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RESEARCH ARTICLE

QUALITY ASSERTIVENESS BY INDUSTRIAL PROCESS VALIDATION PROGRAM OF SUPERLIV DS PREMIX FORMULATION

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ABSTRACT

The axial aim of this study is to create a valuable Risk Management Approach that enables a Process Validation over products lifecycle. Quality risk management has been described in regulatory guidance for several aspects of process validation, such as product lifecycle, extent of validation, determination of critical quality attributes, critical process parameters, process design space, sampling plans and statistical confidence levels. Verification of the process in every single produced batch over the product life time is now an expectation from regulatory authorities. In accordance to this Ayurvet Limited has compulsory adopted Process Validation as collection and evaluation of data, from the process design phase, commercial production phase, establishing scientific evidence that a process is in state of control and therefore capable of consistently and effectively assure product quality. Since Herbal formulations and processes are complex and multivariate by nature, a scientific understanding of relevant multi-factorial relationships requires risk-based approach. In this context, planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, are formally documented and the impact on the validated status or control strategy assessed. Validation study inevitably leads to process optimization, better productivity and lower manufacturing cost. It is implicit that a robust product development process is in place to enable successful process validation. The aim was successfully achieved on Superliv DS Premix formulation, and a systematic approach that enables process validation study for the assessment, control, communication and review of risks, targeting the highest quality of herbal formulations is now available to be applied - Ayurvet Limited Process Validation Program.

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INTRODUCTION

Good manufacturing Practice of medicinal products for human and veterinary use stated clear principle of validation which is applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal formulations. It is a GMP requirement that, manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any of the planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed (European Commission, 2010; Guidance for Industry, 2006; Guidance for Industry, 2006). Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities. As per the ICH Q8 guidelines of pharmaceutical development the method by which the process will be verified should be defined. There should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realization. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product (Jain et al., 2011; Guidance for Industry, 2011; ICH harmonized tripartite guideline, 2009).

Process Validation: Is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process

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is capable of consistently delivering quality product. The activities relating to validation studies may be classified into three stages: Process design, process qualification and continued process verification.

Manufacturing Process: Is "the sequence of activities, people, and systems involved in achieving some desired result".

Operating Parameters: Are the conditions under which a process is performed. These conditions can be physical or chemical (Blender time, Agitator RPM, Flow rate, pH, Temperature, Pressure etc.). Process parameters are usually controlled within defined operating ranges to set-point values. There are some measured product attributes that are deemed critical to ensure the quality requirements of either an intermediate or final product. The identified attributes are termed Critical Quality Attributes (CQAs). CQAs are the physical, chemical, biological, or microbiological property or characteristic that should be within a predetermined range to ensure the desired product quality. During development, process validation and characterization studies identifying the Critical Process Parameters (CPPs) is also one of the essential requirement. CPPs is a process input that, when varied beyond a limit range has an impact with significant influence on a critical quality attribute (CQA) and therefore should be monitored or controlled to ensure that the process produces the desired quality. Failure to stay within the defined range of the CPP leads to a high likelihood of failing to conform a CQA. It is also important to distinguish between parameters that affect critical quality attributes and parameters that affect the efficiency, yield, or worker safety or other business objectives; those are Non Critical (non Key) Process Parameters unless they also impact product quality. The cGMP regulations require that manufacturing processes be designed and controlled to guarantee that materials and finish product meet pre-determined quality requirements and do so consistently and reliably. This regulation requires manufacturers to design a process, including operations and controls, which results in a product meeting these attributes (Kotagiri Ravikanth, 2015; Tomoney, 2009). Manufacturing process of Superliv DS Premix, a liver formula for better growth and production a proprietary product of AYURVET LIMITED was under taken for its process validation. Process validation life cycle under Ayurvet limited process validation program ensure the predefined product specifications are met. It includes the development of authentic analytical methods which can reliably profile the phytochemical composition and help in validation of manufacturing process is a major challenge to scientists. Prior standardization of formulation during its designing and development stage with respect to its bioactive marker compounds as a key feature of CQA (critical quality attribute) ensures the phytoequivalence during the manufacturing of product on commercial scale. This will ensure the batch to batch consistency in quality & efficacy.

