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Prospective Process Validation of Vitamin-E 200 (Alpha Tocopherol Acetate BP 200 Mg) Capsule

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Abstract

Process validation is a documented evidence which provides a high degree of assurance that a specific process will consistently produce a result meeting its predetermined specifications and quality attributes. Validation is documented act of proving that any procedure, process or system that actually leads to a expected result. The purpose of this investigation is to study prospective process validation of Vitamin-E 200 (Alpha Tocopherol Acetate BP 200 mg) capsule. Quality cannot be adequately assured by in-process inspections and testing but it should be built into the manufacturing process. This process should be controlled in order that the finished product meets all quality specifications. Therefore, building of quality requires careful attention to a number of factors, such as the selection of materials, product and process design, control variables in-process inspection. The critical process parameters were identified with the help of process capability and evaluated by challenging its lower and upper release specifications. Three initial process validation batches of same batch size, method, equipment, & validation criteria were taken. The critical parameters involved in dispensing, mixing (preparation of bulk solution), band solution preparation, encapsulation and band sealing stages were identified and evaluated as per validation plan. The outcome indicates that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes which is in compliance with the GMP.

Keywords: Prospective Process Validation; Control Variables; In-Process Control

Abbreviations

CGMP: Current Good Manufacturing Practices; BMR: Batch Manufacturing Record; BPR: Batch Packaging Record.

Introduction

In the mid-1970s, Ted Bayer and Bud Loftus, two officials from the FDA, introduced the concept of validation. Validation aims to guarantee that quality is integrated into the system at every stage, rather than solely being tested at the end. Therefore, validation activities frequently encompass training on production materials and operating procedures, educating the individuals involved, and overseeing the system during production. This has become a valuable component of current good manufacturing practices (cGMP).

According to US FDA: Establishing documented evidence for process validation provides a high level of confidence that a particular process will consistently meet its earlier set-up specifications and quality standards.

According to WHO [1]: Validation studies are a very important aspect of GMP and must adhere to a predetermined protocol. The results and conclusions should be documented, compiled, and stored in writing. Processes and procedures should be developed based on the WHO's validation study and should undergo regular revalidation to ensure they are still capable of achieving the desired results. Process validation is the gathering and analysis of data from the process design phase through commercial production, providing scientific proof that a process can consistently produce high-quality products. It encompasses a series of activities throughout the product and process lifecycle, including process design, process qualification, and ongoing process verification.

Types of Process Validation

Prospective Process Validation: In prospective process Validation, prior to the process being used commercially, an experimental plan known as the validation protocol is carried out in prospective process validation. Before launching the product commercially into the market, a pre-planned protocol, it is the verified, documented proof that a system performs as intended [2].

Retrospective Validation: For well-known items with stable manufacturing processes, the retrospective validation option is selected. Establishing recorded proof that a process performs as intended through the examination and analysis of past data is known as retrospective validation.

Concurrent Validation: Concurrent validation is considered for the running production products because somehow their validation was not performed before launching the products i.e. at the Prospective Process Validation stage. Based on data produced during the actual execution of the process, concurrent validation is used to create documented proof that a facility and its procedures perform as intended. To demonstrate that the manufacturing process is under control, this method entails evaluating the finished product of ongoing production and monitoring crucial processing steps.

Revalidation: Revalidation is conducting an investigative evaluation of the performance data that has already been collected and involves repeating the first validation effort or any portion of it. Maintaining the validated condition of the plant, machinery, manufacturing procedures, and computer systems require this strategy. The followings are some potential justifications for initiating the revalidation process:

- The movement of a product from one plant to another.
- Changes to the product, the factory, the producing procedure, the cleansing procedure, or different adjustments that would have an effect on product quality.
- Significant (generally order of magnitude) boom or lower in batch size.
- Sequential batches that fail to satisfy product specifications and validated standard procedure.
- The scope of revalidation tactics relies upon at the volume of the adjustments and the impact upon the product quality [3].

Process Validation Protocol

Prior to beginning any process validation works, the following items must be finished in order to complete the qualification process. The process validation will begin once the qualification work is finished [4].

Design Qualification: The recorded review of technical specifications and planning papers to ensure that the design complies with manufacturing process, GMP, and regulatory standards is known as DQ.

Installation Qualification: The documented confirmation that the building, HVAC system, auxiliary utilities, and equipment were constructed and installed in accordance with their authorized design specifications is known as IQ

Operational Qualification: OQ serves as the documentation proof that the equipment performs as intended across all expected operating ranges and complies with design specifications within its typical operating range.

