IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 14, Issue 3 Ser. I (May – June 2019), PP 44-69
www.Iosrjournals.Org

In Process Validation of Nevilast-30

Thejovathi B,* Kondal Reddy J, Kondla Usha
Thejovathi B, Associate Professor,
Department of Pharmaceutics,
Vision College of Pharmaceutical Sciences & Research,
RNS Colony, Boduppal, Hyderabad 500092
Corresponding Author: Thejovathi B

Abstract: *Process validation and optimize the manufacturing process and established key process parameters involved in the manufacturing of NEVILSAT – 30 Tablets. The objective of present study was to develop a stable and robust manufacturing process for NEVILAST – 30 Tablets. The process parameters will yield product which meets predetermined quality attributes .The prospective process validation was performed on three consecutive batches. The future scope of the work is to enable the process on commercial production of tablet meeting its predetermined specification and quality attributes after these validation batches. Concurrent process validation is carried out for the NEVILAST 30 -700mg. NEVILAST-30 is indicated for the treatment of Human Immunodeficiency virus Type 1 infected adults and adolescents. The bioavailability of the drug in adults is normally 80-90 %. This fixed combination replaces the three components (lamivudine, stavudine, nevirapine) used separately in similar dosages. Process controls included raw materials inspection, in-process controls and targets for final products. The purpose was to monitor the on-line performance of the manufacturing process and then validate it. Even after the manufacturing process was validated, current good manufacturing practice required a well written procedure for process controls which was established to monitor its performance. The bioavailability of the drug in adults is normally 80-90 %.*

Key Words*: Nevirapine, Lamivudine, Stavudine, Croscarmellose Sodium (Primellose), Croscarmellose Sodium (Primellose), 3batches, Bowl & Lots.*

Date of Submission: 20-04-2019 Date of acceptance: 04-05-2019

I. Introduction

Process validation is establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce product meeting its predetermined specifications and quality attributes. The concept of validation has expanded through the years to encompasses a wide range of activities from analytical methods used for the quality control of drug substances and drug products & to computerized systems for clinical trials, labeling or process control. The validation simply means, "Assessment of validity" or action of proving effectiveness.

Validation Protocol:

- General information
- Objective
- Background/revalidation activities
- Summary of development and technical transfer (for R&D or another site) activities to justify in process testing and controls any previous validations.
- List of equipment and their qualification status
- Facilities qualification
- Process flow chart
- Manufacturing procedure narrative
- List of critical processing parameters and critical excipients
- Sampling, tests and specifications
- Acceptance criteria

Concurrent process validation is carried out for the product NEVILAST 30 -2.5 mg. Consecutively 3 batches or lots were taken for process validation. All the critical parameters were evaluated for fixing the optimum process parameters. The following is the plan of work designed based on Master Manufacturing Formula

1. Literature Review 2. Preparing process flow chart 3. Preparing the validation protocol
4. Execution of validation 5. Documentation of the same process.

Lamivudine is ananalogue of cytidine. It can inhibit both types of (1 and 2) of HIV reverse transcriptase. Lamivudine enters the cell by passive diffusion. Stavudine inhibits the activity of HIV-1 reverse transcriptase both by competing with natural substrate dGTP and by its incorporation into viral DNA. Nevirapine is a non-nucleoside reverse transcriptase. Nevirapine binds directly to reverse transcriptase (RT) and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

