Original Article

Prospective process validation of polyherbal cough syrup formulation

Lay Desai[1], Jignasa Oza[2], Kapil Khatri*[1]

[1]Department of Quality Assurance, I.S.F. College of pharmacy, Moga, Punjab – 142001, India
[2]GM –Operations, Vasu Healthcare Private Limited, 896/A GIDC, Makarpura, Vadodara, Gujarat-India
*ISF College of Pharmacy, Moga, Punjab – 142001, India
Contact No. +917837211519
E-mail: kapil.12@gmail.com

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ABSTRACT

Context: Validation study is the core subject of study in quality assurance field. Validation is necessary for the efficient use of the resources. The cost of product failure, rejects, reworks, recalls, complaints are the sufficient part of total production cost. Validation study inevitably leads to process optimization, better productivity and lower manufacturing cost. Validation concept is somewhat less implemented in herbal industries. But in today's competitive era it is essential to adopt this approach for survival.

Objective: Present work is carried out to validate the manufacturing procedure of Vasu cough syrup which is a polyherbal preparation and to provide assurance that it meets with predetermined specifications.

Material and methods: Vasu cough syrup was developed and manufactured at Vasu Healthcare Private Limited, Vadodara, Gujarat. In this prospective process validation, critical process parameters were identified, the protocol and report were made and results of critical parameters were checked for three consecutive batches to assure reproducibility of the results. The activity was carried out in quality assurance department of Vasu Healthcare Private Limited.

Results and discussion: Results of identified critical process parameters were checked for their compliance and also for their reproducibility for three batches. The filling and sealing quality were also determined for each batch.

Conclusion: The results for all batches were complying with specifications, hence the product can be considered for scale up batches. Thus, the process of technology transfer was successfully completed.

Key words: Process validation, Polyherbal formulation, Critical process parameters, Specifications, Critical Quality Attributes, Formulation Development.

INTRODUCTION

USFDA defines validation as: "Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics. [1] According to European commission: Validation is defined as "Action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results. [2]

"Process Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. [3] Process development is carried out by F & D/ R & D and, actual transfer of the manufacturing process from R & D to production, along with required documents and qualified personnel are referred to as technology transfer. The ultimate objective for successful technology transfer is to have documented proof that the process is robust and effective in producing product meeting with pre-defined specification & cGMP requirements. [4, 5]

Address for correspondence

Dr. Kapil Khatri
Associate Professor, ISF College of Pharmacy
Moga (Punjab) – 142001 – INDIA
Contact No. +917837211519
E-mail: kapil.12@gmail.com

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Process validation generally has four types: Prospective process validation, concurrent process validation, retrospective process validation and revalidation.

Prospective validation is defined as the establishment of documented evidence that a system does what it purports to do based on a pre planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally under taken whenever new formula, process or facility must be validated before routine pharmaceutical formulation commences. In fact validation of process by this approach often leads to transfer of the manufacturing process from the development function to product. The objective of prospective validation is to prove or demonstrate that the process will work in accordance with a predefined validation protocol prepared for pilot product trails.

Concurrent process validation is similar to the prospective validation. This validation involves in process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control. This study can be carried out on commercial batches.

Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of past experience of production on the condition that composition, procedures, and equipment remain unchanged & historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past.

Revalidation is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment or site location, batch size and in the case of sequential batches that do not meet product specifications. In case of no changes revalidation shall be carried out at specific time intervals. [6]

Process validation of any formulation is carried out in three stages: First stage is process design stage**.** The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. Second stage is process qualification stage. During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. Third stage is continued process verification stage. Ongoing assurance is gained during routine production that the process remains in a state of control. Effective process validation contributes significantly to assuring product quality. Validation study is the core subject of study in quality assurance field. [7]

To carry out process validation, it is essential to determine critical quality attributes and control variables. The process is validated based on these parameters. ICH Q8 guidelines of pharmaceutical development describes about role of critical quality attributes in process validation. A critical quality attribute is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients,

intermediates, and drug product. [8] Potential drug product CQAs derived from the quality target product profile and/or prior knowledge is used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product. [9]

MATERIALS AND METHODS

Following raw materials were used in formulation of Vasu Cough Syrup. All the raw materials were tested in quality control department of Vasu Healthcare Private Limited. Individual certificate of analysis was generated and it was assured that all the materials are complying with in-house specifications of the industry. Vasu Cough Syrup contains: Extracts of glycerhiza glabra (K.Patel phyto extraction ltd), occimum sanctum (K.Patel phyto extraction ltd), terminellia belerica, Amruta herbals pvt. Ltd.), adhatoda vasica (Amsar pvt. Ltd.), Solanum xanthocarpum (Amsar pvt. Ltd.), zingiber officinale (Prashant Pharmaceuticals, rajpipla, Gujarat), trikatu (Amruta herbals pvt. Ltd.), curcuma longa (Konarc herbals and healthcare), Powder of navsar (Canton laboratories), mentha sylvestaris (Shree akshat pharma pvt ltd.), shudha tankan (Vishal traders), sorbitol IP, glycerin, propylene glycol and xanthan gum and Preservatives like sodium benzoate IP, sodium methyl paraben IP, sodium propyl paraben IP, bronopol BP, and flavored syrupy base.