Experimental: The aim of this stage is to design a process (e.g., process development, scale-up, and characterization) suitable for routine commercial manufacturing that can consistently deliver a product within specifications. In order to assure Product validation Lifecycle Quality by Design is the start concept of Process Design. Design space can illustrate understanding of parameter interactions and provides manufacturing flexibility. A good planning Process Development Project accomplishes the following tasks:

- Understand the process.
- Assessment of CQAs.
- Design Space (and Proven Acceptable Range).
- Analysis of Critical Control Parameters (CCP) (or also called CPP) in order to ensure that the process will be under control.
- Develop a control Plan.
- Scale-up.
- Process Validation.

Table 1. Interpretation of Blender homogeneity results

Coefficient of variation (CV)	Assessment
CV ≤ 8%	Good homogeneity
8% < CV < 12%	Acceptable homogeneity
CV ≥ 12%	Insufficient

The functionality and limitations of industrial manufacturing equipment should be considered in the process design, as well as predicted contributions to variability posed by different raw-materials lots, production operators, environmental conditions, and measurement systems in the production setting. It is crucial that activities and studies resulting in process understanding be reported. Out of four validation processes namely prospective process validation, concurrent process validation, retrospective process validation and revalidation, we opted for concurrent process validation for our products manufacturing. This validation involved in process monitoring of critical processing step i.e blending which leads to homogeneity and helped us to generate and document evidence to show that the production process was in a state of control and the reproducibility of the production process will mainly ensure the batch-to-batch consistency of quality, efficacy and safety. As per GMP+ the results must be interpreted based on the limits of Coefficient of variation (CV) as given in Table 1 (GMP+ International B.V. Version EN).

As a part of manufacturing process validation pre requisites, the protocol was designed with the objective to validate the manufacturing process of the product under study. The protocol specified how the process validation will be conducted, identifying critical steps & parameters to be monitored, sampling plan and acceptance criteria. As a part of protocol all the raw materials and packaging materials used in the manufacturing were procured from approved vendors. Testing was done and materials were accepted as per compliance to the respective specifications. A team comprising of F&D, Production, Engineering, ARD–R&D and QA was set with well assigned responsibilities to carry out all the activities as per protocol. As shown in flow chart (Figure 1) all the manufacturing activities were prepared and shared with the team. Relevant SOPs (Standard Operating Procedure) were prepared and training was given to the relevant persons on equipment operation, manufacturing and sampling strategy. The manufacturing equipment and control instruments used for manufacturing and analysis of the product were maintained as per GMP. All the instruments used in the process were duly calibrated as per the calibration schedule. The environmental conditions were considered as per pre defined acceptance criteria prior to conducting the process validation study. A well designed sampling plan defining all the locations with time intervals from where the samples were to be collected was prepared and sampling was done accordingly. In total 81 samples were collected from the different positions of ribbon blender at the time interval of 15, 30 & 45 minutes (Figure 2, Table 2).