Performance Qualification: PQ is the documented confirmation that the process, or the system's entire process, operates as planned across all expected operating ranges. And for the confirmation of the process, or the systems, three consecutive successful process validation batches have to be produced, and subsequently all the crucial process parameters will be checked with their predetermined specifications. Establishing documented proof that a particular process (like the production of pharmaceutical dosage forms) will reliably yield a product that satisfies its predefined specifications and quality attributes is known as process validation. A documented plan outlining the steps are involved in conducting Process Validation, including test parameters, product attributes, production tools, and design points regarding acceptable test results. In addition to being signed, dated, and numbered (document, protocol reference, and revision numbers), the validation protocol should include the following details at the very least [5]:

Principle

Process validation ensures that the manufacturing process controls are flexible enough to achieve desired qualities in the drug product while avoiding undesirable ones. This idea is crucial because it supports the definition of validation, which is a methodical process for identifying,

quantifying, assessing, recording, and reassessing a number of crucial manufacturing process steps that need to be controlled in order to guarantee a repeatable end product. Machines and equipment used in the production of process validation batches must have their qualifications (IQ, OQ) fulfilled. This product's raw materials must be purchased from authorized suppliers. Vitamin-E 200 (Alpha Tocopherol Acetate BP 200 mg) capsule analysis will be conducted using test methods for final product testing that have been satisfactorily validated by the R&D department. Every employee who makes Vitamin-E 200 (Alpha Tocopherol Acetate BP 200 mg) capsules has received specialized training on how to follow SOP, BMR, and BPR during the manufacturing process. The factors that affect each processing step's outcome are first determined, and they are then further separated into those that changed during processing and could affect the final product's quality and outcome. A Batch Manufacturing Record (BMR) and Batch Packaging Record (BPR) must be finalized for use in regular manufacturing after the validation process is finished. Change control management must be applied, if any deviation is found in the Batch Manufacturing Record (BMR) and Batch Packaging Record (BPR) after finalization the BMR & BPR [6].

General Information

Product name	Vitamin-E 200 (Alpha Tocopherol Acetate BP 200 mg) capsule
Active ingredient	Alpha Tocopherol Acetate BP
Strength	Each capsule Contains Alpha Tocopherol Acetate BP 200 mg
Appearance of capsule shell	Colorless transparent cap & body with yellow band. The capsule is filled with clear colorless or slightly greenish yellow viscous, oily liquid.
Color of band	Yellow
Size of capsule shell	2
Printings	Cap and body both are imprinted with "Vitamin-E" in black ink.
Average Filling weight	250.00 mg
Average weight per capsule	312.00 mg (capsule shell weight+ filling weight)
Batch Quantity	1,50,000 capsules
Batch Size	37.50 Kg.
Analytical Test method	HPLC. Alternative method: UV Spectrophotometric.

Objective

The duties and tasks to clarify the essential details of the production process of vitamin-E 200 (Alpha Tocopherol Acetate BP 200 mg) capsules are described in this process validation protocol. This protocol's goal is to specify the tests, steps, and acceptance standards required to confirm that, when process parameters are set within acceptable bounds, the manufacturing process used to produce vitamin-E 200 capsules (Alpha Tocopheryl Acetate BP 200 mg per capsule) will produce batches of consistent quality [7].

Scope

This guidance document covers everything from packaging to the manufacturing process.

Qualification and Training of Personnel

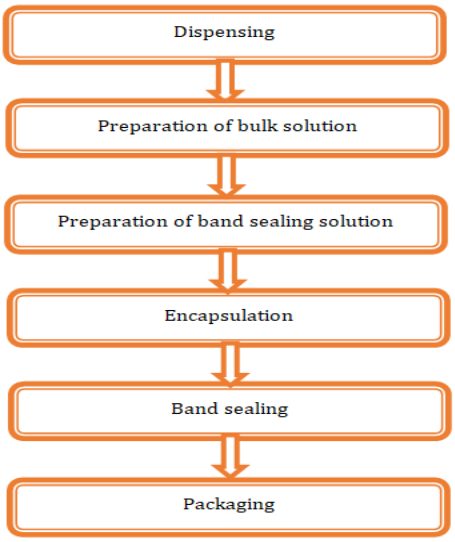
Employees working on the validation project must be suitably qualified, trained in the fundamentals of validation, and fully briefed on the production of Vitamin-E 200 Capsules (Alpha Tocopheryl Acetate BP 200 mg per capsule) as well as the specific methodology to be used for the process' performance qualification [8].