Based on the pilot batches studies, following parameters were identified as critical quality attributes which have impact on finished product quality.

- The quality of purified water used in manufacturing of cough syrup.
- Stirrer speed at which the liquid mixture is stirred throughout the process.
- pH, viscosity and density of final product.
- Description and taste of the final product.
- The filled volume of final product which is delivered with filling nozzle.
- Sealing quality of the packed bottle.

Three batches were checked for above mentioned parameters and finally validation protocol and report were generated. Viscosity of the cough syrup was measured with Brookfield TT-220 Portable Viscometer. Conductivity of the purified water was measured with CM 183 EC-TDS Analyzer & Conductivity Meter.

Manufacturing process

All the excipients & preservatives were mixed with purified water in S.S. jacketed manufacturing vessel. Simultaneously decoction of all herbal extracts was prepared in preheated purified water under stirring in another jacketed tank for decoction. The hot liquid was allowed to cool to room temperature. Then, the decoction solution was filtered and transferred to mixture of jacketed manufacturing vessel under continuous stirring. To the filtered solution syrupy base was added to the mixture under continuous stirring. Then, flavor was added to the syrup under stirring. Subsequently syrup volume was made to the desired volume with

purified water. Final syrup was mixed using stirrer for 60 minutes. The steps of manufacturing process are shown in figure no.1.

Details of equipments used in manufacturing process of Vasu Cough Syrup:

Following equipments were used for production of Cough Syrup:

1. Stainless Steel Jacketed decoction tank
2. Stainless Steel Jacketed manufacturing vessel
3. Stainless Steel storage vessel
4. Filter press
5. Stainless Steel material transfer bucket
6. Stainless Steel Jug.

All the volumetric equipments were calibrated with 0.9% sodium chloride solution and marked according to desired volume. 0.9% Sodium chloride was used instead of water because density of water varies with temperature while density of isotonic solution of sodium chloride remains constant with temperature.

Details of sampling for process validation:

Initially, 30 ml of purified water sample was taken and tested for its appearance, pH and conductivity. Finally 30 ml of syrup sample was taken which was kept in storage vessel after filtration and then tested for critical process parameters mentioned in process validation protocol. The samples were collected in amber colored pet bottles. Sampling location for each batch is shown in figure no: 2.

RESULTS AND DISCUSSION

Samples from batch no. 101, 102, and 103 were tested for critical process parameters. Following tables show the results for individual batches. Table No. 1, 2, and 3 describes the results obtained from three individual batches.

Control variables for purified water were decided based upon its description given in the USP. The water quality was checked for its compliance with USP specifications or not. Conductivity of purified water was measured using conductivity meter at 25°C. [10, 11] All the specifications of the remaining parameters were set based on pilot study in the R&D department of Vasu Healthcare Private Limited. The purified water was heated in jacketed decoction tank and temperature of water was measured with inbuilt thermometer of decoction tank. Syrup was filled in the washed pet bottle through automated four head filling line. Fill volume was checked to ensure accurate quantity of syrup being filled in the bottle. The syrup bottle is closed with round orange colored cap. The cap was sealed on automated four head sealing machine and sealing was checked periodically for integrity. The results of filling and sealing evaluation are given in Table No. 4. The filled volume and sealing integrity was found to be satisfactory for all batches. Description and taste of syrup was also complying according to pre determined specifications and was found to be reproducible. pH, density and Viscocity are the important parameters affecting the syrup quality. These parameters were within the limits for all three batches.

CONCLUSION

The manufacturing process was found to be reproducible for three batches and each parameter was complying with the specification. No change as well as deviation was reported during manufacturing process. Thus no change control or deviation control was filed. The manufacturing process for vasu cough syrup was validated as per the guidelines mentioned in

Prospective Process Validation. The results of the validation exercise were found within the specification limit. Hence the technology transfer process of Vasu Cough Syrup was completed successfully and the objective of this process validation "to manufacture desired quality cough syrup" was achieved.

Fig 1: Steps for manufacturing of Vasu Cough Syrup

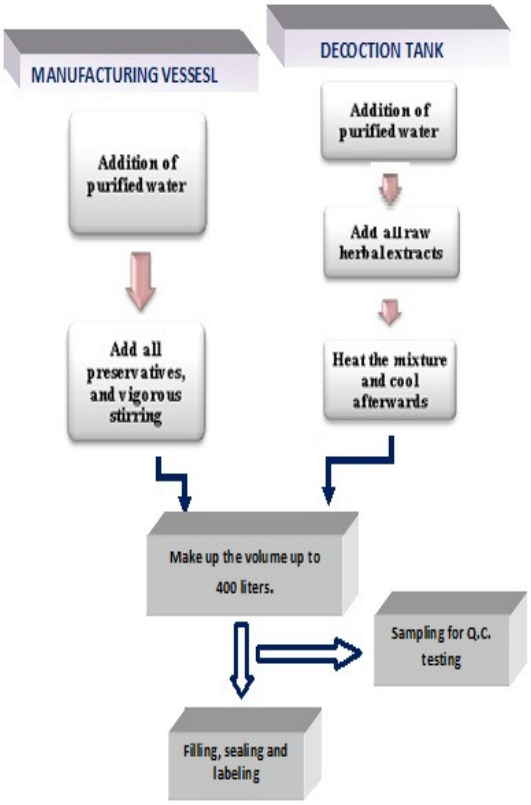

Fig. 2: Sampling locations for process validation of Vasu cough syrup.