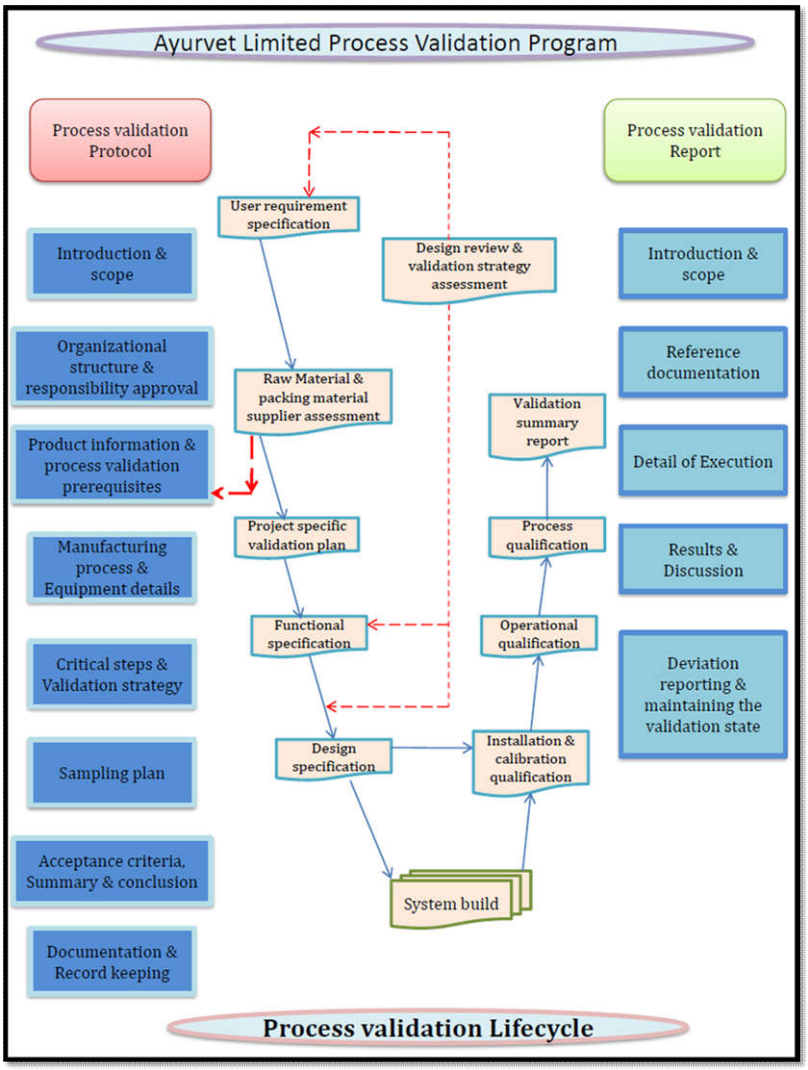

Figure 1. Process validation Lifecycle

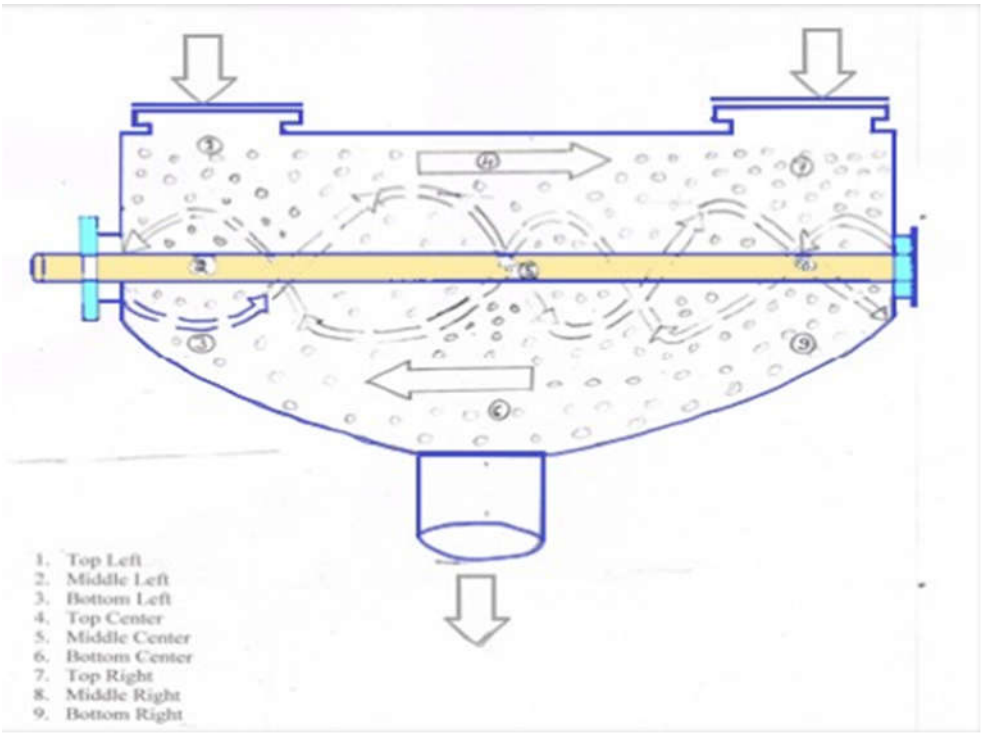

Figure 2. Sampling plan diagram

Analytical method for the estimation of active marker content in the samples was developed as the integral part of the exercise at R&D. The method was validated on the basis of its selectivity, linearity, precision, accuracy, limit of detection and limit of quantification according to International Conference on Harmonization (ICH) guidelines. Estimation of % active content Andrographolide (Figure 3) was carried out as per its validated analytical method. The process was supposed to be validated if % CV (Coefficient of Variance) is observed under 12.0 % between the two extremes of % active content obtained after analysis.

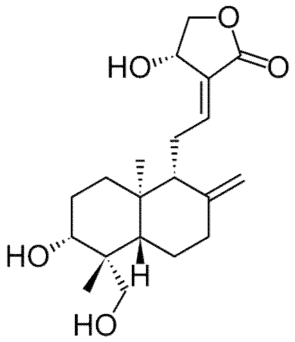

Figure 3. Andrographolide

MATERIAL AND METHODS

Reagents and materials: All the reagents and solvents were of AR or HPLC grade as per requirement. The active compound Andrographolide was isolated in our lab and structure was established by interpreting the 1H, 13C & 2D NMR spectra, samples of Superliv DS Premix were obtained from the production department of AYURVET LTD, Baddi.

Preparation of standard solution of Andrographolide: Accurately weighed around 5 mg of standard Andrographolide was dissolved in 25 ml of methanol to obtain stock concentrations of 200 µg/ml. Stock solution was further diluted to obtain the dilution range of 20–100 µg/ml and then injected in HPLC in order to prepare the calibration graphs and quantification of bioactive.