Formulation

The product formulation is as below:

Name of Materials	Specification	Standard Quantity/ Batch	Qty / Capsule
all-rac-Alpha Tocopheryl Acetate	BP	30.000 kg	200.00 mg
Arachis Oil	BP	7.500 kg	50.00 mg
Butylated Hydroxyanisole	BP	0.600 g	0.004 mg
Butylated Hydroxytoluene	BP	0.600 g	0.004 mg
EHG Shell (Flotit)of LHGC, Size # 2	Pharma grade	1,50,000 pcs	1 piece
Lemon Yellow color	Pharma grade	9.8737 g*	0.050635 mg
Gelatin Powder	BP	1.815 kg*	9.300 mg
Polysorbate 80	BP	0.075 kg*	0.385 mg
Purified Water	BP	7.260 kg*	37.230 mg
* 30% Overage			

Process Flow Diagram



Details of the Manufacturing Process

The manufacturing process of vitamin-E 200 capsule (Alpha Tocopheryl Acetate BP 200 mg per Capsule) is encapsulation type. And the Blister packing is Alu-PVC type. The process has been completed as at the following mentioned sequences [9]:

Manufacturing Process Sequences	
Product Name: Vitamin-E 200 Capsule (Alpha Tocopheryl Acetate BP 200 mg per Capsule)	**Strength:** 200 mg
Generic Name: Alpha Tocopheryl Acetate	**Dosage Form**: Capsule
Batch Quantity: 1,50,000 Capsule	

The process has been completed as per BMR (Document No.: BMR-CAP-001 and BPR (Document No.: BPR-CPP-001 and Document No.: BPR-CSP-001) [10].

Checklist for manufacturing process observation								
Steps		Obtained Results						Remarks
		Batch No. XX		Batch No. YY		Batch No. ZZ		
		Yes	No	Yes	No	Yes	No	
Dispensing Section III as BMR	Check and ensure dispensing booth is clean and line check is given as per current Standard operating procedure.	√		√		√		Checked & Ensured
	Check and ensure that balance is not due for calibration. Check for zero error in the balance.	√		√		√		Checked & Ensured
	Check and ensure that the expiry date and potency of all rac Alpha Tocopheryl acetate.	√		√		√		Checked & Ensured

Checking of Dispensed Material Section IV as BMR	Check and ensure that the all materials are issued as per BMR.	√		√		√		Checked & Ensured
	Check and ensure that all the scoops for dispensing are cleaned.	√		√		√		Checked & Ensured
	During dispensing all other required points to be checked as per BMR.	√		√		√		Checked & Ensured
Mixing Section V as BMR Step 1	Check and record the temperature and relative humidity in processing area. Temperature should be (22±2)°C and Relative Humidity (45±5)%	√		√		√		Checked & Followed
	Mix the following materials into a ss container with stirring and mix for 10-15 minutes. All-rac-Alpha Tocopheryl Acetate 30.00 kg and Arachis Oil 7.00 kg	√		√		√		Checked & Followed
Mixing Section V as BMR Step 2	Dissolve the following material into a ss vessel one by one with 0.500 kg Arachis oil and mix for 5-10 minutes. Butylated Hydroxyanisole 0.600 gm. Butylated Hydroxytolune 0.600 gm	√		√		√		Checked & Followed
Mixing Section V as BMR Step 3	Mix the material of step 2 into step 1 with continuous stirring for 10-15 minutes. Stand the content of ss container for deaeration.	√		√		√		Checked & Followed
Weighing of bulk solution in Section VI as BMR	Weigh the bulk solution at the end of the operation.	√		√		√		Checked & Followed
Band solution preparation in Section VII as BMR Step I	Dissolve Lemon yellow color in purified water into a SS container with stirring. Lemon yellow color 9.8737 gm and Purified water 7.260 Kg	√		√		√		Followed
Band solution preparation in Section VII as BMR Step II	Add gelatin into step 1 with continuous stirring and keep the dispersed materials with proper wrapping for 1-2 hours. Gelatin 1.815 Kg	√		√		√		Followed
Band solution preparation in Section VII as BMR Step III	Warm the dispersed material at 60°C-65°C until dissolved the materials.	√		√		√		Followed
Band solution preparation in Section VII as BMR Step IV	Add Polysorbate 80 into the solution slowly with stirring for 5 to 10 min. Polysorbate 80-0.075kg	√		√		√		Followed
Band solution preparation in Section VII as BMR Step V	Withdraw the bubble from the upper surface of the solution and close the container with clean SS lid as well as maintain the temperature of about 60°C throughout the hold till usage.	√		√		√		Followed