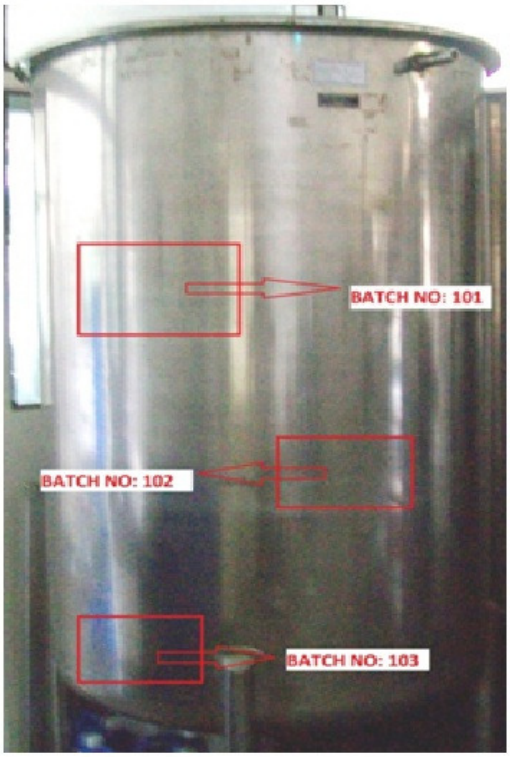

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Table no: 1 Details of critical process parameters for BATCH NO. 101 (400L)

TEST PARAMETERS	SPECIFICATIONS	RESULTS
Quality of purified water		
Description	It should be clear colorless liquid, odorless and tasteless.	Complies
pH	5.00-7.00	6.35
Conductivity (25^0c):	1.0-1.5 µs/cm	1.4 µs/cm
Temperature of purified water	Should not exceed 80° C	65◦ C
Stirrer speed	2000-3000 rpm	2000rpm
Final mixing Time	50-60 mins.	50 mins.
Clarity of final batch	Must be clear	Clear Liquid
Description of Syrup	Dark brown color viscous liquid with aromatic odour	Complies
pH	3.5-5.50	4.20
Density	1.10-1.20mg/ml	1.14mg/ml
Viscosity	100-200poise	161poise
Taste	Characteristic sweet taste	Complies

Table no: 2 Details of critical process parameters for BATCH NO. 102 (400L)

TEST PARAMETERS	SPECIFICATIONS	RESULTS
Quality of purified water		
Description	It should be clear colorless liquid, odorless and tasteless.	Complies
pH	5.00-7.00	6.30
Conductivity (25^0c):	1.0-1.5 µs/cm	1.1µs/cm
Temperature of purified water	Should not exceed 80° C	65◦ C
Stirrer speed	2000-3000 rpm	2500rpm
Final mixing Time	50-60 mins.	55 mins.
Clarity of final batch	Must be clear	Clear Liquid
Description of Syrup	Dark brown color viscous liquid with aromatic odour	Complies
pH	3.5-5.50	4.54
Density	1.10-1.20mg/ml	1.124mg/ml
Viscosity	100-200 poise	170 poise
Taste	Characteristic sweet taste	Complies

Table no: 3 Details of critical process parameters for BATCH NO. 103(400L)

TEST PARAMETERS	SPECIFICATIONS	RESULTS
Quality of purified water		
Description	It should be clear colorless liquid, odorless and tasteless.	Complies
pH	5.00-7.00	6.40
Conductivity (25^0c):	1.0-1.5 µs/cm	1.3 µs/cm
Temperature of purified water	Should not exceed 80° C	62◦ C
Stirrer speed	2000-3000 rpm	3000rpm
Final mixing Time	50-60 mins.	60 mins.
Clarity of final batch	Must be clear	Clear Liquid
Description of Syrup	Dark brown color viscous liquid with aromatic odour	Complies
pH	3.5-5.50	4.45
Density	1.10-1.20 mg/ml	1.14 mg/ml
Viscosity	100-200 poise	170 poise
Taste	Characteristic sweet taste	Complies

Table No: 104 Details of filling volume and sealing quality

BATCH NO:101		BATCH NO:102		BATCH NO:103	
FILL VOLUME	SEALING QUALITY	FILL VOLUME	SEALING QUALITY	FILL VOLUME	SEALING QUALITY
101 ml	OK	101 ml	OK	101 ml	OK
101 ml	OK	101 ml	OK	101 ml	OK
101 ml	OK	101 ml	OK	101 ml	OK
101 ml	OK	101 ml	OK	101 ml	OK
101 ml	OK	101 ml	OK	101 ml	OK

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