Preparation of test solution: For the quantification of Andrographolide, Superliv DS Premix (5g) was refluxed with 100 ml of petroleum ether (60ºC – 80ºC) for 3 hours and filtered repeated the process one more time. The defatted sample was extracted with 70 ml of methanol under reflux conditions for 3 hours and filtered, repeated the process twice. The final volume was made to 200 ml with methanol, filtered the solution through 0.45 µm membrane filter before injecting into HPLC.

High Performance Liquid Chromatography Apparatus and Conditions: Andrographolide content was analyzed by High Performance Liquid Chromatography (WATERS, binary pump 515 with PDA 2996 detector, USA). The data was acquired on the Empower 2.0 controlling software. Separation was obtained on Phenomenex Luna C18 column (250 mm x 4.6 mm, 5µm).

Selection and Optimization of chromatographic condition: To optimize the RP-HPLC parameters, several mobile phase compositions were tried. A satisfactory separation and good peak symmetry for andrographolide (Figure 4,a) was obtained by using Acetonitrile : 0.1 % ortho phosphoric acid in Water (40:60) as a mobile phase in isocratic mode. The mobile phase was filtered through 0.45 µm Millipore filter and degassed before use. The flow rate was adjusted to 0.8 ml/min. Injection volume was adjusted to 20 µl and detection was made at 228 nm.

System suitability: The analytical results obtained by the method developed are only valid if the defined system suitability criteria are fulfilled. In this investigation, the experimental result (Table 4) indicates that the chromatographic system was suitable for intended analysis. Standard solution mixture containing known concentration of Andrographolide was injected six times, separately. RSD values for peak area and retention time of standard suggested the reproducibility for these parameters. The low RSD values for tailing factor and theoretical plates suggested good peak symmetry of Andrographolide and good efficiency of column.