Capsule filling Encapsulation	Check and ensure the temperature and relative humidity of the encapsulation area. Temperature should be (22±2)°C and Relative Humidity (45±5)%	√		√		√		Checked & Ensured
	Check and record the integrity of the capsule filling machine before and after capsule filling throughout the processing activity.	√		√		√		Checked & Ensured
	Conduct filling into transparent EHG Capsule shells, size # 2 and adjust the weight of capsule until achieve the intended weight.	√		√		√		Followed
Band sealing	Transfer the filled capsule into the band sealing channel through hopper. Seal the capsule by gelatin solution and dry them within the drying panel.	√		√		√		Followed
Packaging as per BPR	Check and record the temperature and Relative Humidity. Temperature should be (22±2)°C and Relative Humidity (45±5)%	√		√		√		Checked & Ensured
	Check and record all the parameter before blister sealing as per BPR.	√		√		√		Checked & Ensured
	Check and record that the over printing instructions on labels and cartons.	√		√		√		Checked & Ensured
	Check and verify that price, manufacturing date and expiry date overprinted on label and carton is as per current price list.	√		√		√		Checked & Ensured
	Check and ensure that all packaging materials (Primary & Secondary) are arranged for VITAMIN-E 200 capsule (Alpha Tocopheryl Acetate BP 200 mg per Capsule) as per BPR.	√		√		√		Checked & Ensured

Identification of Critical Process Parameters During Manufacturing

The critical process parameters as per manufacturing steps are described one after another as the following [11]:

Steps	Critical Parameter to be checked	Obtained Results			Remarks
		Batch No. XX	Batch No. YY	Batch No. ZZ	
Dispensing	Room Condition: Temperature: (22±2)°C Relative Humidity: 45±5%	(20.9-21.4) °C (46.2-46.7) %	(20.4-22.8) °C (46.2-47.2) %	(20.9-22.4) °C (46.5-47.5) %	Complies
Mixing (Preparation of bulk solution)	Room Condition: Temperature: (22±2)°C Relative Humidity: 45±5%	(21.5-22.6) °C (43.7-48.6) %	(21.3-21.5) °C (45.2-48.2) %	(20.6-22.2) °C (43.2-44.6) %	Complies
	Mixing time of step: I: 10-15 minutes	15 min	15 min	15 min	Complies
	Room Condition: Temperature: (22±2)°C Relative Humidity: 45±5%	(21.5-22.8) °C (43.5-47.42) %	(21.7-22.5) °C (44.5-48.4) %	(21.6-22. 3) °C (42.4-44.6) %	Complies
	Mixing time of step II: 5-10 minutes	5 min	5 min	5 min	Complies
	Room Condition: Temperature: (22±2)°C Relative Humidity: 45±5%	(21.8-22.4) °C (42.5-45.2) %	(21.8-22.5) °C (42.4-45.2) %	(21.1-22.4) °C (43.6-44.5) %	Complies
	Mixing time of step III: 10-15 minutes	15 min	15 min	15 min	Complies

Band solution preparation	Room Condition: Temperature: (22±2)°C Relative Humidity: (45±5)%	(21.6-22.8) °C (43.7-45.6) %	(21.7-22.6) °C (42.6-44.6) %	(22.1-22.6) °C (43.4-44.6) %	Complies
	Mixing time of step-I: 5-10 min.	5 min	5 min	5 min	Complies
	Mixing time of step IV: 5-10 min.	5 min	5 min	5 min	Complies
	Solution holding time: 60 -120 minutes	60 min	60 min	60 min	Complies
Encapsulation	Room Condition: Temperature: (22±2)°C Relative Humidity: 45±5%	(20.9-22.5) °C (44.2-45.7) %	(21.7-22.5) °C (43.1-45.4) %	(22.-22.8) °C (42.6-45.1) %	Complies
	Average weight: ±4% of calculated weight.	311.5 mg	311.5 mg	311.5 mg	Complies
	Uniformity of weight: ±10% of average weight.	-0.48% to +0.80	-1.08% to +0.82	-1.06% to +0.86	Complies
	DT at 37°C temp.:NMT 30 min.	2 min 30 sec. to 3 min 10 sec.	3 min 10 sec. to 4 min	3 min 20 sec. to 3 min 50 sec.	Complies
	Machine speed (SPM): 50-60	53 SPM	57 SPM	55 SPM	Complies
Band sealing	Room Condition: Temperature: (22±2)°C Relative Humidity: (45±5)%	(22.2-23.1) °C (43.8-44.5) %	(21.8-23.6) °C (43.2-45.7) %	(21.3-22.8) °C (41.7-43.6) %	Complies
	Temperature in drying panel:(30±5)°C	32°C	32°C	32°C	Complies
Packaging (Primary Packaging)	Room Condition: Temperature: (22±2)°C Relative Humidity: (45±5)%	(21.4-23.8) °C (41.3-45.1) %	(22.5-23.4) °C (41.0-43.4) %	(21.4-23.8) °C (41.-45.1) %	Complies
	Sealing Temperature (°C): 180±10	181°C	185°C	190°C	Complies
	Forming Temperature (°C): 120±10	122°C	125°C	127°C	Complies
	Cooling Temperature (°C): 20±5	20°C	19°C	21°C	Complies
	Machine Speed (RPM):50 - 60	55RPM	58RPM	59RPM	Complies
	Draw off position (mm): 186.0±1.0	186.0 mm	186.0 mm	186.2 mm	Complies
	There must be no leakage of the blister Pack	Complies	Complies	Complies	Complies

