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Research Article

Process Validation: An Approach for Herbal Tablet Standardization

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ABSTRACT

Validation is a concept that is fundamental to GMP and any quality assurance programme. Validation of the individual steps of the process is called process validation. Process is developed in such way that the required parameters achieved and it ensures that the output of process will consistently meet the required parameters during routing production. This concept is applied in pharmaceutical industry, but not that much deeply methodologically studied in herbal industry. The use of herbal medicine is the oldest form of healthcare. About 80% of the world's population has faith in traditional medicine, particularly herbal drugs for their primary healthcare. India has a rich tradition of herbal medicine as evident from Ayurveda. As growing public interest in use of herbal medicines, it is necessary to development of modern and objective standards for evaluating quality of herbal medicines. So that it is a need process validation in manufacturing of herbal drugs for control the quality of herbal drugs. The reasons for doing process validation in herbal manufacturing industry are manufacturers are required by law to confirm to GMP regulations, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches, process validation helps to ensure product uniformity, reproducibility, quality and to make process economical.

Keywords: Process validation, Process consistency, Quality assurance, Herbal formulation, Standardization

INTRODUCTION

Validation

The concept of validation was first proposed by Food and Drug Administration (FDA) in 1970. Validation is a concept that is fundamental to GMP and any quality assurance program. USFDA defined validation as "establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics." Assurance of product quality is derived from careful attention on number of factors including selection of quality materials, adequate product and process design, control of process and in process and end product testing[1,2]. 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 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[3-5]. The validation of herbal products is a major public health concern. In this regard, there is no control by the government agencies, despite the existence of certain guidelines in some individual countries and those outlined by the WHO. If the herbal products are marketed as therapeutic agents, and irrespective of whether the products really have any positive effects to cure and reduce the severity of the disease, it is necessary to ensure scientific validation and periodic monitoring of the quality and efficacy[6-8]. This concept of validation is getting well applied to manufacturing of synthetic drugs from long time back. But this concept is not that much deeply or methodically studied and applied for the manufacturing of herbal drugs. All international regulations like USFDA, MCC, MHRA, TGA etc. shows the applicability of validation to pharmaceutical manufacturing but no one regulation except WHO applies the validation concept to manufacturing of herbal drugs[9]. WHO also emphasize on very little part of validation. Therefore introduction of scientific validation would control the production of impure and adulterated herbal product[10,11].

MATERIAL AND METHOD

Material

Vrikshamla Ghan, Suddha Guggul, Triphala ghan, Sodium Nipagin, Sodium Nipasol, Sodium Benzoate, PVP (Povidone K30), Gum Acacia, Dibasic Calcium Phosphate (D.C.P), Talcum, Magnesium Sterate, Gelatin, Isopropyl Alcohol

Method

Standardization of Vrikshamala ghan, Suddha guggul, Triphala ghan

Standardization is an important step for the establishment of a consistent biological activity, a consistent chemical profile, or simply a quality assurance program for production and manufacturing of an herbal drug. Each one was standardized as per the WHO guidelines.

Physical methods:

In physical methods quantitative standards like foreign matter percentage, total ash, water soluble ash, moisture

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Table 1: Critical process parameters for process validation of tablets

Sr. No.	Process stage	Sampling Frequency	Controlled Parameter	Tests	Rationale
1.	Dry mixing	At end of mixing	Mixing time, Speed	Bulk density, Tapped density, Angle of repose	To ensure proper Mixing
2.	Drying	At end of mixing	Inlet temperature	Percent LOD	To get desired moisture content in Granules
3.	Lubrication	At end of Blending	Time, Speed	Bulk density, Tapped density, Angle of repose	To obtain final blend for compression
4.	Compression	Start, middle, End	Machine speed, compression force	Appearance, Thickness, Hardness, Friability, Disintegration time	To meet the desired specification
5.	Coating	At end of coating	Pan rpm, spray rate, pump rpm, spray pattern, nozzle to bed distance, air temperature	Appearance, Thicknesses, Friability, Weight variation, Disintegration time	To meet the desired final product specification

Table 2: Presence of foreign matter

Sr. No.	Parameters	Vrikshamla ghan	Shuddha guggul	Triphala ghan
1.	Foreign matter	Nil	Nil	Nil

No any foreign matter was observed in drug sample.

content, acid value, and extractive value, P^H value and FTIR Spectroscopy were determined. Fourier Transfer Infrared spectroscopy (FTIR) was done to evaluate the authentification. The spectrum of Vrikshamla ghan, Shuddha guggul and Triphaaaala ghan were recorded in the range of 4000 to 650 cm^{-1} by using Agilent Cary 630 FTIR spectrophotometer.