Validation of the Method: The proposed method was validated for the determination of Andrographolide using following parameters as per ICH guidelines:

Calibration: The marker compounds in the formulation were quantified using a calibration curve established with five dilutions of the standard. The corresponding peak area in formulation was plotted against the concentrations of the standard injected. Peak identification was achieved by comparison of both the retention time (RT) and UV absorption spectrum with those obtained for standard.

Linearity: Linear regression analysis was used to calculate the slope, intercept, and /regression coefficient (r2) for calibration plot. Linearity was determined by using five concentrations of the standard solution. Response was found to be linear in the concentration ranges investigated and Correlation Coefficient (r2) was 0.999 (Table 3).

Range: Range is the interval between upper and lower concentration of analyte in sample for which it has been demonstrated that the analytical method has suitable level of precision, accuracy and linearity. The linear response was observed over a range of 20-100 µg ml^{-1} (Table 2).

Precision: Three different concentrations of marker compound solution in triplicates were Injected on three different times within the same day and repeating the same on three different days to record intra-day and inter-day variations in the results. The low % RSD values of intraday and interday (Table 3) for the marker compounds Andrographolide reveals that the proposed method is precise.

Limit of Detection (LOD) and Limit of Quantification (LOQ): For determination of limits of detection and quantification, different dilutions of the marker was injected with mobile phase as blank and determined on the basis of signal to noise ratio 3:1 and 10:1 respectively. The LOD and LOQ for the standard compounds were calculated and tabulated (Table 3).

Selectivity: The retention time of Andrographolide and their counterpart in the formulation was 5.64 ±0.02 minute. The UV-Vis spectrum of marker compound was compared with its counterpart in formulation at three different positions, the peak start, peak center, and peak end.