List of Equipment and their Qualification Status

The list of equipment and their qualification status are stated in the following [12]:

Name of the Equipment	Machinery ID	Qualification Status		Remarks
		IQ	OQ	
Automatic liquid capsule filling, sealing machine	PRO-ALFM-01	√	√	Done
Automatic band sealing machine	PRO-ABSM-01	√	√	Done
Blister Sealing Machine	PRO-BSPM-07	√	√	Done
NB: √ implies that all equipment were verified and certified that they have proper qualification status.				

Calibration and Qualification Status of Lab Equipment

The calibration and qualification status of the following equipment used in the Performance Qualification of process VITAMIN-E 200 capsule (Alpha Tocopheryl Acetate BP 200 mg per Capsule) shall be checked and listed in the following [13]:

Equipment	Code/ Identification No.	Qualification Status	Calibrated on	Next Due date of Calibration
UV Spectrophotometer	QCID-001	Done	23.08.24	22.08.25
Electronic Analytical Balance	QCID-002	Done	16.08.24	15.08.25
Ultrasonic Bath	QCID-015	Done	01.08.24	30.08.25
Disintegration Tester	QCID-020	Done	05.07.24	04.07.25
Pack Integrity Tester	QCID-022	Done	04.07.24	03.07.25

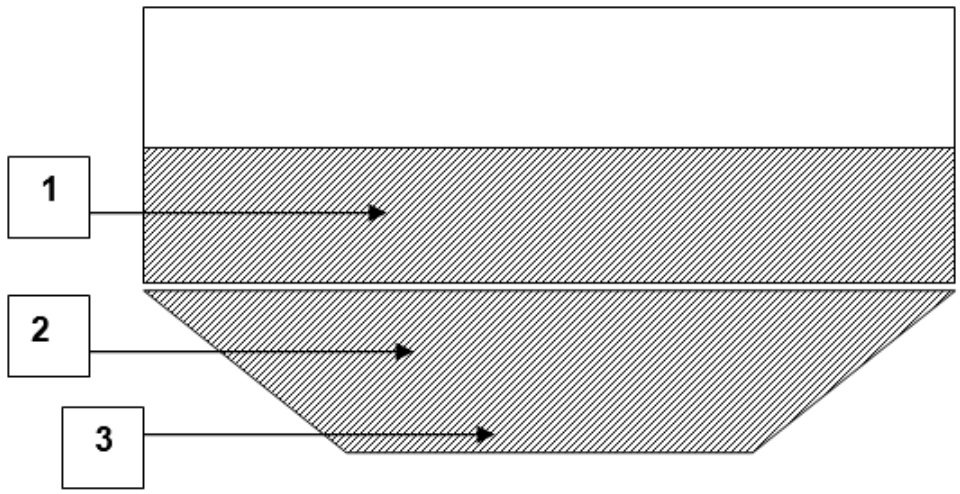
Analytical Schedule

	Analytical Schedule									
Unit operation	**Appearance**	**Specific gravity**	**Active distribution**	**Average weight**	**Uniformity of Weight**	**Average filling weight**	**Disintegration time**	**Identification of Alpha Tocopheryl acetate**	**Assay**	**Mass variation**
Bulk Solution preparation	√	√	√	-	-	-	-	-	-	-
During encapsulation	√	-	-	√	√	-	√	-	-	-
After Encapsulation (Finished Product)	√	-	-	-	-	√	√	√	√	√
Note: √ Denotes the test is required										

Sampling Details

	Sampling details
Mode of analytical sample	**Method of Sampling**
Bulk solution	Collect some fresh double small size polybags and write down the following information on each bag with a suitable marker. a) Product Name b) Batch No. c) Sample location d) Date of sampling
	After mixing, collect at least 3 samples (1-2 gm each sample) from top, middle, bottom of the SS Vessel and subject it to analysis i.e active distribution. Collect sample for checking the specific gravity of the bulk solution.
	On collection, Sample is kept in double polybag and ties the samples bag with a rubber band. Then preserve the sample on a sample tray or box in a suitable manner till the test is carried out.
During Encapsulation	Collect 15-20 Capsules every 15 minutes and keep it into a small container and finally 200 Capsules take out from that container.
After Encapsulation (Finished Product)	On collection, tie the sample bag with a rubber band. Then preserve the sample on a sample tray or box in a suitable manner and subject it to analysis.

