacturing Step: **Primary Packing**

Batch No.	Test No.	Forming Roller Temperature (ºC)	Sealing Roller Temperature (ºC)	Speed of Machine Blister/Per Minutes	Leak Test Pass/Fail
A	1	130 ºC	140 ºC	120Blisters/Min.	Fail
	2	140 ºC	150 ºC	120Blisters/Min	Fail
	3	150 ºC	160 ºC	120Blisters/Min	Pass
	4	160 ºC	170 ºC	120Blisters/Min	Fail
B	1	130 ºC	140 ºC	120Blisters/Min	Fail
	2	140 ºC	150 ºC	120Blisters/Min	Fail
	3	150 ºC	160 ºC	120Blisters/Min	Pass
	4	160 ºC	170 ºC	120Blisters/Min	Fail
C	1	130 ºC	140 ºC	120Blisters/Min	Fail
	2	140 ºC	150 ºC	120Blisters/Min	Fail
	3	150 ºC	160 ºC	120Blisters/Min	Pass
	4	160 ºC	170 ºC	120Blisters/Min	Fail

COMMENT: Forming temperature at 150 ºC - 160 ºC, Sealing temperature at 170 ºC -180 ºC was found to be suitable temperature for proper forming and sealing of PVC (82 mm Pearl Pac Peach) for three consecutive batches.

FINISHED PRODUCT ANALYSIS REPORT

TESTS	**SPECIFICATIONS**	**RESULTS**		
		A	**B**	**C**
1. Description	**Product:** Green colored, round biconvex, film coated tablet having smooth surface on both sides	Complies	Complies	Complies
	Primary Packing: Packed in Aluminium Foil for Voriconazole tablet	Complies	Complies	Complies
	Secondary Packing: Packed in duplex box for Voriconazole tablet	Complies	Complies	Complies
	Batch Coding: As per BMR	Complies	Complies	Complies
2. Identification	The retention time of the sample in the assay corresponds to that of the standard preparation obtained in the assay.	Positive	Positive	Positive
3. Average Weight	315 mg ± 5%	310.665mg	310.61mg	308.505 mg

4. Weight Variation	Max: +5% of Average Weight	1.17%	2.79 %	0.22 %
	Min: -5% of Average Weight	2.79 %	2.80 %	4.53 %
5. Thickness	4.20 mm – 4.40 mm	4.244 mm	4.26mm	4.224 mm
6. Hardness	Not less than 2 Kg/cm^2	6.816 Kg/cm^2	7.71 Kg/cm^2	6.93 Kg/cm^2
7. Disintegration	Within 30 minutes	2.12 Mins.	3.32Mins.	2.42 Mins.
8. Dissolution	Not less than 80 % (D+5) of label claim	94.56 %-104.02%	87.20 %-99.17 %	90.60 %-99.21 %
9. Assay	Between: 90.0% - 110.0% of label claim of Voriconazole	98.885 %	102.89%	99.055%

CONCLUSION

Voriconazole tablet validation batches were created in accordance with batch production records that were approved. The results of all necessary validation tasks were finished, and they are compiled in this report. Critical process parameters were observed during the validation research as specified in the protocol. The results of the in-process tests revealed that every parameter was well within the allowed range. All these validation batches were manufactured using the same manufacturing process.

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