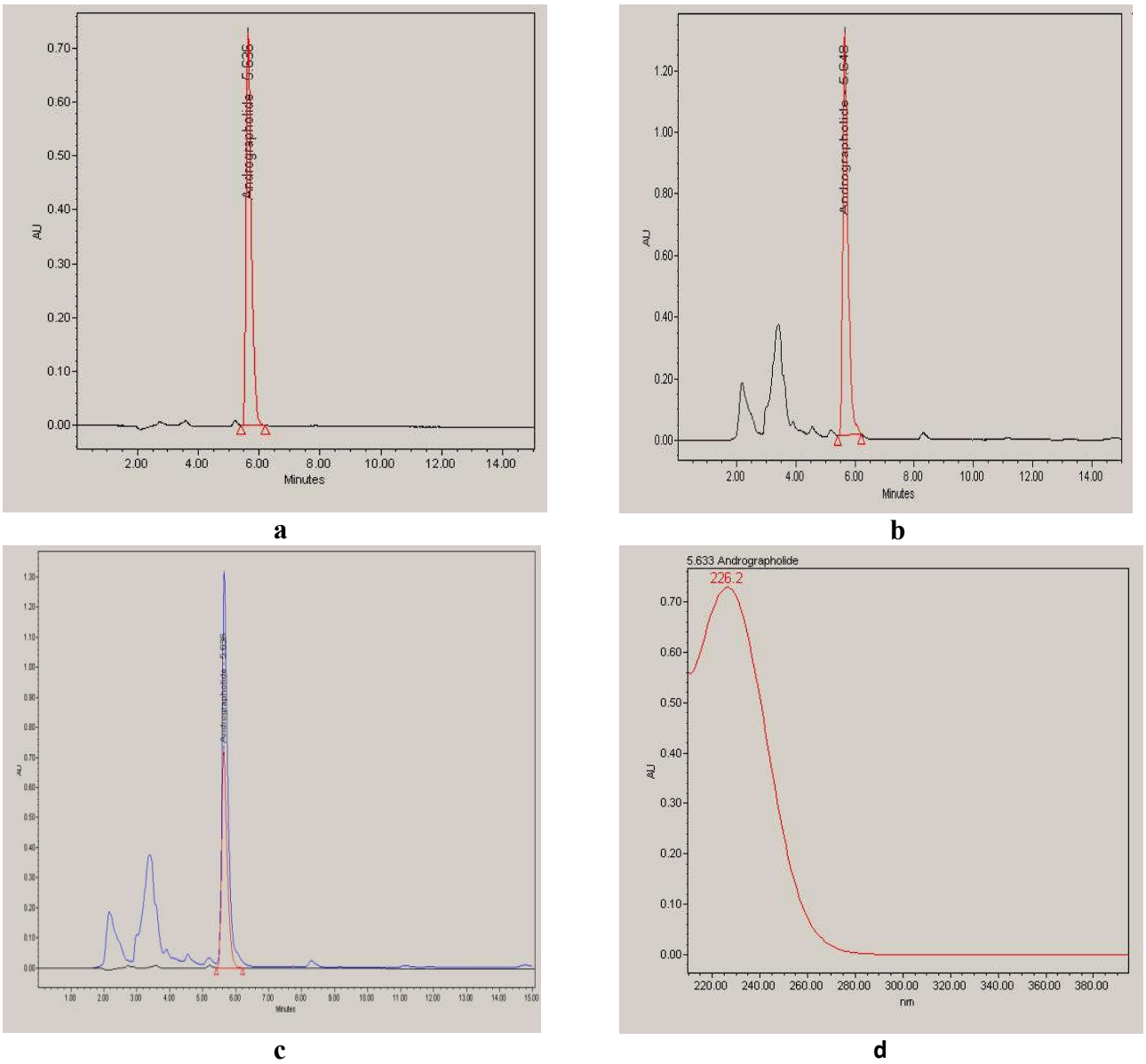

Figure 4. Chromatograms showing the resolution of marker compound in the formulation Superliv DS Premix. (a) Chromatogram of standard Andrographolide. (b) Chromatogram of sample Superliv DS Premix. (c) Overlay of the Andrographolide chromatograms i.e. sample against standard. (d) Spectral scan of standard Andrographolide and Spectral scan of Andrographolide in Superliv DS Premix.

There was good correlation between spectra obtained at each of the three positions. The Andrographolide peak was, therefore, not masked by any peak of other compound present in the formulation (Figure 4,c), which was indicative of peak purity.

Accuracy: Recovery experiments were conducted to check for the presence of positive or negative interferences from other ingredients/excipients present in the formulation and to study the accuracy of the method. Recovery was determined by the standard addition method. Andrographolide standard was added to the formulation at two different concentrations, extraction and analysis was performed as described above. Recovery was calculated for each standard at each concentration (Table 3). The low value of relative standard deviation indicates that the proposed method is accurate.

RESULTS AND DISCUSSION

Manufacturing process of Superliv DS Premix was taken up for the validation of blending time to ensure the consistency of product quality and justify the optimal time required for achieve it.

Samples were collected as per the sampling plan, analyzed for Andrographolide using RP-HPLC and found to be in the range of 0.098 % - 0.139 % (Table 3). The manufacturing process of product gave a % CV i.e. percent coefficient of variance ranging from 2.59 – 3.65 at the 15, 30 & 45 minutes blending time intervals and gets the rating of good homogeneity blending by standard norms and procedure applicable to blending of any particular.

Quality Risk Assessment: Failure mode effect analysis (FMEA) approach as per ICH Q9 Quality Risk Management guideline was used to identify all potential variables. Raw material specifications of each individual herb was in place to control the quality of herb in the initial stage itself which otherwise could have an impact on a particular CQA.

Control Strategy: It ensures process performance and product quality through planned set of controls. Control of raw material attributes (e.g., herb raw material, excipients and primary packaging materials), FPS (finished product specifications), Procedural controls & Facility controls such as utilities, environmental systems and operating conditions were all taken care of to ensure the process validation.