Sampling Points: Intermediate bulk Container (SS Vessel).
Sample size: For checking uniformity (1 gm ~ 2 gm each sample).



Testing Frequency

Steps	Testing Frequency		
	Analysis	Test Frequency Per Batch	Number of analysis
Bulk solution	Appearance	Once	1 individual Test
	Specific gravity	Once	1 individual Test
	Active distribution	Once	3 individual assays
During Encapsulation	Appearance	Once	1 individual Test
	Average weight	Start of run & Every 30 minutes	10 individual Unit
	Uniformity of weight	Start of run & Every 30 minutes	10 individual Unit
	Disintegration time	Once	6 individual Test
Finished product	Appearance	Once	1 individual Test
	Average filling weight	Once	10 individual units
	Disintegration time	Once	6 individual tests
	Identification of Alpha Tocopheryl acetate	Once	1 individual Test
	Assay	Once	1 individual assay from a composite sample
	Mass variation	Once	1 individual test from assay result of a composite sample

Method of Analysis

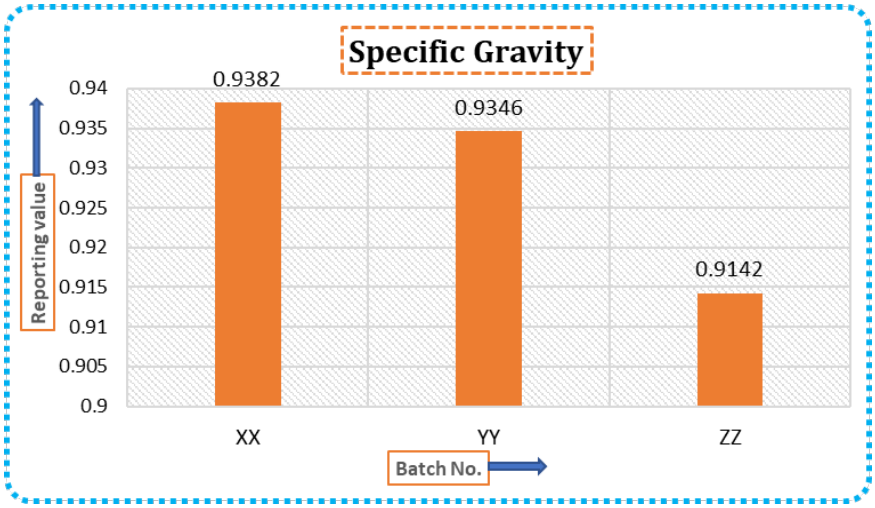
Analysis has been conducted as per validated & approved procedures