Chemical method

UV Analysis

UV analysis of Vrikshamla ghan, Shuddha guggul and Triphala ghan were done for identification by using Shimadzu 1800 UV Spectrophotometer.

Botanical Method

Macroscopic Studies

Macroscopic characters of the medicinal material were based on colour, odour, and taste.

Microchemical Studies

The powders were examined microscopically by mounting in alcoholic picric acid, iodine solution and by staining with phluoroglucinol: HCl, sudan red III.

Process flow

Sifting

The materials Vrikshamla ghan, Shuddha guggul, and Triphala Ghan were sifted through 40 mesh S.S. sieve fitted to turbo-sifter and collected it in RMG.

Dry Mixing

The dry-mixing step involves mixing of active ingredients with other additives using Rapid Mixer Granulator (RMG). Mixing speed and mixing time are the critical variables. Mixing speed is kept constant, mixing time shall be studied to validate dry mixing step. In dry mixing stage 3 batches like I, II and III are considered for validation.

Binding

The mixer was started and added slowly the binder solution into RMG within 1 to 3 minutes by keeping impeller at “slow” speed and chopper "off”. Mix for 2 minutes by keeping chopper and impeller at “slow” speed. Stop the Rapid mixer granulator and scrap the contents from the sidewalls of bowl and blades with S.S. scrapper. Again start the mixer and mix up to 1 minute by keeping impeller and chopper at “Fast” speed, till granulation end point is reached to get required consistency of tough mass. The ammeter reading of impeller and chopper at granulation end was recorded. Repeat this same procedure for the second lot.

Wet Milling

Pass the wet mass through conical mill using 16.0 mm screen. Collect the milled granules in to FBD bowl.

Drying

The 1st FBD bowl containing wet granules was placed under the retarding chamber and fitted it to the retarding chamber by operating the control panel. Initially air-dry the wet mass in the fluid bed dryer. Then further the dried at inlet air temperature of 60-65°C. Check the LOD when outlet temperature reaches around 40°C.

Lubrication

Load the granules in octagonal blender. Add all lubricants previously weight and sifted mix for 10 minute at slow speed.

Compression

The compression was performed on rotary compression machine as per specifications.

Coating

The coating was performed in pan coater. Critical process

Table 3: Percentage of moisture in dry powders of Vrikshamla ghan, Shuddha guggul and Triphala ghan

Sr. No.	Parameters	Vrikshamla ghan	Limit %	Shuddha guggul	Limit %	Triphala ghan	Limit %
1.	LOD (% w/w)	4.3±0.15	Max 5	3.9±0.15	Max 5	5.3±0.20	NMT 11

Table 4: Ash values of Vrikshamla ghan, Shuddha guggul and Triphala ghan

Sr. No.	Parameters	Vrikshamla ghan	Limit %	Shuddha guggul	Limit %	Triphala ghan	Limit %
1.	Total ash	11.02± 0.16	NMT 15	3.5 ± 0.64	NMT 5	10.2± 0.45	NMT 7
2.	Acid insoluble ash	3.5± 0.30	NMT 5	1.7 ± 0.13	NMT 2	2.5± 0.14	NMT 3
3.	Water soluble ash	4.5± 0.14	NMT 7	2.6 ± 0.42	NMT 5	1.2± 0.27	NMT 2

Table 5: Extractive value of Vrikshamla ghan, Shuddha guggul and Triphala ghan:

Sr. No.	Parameters	Vrikshamla ghan	Limit %	Shuddha guggul	Limit %	Triphala ghan	Limit %
1	Water soluble extractive (% w/w)	53.07± 0.34	NLT 45	59.96 ± 0.45	NLT 53	38.35± 0.11	NLT 35
2	Ethanol soluble extractive (%w/w)	27.11± 0.32	NLT 22	39.05 ± 0.22	NLT 27	15.02± 0.14	NLT 10
3	Ether soluble extractive (% w/w)	13.5± 0.15	NLT 7	24.06± 0.27	NLT 20	12.44± 0.36	NLT 6

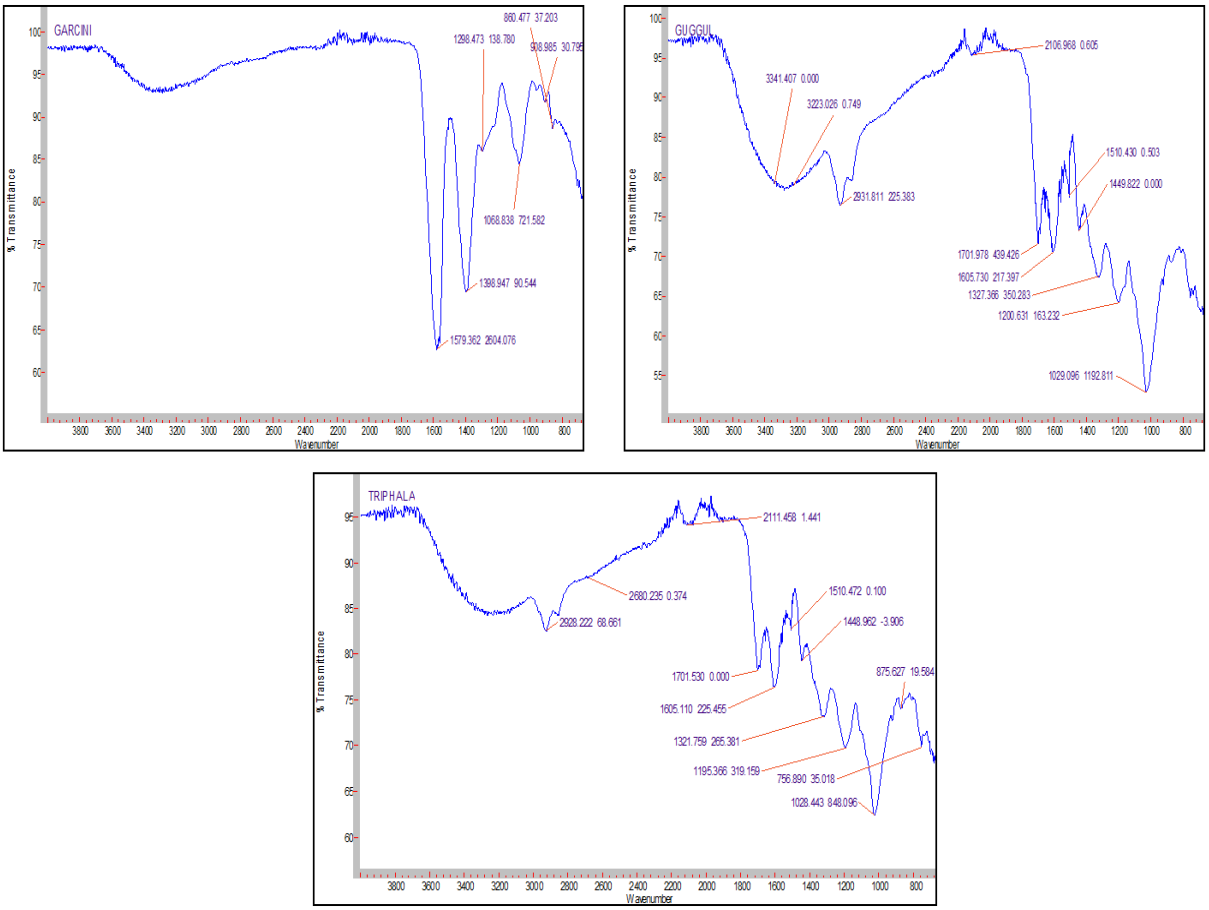

Figure 1: FTIR spectra of Vrikshamla ghan, Shuddha guggul Triphala ghan

parameters considered for Validation. The critical process parameter considered for validation was represented in table 1.