Table 2: Sampling plan

S. No	Sampling Point In Ribbon Blender*	Sample Quantity	Sample Code	Test Parameters
1.	Top Left	50gm sample in triplicate from each position as shown in sampling plan. Sampling after 15, 30, 45 minutes	TL	Quantification of active marker compound by HPLC
	Middle Left		ML	
	Bottom Left		BL	
2.	Top Center		TC	Quantification of active marker compound by HPLC
	Middle Center		MC	
	Bottom Center		BC	
3.	Top Right		TR	Quantification of active marker compound by HPLC
	Middle Right		MR	
	Bottom Right		BR	

*Sampling to be done from approximate equal distance from dorsal and ventral side of the blender

Table 3. Results of precision, linear regression analysis and their correlation coefficient for quantitative analysis of marker compound

Parameters	Andrographolide
Concentration range for linearity [µg ml^{-1}]	20.0 – 100.0
Correlation Coefficient (r2)	0.999
Recovery Studies (w/w)a	100.07 % w/w
Amount of marker compound in Superliv DS Premix [%] (w/w)b	0.113
Method precision (Repeatability)c – RSD %	0.4
Intermediate precision (Reproducibility) - RSD [%]Intraday 1	0.43
Interday 3	0.50
LOD	0.015 µg ml^{-1}
LOQ	0.045 µg ml^{-1}

Table 4. Andrographolide Content in Superliv DS Premix

Sr. No.	Time of sampling	Repetitions	% w/w of Andrographolide content in Superliv DS Premix (19022) samples								
			TR	TC	TL	MR	MC	ML	BR	BC	BL
1	15 min	A	0.117	0.117	0.121	0.119	0.118	0.122	0.121	0.122	0.121
		B	0.110	0.118	0.123	0.122	0.117	0.121	0.122	0.122	0.122
		C	0.111	0.114	0.112	0.126	0.118	0.119	0.120	0.123	0.122
		Mean	0.113	0.116	0.119	0.122	0.118	0.121	0.121	0.122	0.122
		CV						0.0265			
		% CV						2.65			
2	30 min	A	0.121	0.114	0.115	0.115	0.120	0.120	0.113	0.119	0.121
		B	0.119	0.115	0.114	0.114	0.120	0.124	0.122	0.122	0.120
		C	0.121	0.116	0.109	0.110	0.117	0.110	0.116	0.119	0.121
		Mean	0.120	0.115	0.113	0.113	0.119	0.118	0.117	0.120	0.121
		CV						0.0259			
		% CV						2.59			
3	45 min	A	0.118	0.118	0.121	0.113	0.120	0.114	0.116	0.120	0.116
		B	0.119	0.124	0.120	0.110	0.122	0.118	0.121	0.139	0.123
		C	0.123	0.122	0.117	0.120	0.098	0.120	0.119	0.125	0.119
		Mean	0.120	0.121	0.119	0.114	0.113	0.117	0.119	0.128	0.119
		CV						0.0365			
		% CV						3.65			

Where TR = Top Right; TC= Top Center; TL=Top Left; MR = Medium Right; MC= Medium Center; ML= Medium Left; BR = Bottom Right; BC= Bottom Center; BL= Bottom Left.

Life cycle Management and Continuous improvement: CQAs shall be monitored on regular basis to ensure that the process is performing within the defined acceptable variability. As manufacturing experience of the product under consideration grows and opportunities for process improvement are identified, the operating space could be revised within the design space.

Conclusion

The manufacturing process showed the acceptable homogeneity by blender as it met acceptance criteria and gave a % CV $\leq$ 8% i.e. percent coefficient of variance ranging from 2.65 % at 15 minutes, 2.59% at 30 minutes and 3.65% at 45 minutes blending time.

Declarations

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Conflict of Interest: None declared

Ethical Approval: Not required

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