Acceptance Criteria and Results of Analysis

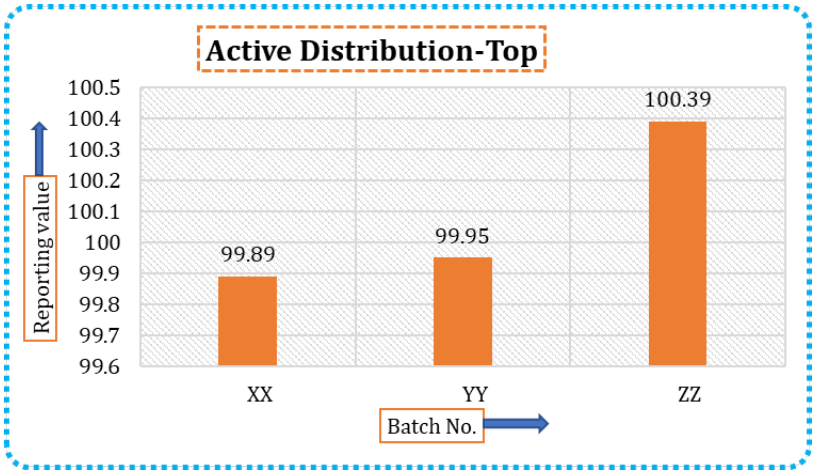
Steps	Acceptance Criteria and Results of Analysis					
	Parameter to be checked	Samples	Obtained Results			Acceptance Criteria
			Batch No. XX	Batch No. YY	Batch No. ZZ	
Preparation of bulk solution	Appearance	01 Composite	Complies	Complies	Complies	Clear colorless or slightly greenish yellow viscous, oily liquid.
	Specific Gravity	01 composite	0.9382	0.9346	0.9142	Report value
	Active distribution	Top	99.89%	99.95%	100.39%	±15% of the theoretical claim of active ingredients
		Middle	101.81%	98.89%	100.39%	
		Bottom	99.79%	98.52%	100.58%	
Finished product	Appearance	01 Composite	Complies	Complies	Complies	Size # 2, colorless transparent cap & body with yellow band. Cap and body imprinted with "Vitamin-E" in black ink. The capsule filled with clear colorless or slightly greenish yellow viscous, oily liquid.
	Identification	01 Composite	Complies	Complies	Complies	The chromatogram of the sample preparation exhibits a major peak for Alpha-Tocopheryl Acetate, the retention time of which corresponds to that exhibited in the chromatogram of the standard preparation as obtained in the Assay. Or The UV absorption spectra of Alpha-Tocopheryl Acetate in the sample solution and the standard solution should exhibit maxima and minima at the same wavelengths in the assay preparation.
	Average filling weight	01 Composite	245.8mg	246.5mg	246.8mg	± 4.0% of calculated filling weight
	Mass variation	01 Composite	2.78%	3.65%	2.89%	Acceptance value, L1 ≤ 15.
	Disintegration time at 105°C	01 Composite	5m 09s-7m 0s	5m 12s-6m 49s	5m 5s-6m 51s	NMT 30 minutes
	Assay	01 Composite	199.1mg	201.3mg	202.2mg	190.00 - 240.00 mg