Analysis of Garcini Tablet

A simple UV spectrophotometric method was developed for the estimation of Garcinia indica in Garcini tablet.

Instruments

Absorbance measurements was made on Shimadzu 1800

Table 6: P^H value of Vrikshamla ghan, Shuddha guggul and Triphala ghan

Sr. No.	Parameter	Vrikshamla ghan	Limit	Shuddha guggul	Limit	Triphala ghan	Limit
1.	P^H	4.22±0.16	3.5- 5.5	3.26±0.18	3.0- 4.5	5.36±0.22	4- 6

Table 7: Interpretation of FTIR spectra of Vrikshamla ghan, Shuddha guggul Triphala ghan

	Vrikshamla ghan		Shuddha guggul		Triphala ghan	
Sr. No.	Frequency (cm^{-1})	bond	Frequency (cm^{-1})	bond	Frequency (cm^{-1})	bond
1	3300-2500	O-H stretch	1701	(s) C=O stretch	2928	(m) O-H stretch
2	1320-1000	(s) C-O stretch	1449	(m) C-C stretch (in Ring)	1449	(m) C-C stretch (in Ring)
3	1000-650	(s) =C-H bend			1028	(s) C-O stretch

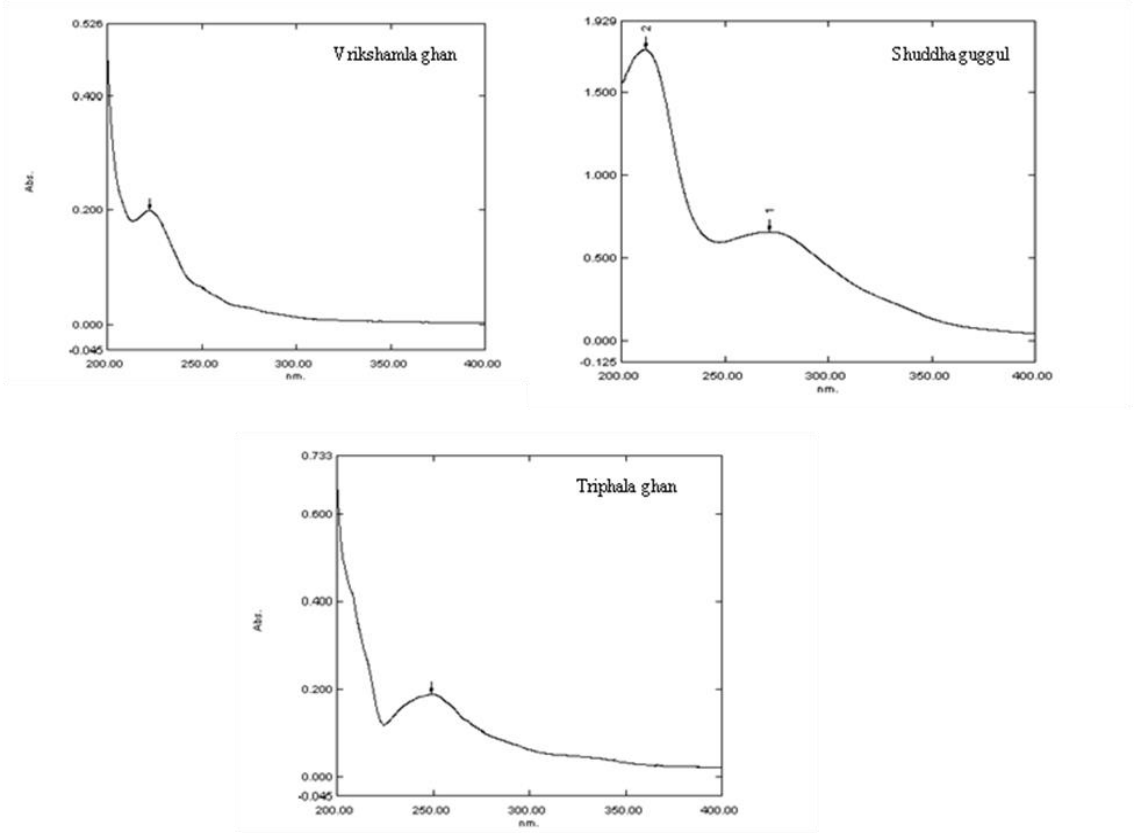

Figure 2: UV spectra of Vrikshamla ghan, Shuddha guggul Triphala ghan

Table 8: Organoleptic characteristics study of Vrikshamla ghan, Shuddha guggul and Triphala ghan

Sr. No.	Characters	Vrikshamla ghan	Shuddha guggul	Triphala ghan
1.	Colour	White	Light brown	Pale brown
2.	Odour	Odourless	Aromatic	Aromatic
3.	Taste	Sour	Bitter	Sour

UV/Visible spectrophotometer with a pair of matched quartz cells of 1 cm width.

Calibration Curve

Aliquots of working stock solution were prepared with distilled water to get concentration in range of 100- 200 µg/mL. The absorbances of resulting solutions were measured at λmax 222nm.

Analysis of Finished Products of Three Batches Quality control test of finished product were performed on three batches and following tests were performed during testing like Appearance, Hardness, Thickness, Friability, Disintegration, Weight uniformity, Assay.

RESULT AND DISCUSSION

Here is the list of results explained individually for concerned three batches as per procedure followed and discussed in experimental section.

A. Standardization of Vrikshamla ghan, Shuddha guggul and Triphala ghan:

Physical methods

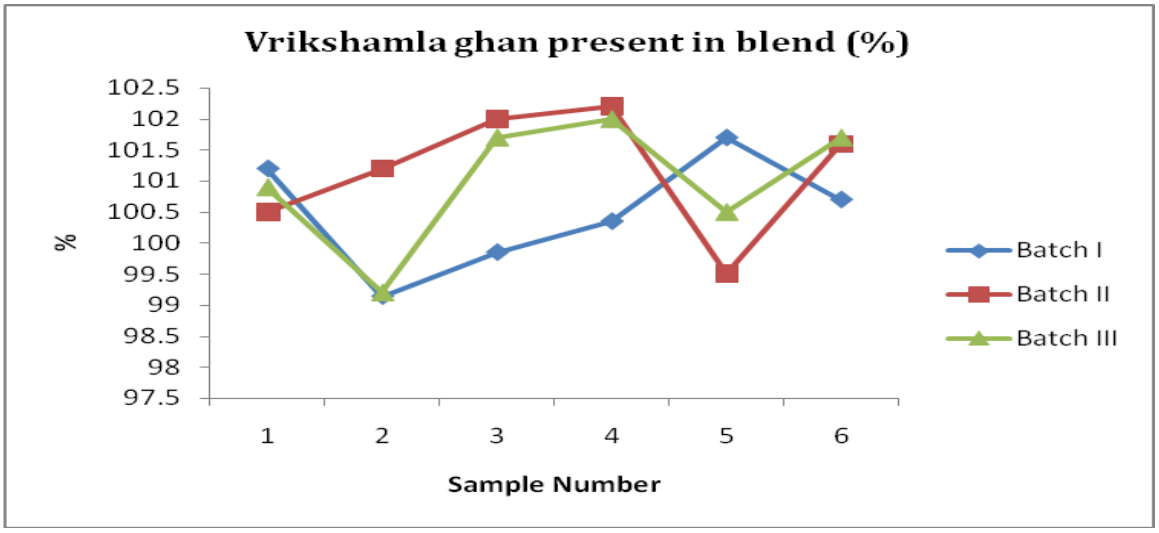

Figure 3: Blend uniformity of Vrikshamla ghan for Batch I, II, III

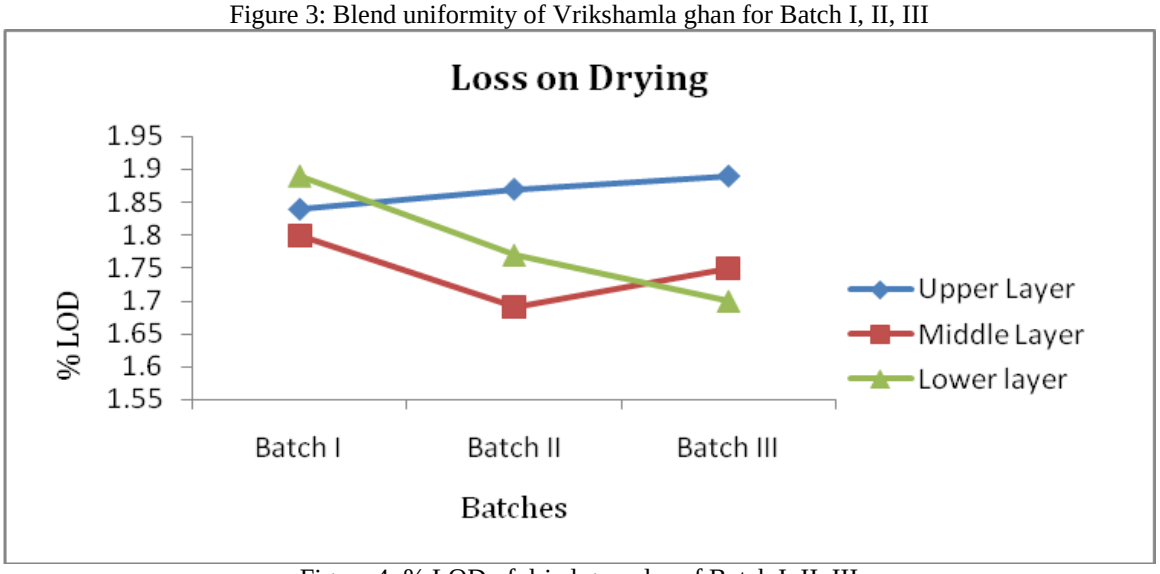

Figure 4: % LOD of dried granules of Batch I, II, III

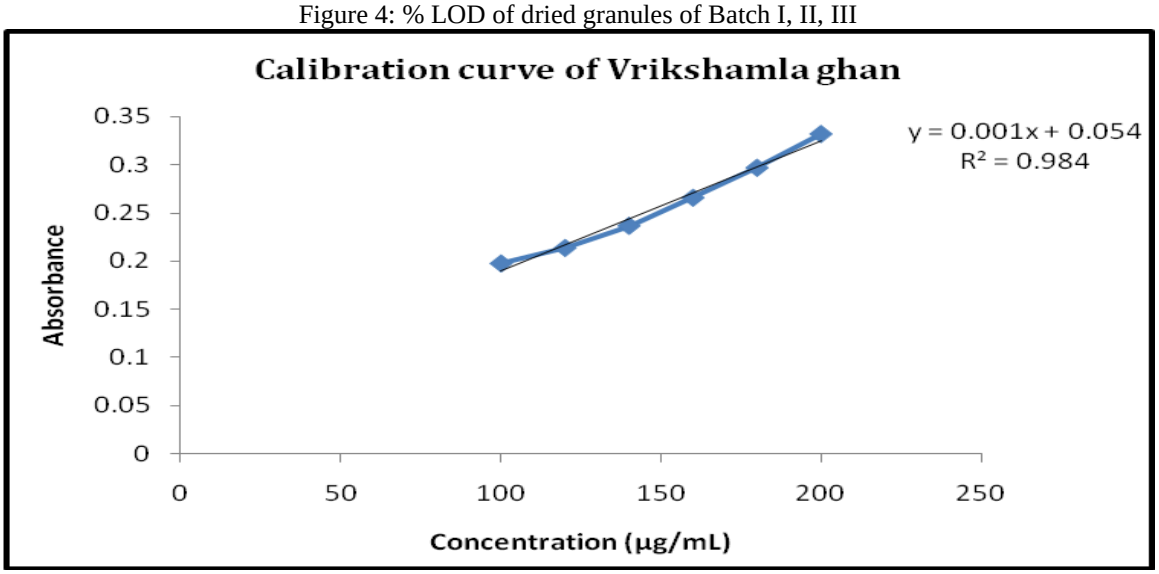

Figure 5: Calibration curve of Vrikshamla ghan

Foreign matter

The foreign matter in the different drug materials was observed by the naked eye (Table 2).

Moisture content

The moisture content of the dried powdered material of all the drugs was determined by loss on drying (LOD) method and is tabulated below (Table 3).