Graphical Presentation of Major Results

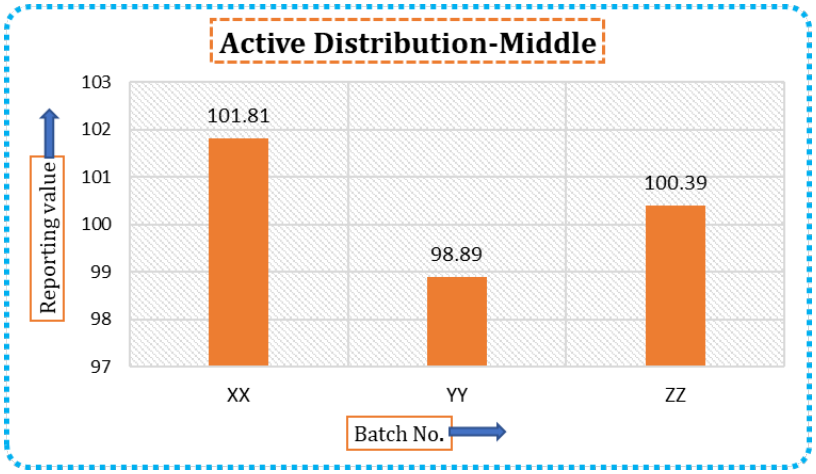
Specific Gravity



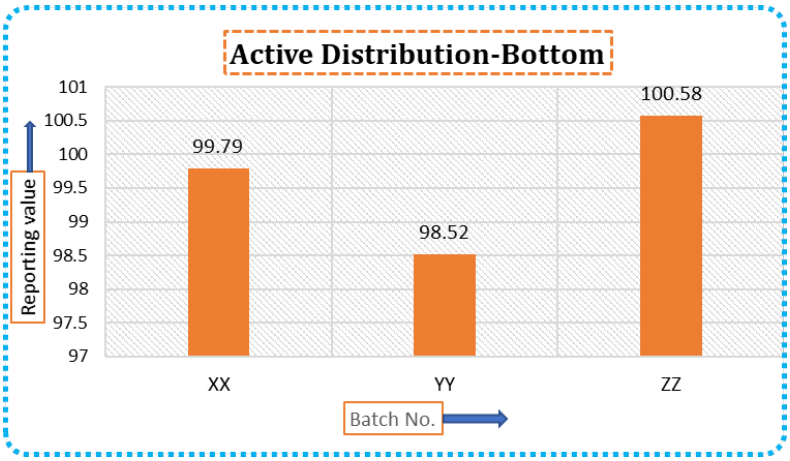
Active Distribution - Top



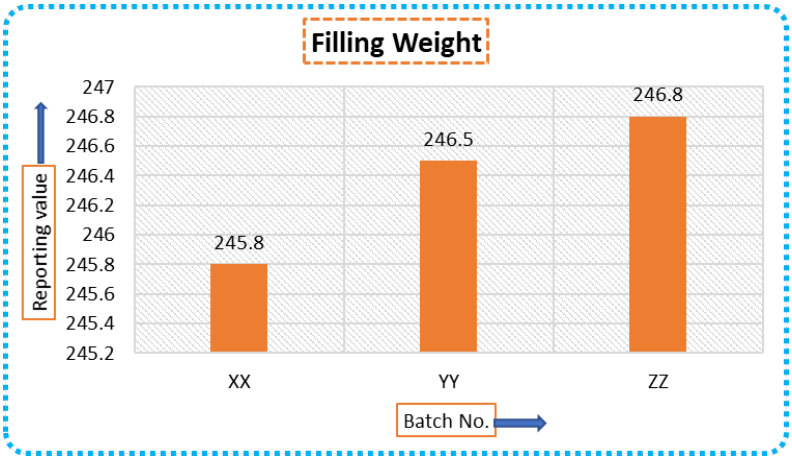
Active Distribution – Middle



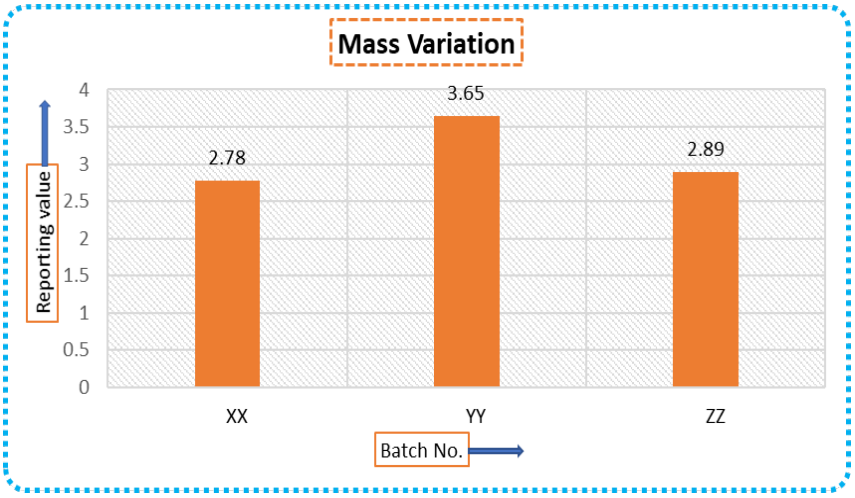
Active Distribution – Bottom



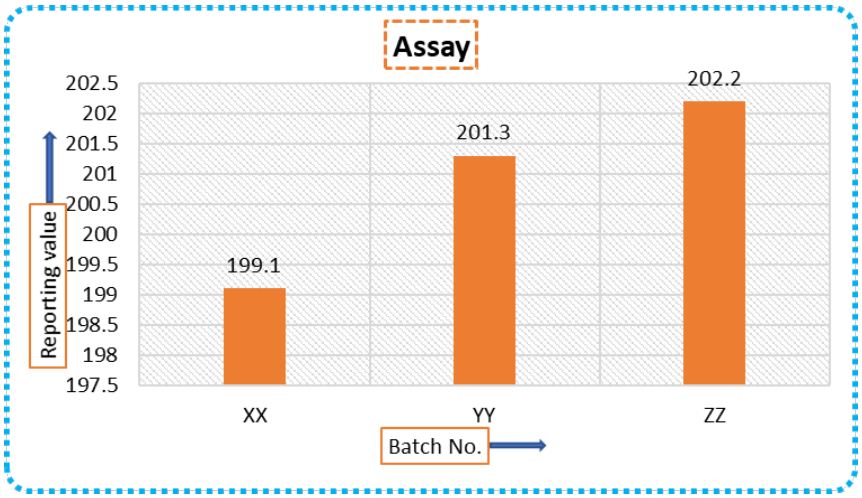
Filling Weight



Mass Variation



Assay



Conclusion

Three consecutive batches (Batch numbers XX, YY, and ZZ) of VITAMIN-E 200 Capsules (Alpha Tocopheryl Acetate BP 200 mg per Capsule) underwent process validation, and all parameters were found to be within the acceptable range. The manufacturing process will reliably produce this product that satisfies its predetermined specifications and quality attributes, according to the results and graph of the validation data for these three batches mentioned above. Consequently, it can be said that the process used to manufacture this product is deemed to be validated and suitable for regular use in the production process.

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