Ash Values

Table 9: Result of microchemical testing of Vrikshamla ghan, Shuddha guggul and Triphala ghan

Sr. No.	Reagent	Vrikshamla ghan		Shuddha guggul		Triphala ghan	
		Observa-tion	Charact-eristics	Observa-tion	Charact-eristics	Observa-tion	Charact-eristics
1	Phluoroglucinol: conc. HCl (1:1)	Pink	Lignified fibers	Yellowish brown	Lignified fibers, xylem parenchyma cells	Yellowish brown	Lignified fibers, xylem parenchyma cells
3	Sudan red III	Red	Oil globules	Deep Reddish	Oil globules	Red	Oil globules
4	Iodine solution	Blue	Starch present	Blackish brown	Starch present	Brown	Starch present

Table 11: Physical parameters study of batches I, II, III after dry mixing

Sr. No.	Parameters	Batch I	Batch II	Batch III
1.	Bulk density (g/cm^3)	0.788 ± 0.04	0.827 ±0.037	0.815 ± 0.039
2.	Tapped density (g/cm^3)	0.867 ± 0.037	0.919 ± 0.034	0.884 ± 0.042
3.	Angle of repose	27.19 ± 0.17	28.09 ± 0.07	26.04 ± 0.21

The ash values (total, acid insoluble and water soluble) of all the three selected drugs were determined in triplicate. A mean of three determinations and its standard error was calculated. The results were expressed as Mean±SE in (Table 4)

Extractive values

The amount of extractable mater in each material, extracted by different solvents namely, water, ethanol and ether was determined by cold maceration, the values are tabulated below (Table 5) the results were expressed as Mean±SE

P^H value

P^H value of Vrikshamla ghan, Shuddha guggul and Triphala ghan were indicated in table 6.

FTIR Interpretation

Fourier Transfer Infrared spectroscopy (FTIR) was done to evaluate the authentification of material. FTIR study of the drug was done for authenticity of Vrikshamla ghan. In this FTIR spectrum of Vrikshamla ghan, Shuddha guggul and Triphala ghan (Fig.1) was established and value compare with official standards, for interpretation.

Chemical method

UV Analysis

UV spectroscopy of Vrikshamla ghan

When 100ppm solution of Vrikshamla ghan, Shuddha guggul and Triphala ghan was studied by UV analysis, the absorption maxima was found at 222nm.

Botanical methods

Macroscopic studies

The organoleptic evaluations of drug materials were done and result were mentioned in table 8.

Microchemical tests

B. Result of Critical Parameter Evaluation

As per the procedure followed and discussed in the experimental section for different stages, here is the list of results explained individually for concerned three batches.

Result of Dry Mixing

As per the procedure followed for dry mixing in process flow part, here is the list of results of percentage of Vrikshamla ghan present in blend given in Fig. 3. From above observations it was found that uniform mixing of drug and excipients were done.

Table 12: Process parameters for drying

Sr. No.	Parameters	Limit	Batch	Observation
1.	Inlet air temperature at end of Drying(˚C)	60-64	I	62
			II	62
			III	62
2.	Outlet temperature at end of Drying (˚C)	40-45	I	40
			II	42
			III	40
3.	Total Drying time (Minutes)	-	I	51
			II	65
			III	60

Table 13: Lubricated blend specifications

Batch No.	Blending time (minutes)	Speed of blender (RPM)
I	10	12±1
II	10	12±1
III	10	12±1

Result of Drying

As per procedure followed in experimental work, here is the list of result of the various parameters for drying given in table 12. As per the procedure followed in experimental section, here is the list of results of % LOD given in fig. 4. As per above observations % LOD of dried granules for all three validation batches was found within limit.

Result of Lubrication

To carry out the lubricated blending, here is the list of specification given in table 13. As per the procedure followed for lubrication in experimental section and specifications for lubrication, the blend of all three batches was carried out and tested for bulk density, tap

Table 14: Physical parameters testing after lubrication

Batch	Bulk density	Tapped bulk density	Carr Index	Hausner's ratio	Angle of repose
I	0.68± 0.12	0.85± 0.14	20± 0.06	1.25± 0.09	28.95± 0.06
II	0.65± 0.06	0.81± 0.09	19.75± 0.13	1.21± 0.04	28.65± 0.14
III	0.64± 0.04	0.75± 0.12	14.66± 0.10	1.17± 0.15	28.98± 0.03

Table 15: Physical parameters testing of three batches

Sr. No.	Parameters	Batch No.	Observation			
			Initial		Middle	End
1.	Appearance	I	Complies		Complies	Complies
		II	Complies		Complies	Complies
		III	Complies		Complies	Complies
2.	Average weight	I	0.6115		0.6116	05982
		II	0.5902		0.6121	0.5856
		III	0.5908		0.5844	0.6125
3.	Uniformity of weight	I	Complies		Complies	Complies
		II	Complies		Complies	Complies
		II	Complies		Complies	Complies
		I	Min.	9.4	9.5	9.4
			Max.	11.6	11.4	10.8
			Avg.	10.5	10.45	10.1
		II	Min.	9.7	9.6	9.6
			Max.	11.9	11.5	10.9
4.	Hardness		Avg.	10.8	10.5	10.2
		III	Min.	9.5	9.6	9.6
			Max.	10.6	11.6	11.4
			Avg.	10.02	10.6	10.5
		I	Min.	4.28	4.29	4.28
5.	Thickness (mm)	II	Max.	4.35	4.38	4.38
		III	Avg.	4.31	4.33	4.33
		I	0.12		0.14	0.15
6.	Friability (%w/w)	II	0.10		0.14	0.12
		III	0.09		0.12	0.13
7.	Disintegration (Hrs: Minutes)	I	1.45		1.47	1.43
		II	1.50		1.53	1.48
		III	1.46		1.50	1.45

density, Carr Index, Hausner's ratio and Angle of repose. As per table 14, the physical parameters such as bulk density, tapped density, compressibility Index, Hausner's ratio and angle of repose for three validation batches it was found that granules having good flow properties. The result were obtained found satisfactory.

Result of Compression Parameter

As per procedure followed in compression section, it is observed that all parameters comply with specification.

Here list of results obtained for the physical parameters of Garcini tablet given in table 15. As per table 15, all physical parameters for three validation batches were found within limits.

Result of Coating

As per the procedure followed for coating in method section, here is the list of results obtained for the coating process was validated by measuring parameters and specification, coating pan RPM, air temperature, spray rate and spray pattern Atomizing air pressure, pump speed given in table 16.

C. Analysis of Garcini Tablet Spectra of Garcinia indica showed maximum absorption at wavelength 222nm.

Table 16: Coating parameter study

Sr. No.	Variables	Batch I	Batch II	Batch III
1.	Pan speed (rpm)	24.5	25	24.6
2.	Air temperature	45.05	44.07	45
3.	Spray rate (mL/min.)	2.4		
4.	Spray pattern	Normal		
5.	Nozzle to bed distance (cm)	6	6	6
6.	Atomizing air pressure kg/cm^2	3.6	3.6	3.6
7.	Pump speed (rpm)	2.5	2.5	2.5

Calibration curve of Vrikshamla ghan shown in Fig. 5 Finished product analysis Finished product of all three batches were tested for quality control of finished formulation, and from above observations it was found that bathes shows results as per predetermined specifications.

Table 17: Analytical results of finished products: Batch I, Batch II and Batch III

Tests	Specifications	Results	Results	Results
Description	Brick red film coated tablet with no surface defect	Complies	Complies	Complies
Average weight (g)	0.6054- 0.6331	0.6328	0.6293	0.6325
Uniformity of Weight of Tablets (g)	± 5 % of average weight	Complies	Complies	Complies
Thickness (mm)	Between 4.2 to 4.8mm	4.33	4.42	4.40
Hardness Kg/cm^{-3}	9-16	12.5	12.65	12.45
Length (mm)	Between 12– 12.5mm	12.4	12.3	12.4
Width (mm)	Between 5– 7.3 mm	7.15	7.09	7.0
Disintegration (Hrs)	NMT 2 Hrs.	1.50	1.52	1.40
Friability %	NMT 1	0.10	0.10	0.15
Assay (%)	_	99.14	99.45	99.37

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