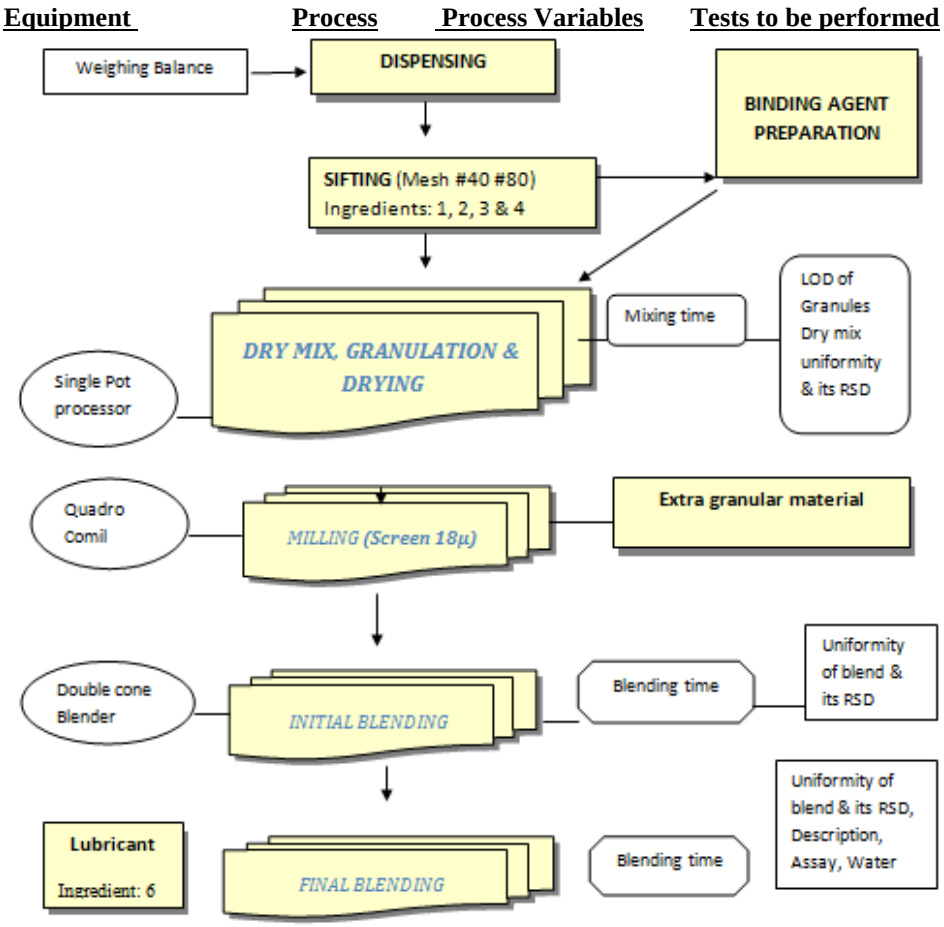
II. Materials and Methods

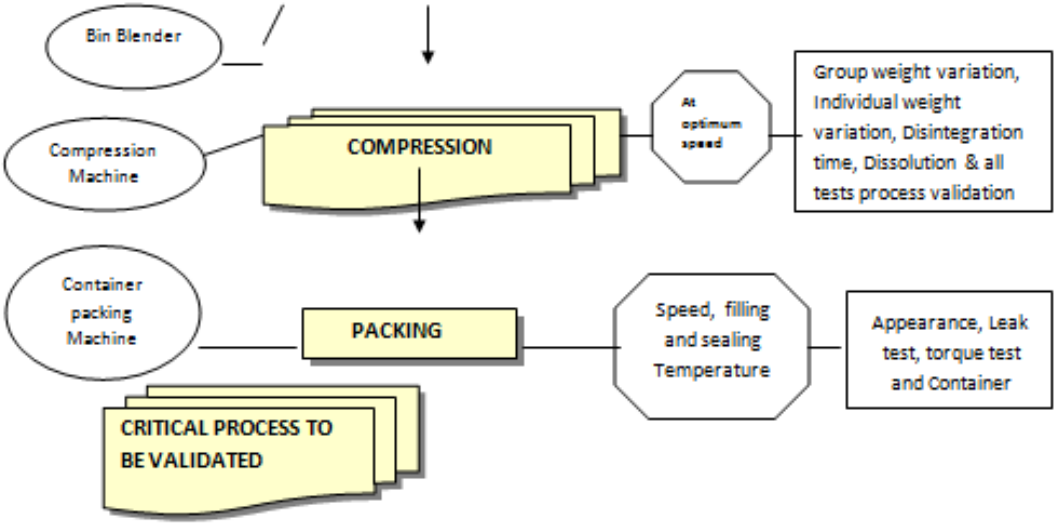
Each tablet of NEVILAST 30- contains 700 mg.

Item code	Item	*Function*	Quantity As Per Tablet(mg)	Quantity As Per Batch(kg)
	Intra Granular Materials			
1	Lamivudine Stavudine Nevirapine	Active ingredient	150 30 200	31.250 6.250 41.666
2	Lactose	Diluent	195.10	41.800
3	Maize Starch	Disintegrant	55.40	11.452
4	Croscarmellose Sodium (Primellose)	Binder	9.00	1.875
5	Povidone (PVPK-30)	Vehicle	17.00	3.542
6	Isopropyl Alcohol	Granulating agent	117. 57	24.494
	Extra Granular Materials			
7	Magnesium Stearate	Lubricant	11.50	7.187
8	Sodium Starch glycollate	Lubricant	19.00	11.875
9	Croscarmellose Sodium	Lubricant	6.00	3.750
10	Colloidal Anhydrous Silica	Lubricant	7.00	4.375
11	Lake Sunset yellow	Coloring agent	4.00	0.833

Validation plan: For batch size: 15 kg (150000 tablets)

Process Flow Chart





Manufacturing procedure

Dispensing

The Following Instructions to be followed during Dispensing

- The Area and Equipment must be cleared by QA before use.
- Follow the Gowning Procedures as per S.O.P.
- Issue only approved Materials.
- Ensure labeling at all stages of Dispensing.
- Check the Accuracy & ensure that Balances are calibrated before use.
- Ensure to fill the details in list of Personnel before starting the Dispensing.
- General Dispensing Instructions
- ✓ Room Temp: NMT 25°C
- ✓ Relative Humidity: NMT 60%

Process instructions

- Follow the Gowning procedure
- The area & Equipment must be cleared by QA before use.
- Check & Ensure that all balances are in calibrated state.
- Ensure that the product is label with all stages of manufacturing.
- Follow the operative instructions & SOP's.
- General manufacturing conditions:
- ✓ Room Temperature: NMT 25°C
- ✓ Relative Humidity: 45±5
- ✓ Pressure Differential: NLT 12.5 Pascal's
- Ensure to fill the details in the list of personnel before executing the batch.
- Ensure that the isolators are showing healthy conditions before starting the operation.
- The recommended process time for manufacturing the finished drug product is within 30 days of
- Start of manufacturing process.
- Record the tare weight of blender before starting of process.

Sifting (Intra Granular Materials)

- Ensure that the Area and Equipment must be cleared by QA before use.
- Check the sieve no's 40&80 before starting.
- Check & ensure that the temperature, RH & DP is within the specified limits.
- Check the integrity of the sieve before and after sifting of material and record the details.
- Sift Lamivudine (31.250Kg), Stavudine(6.250kg), Nevirapine(41.666kg), Croscarmellose Sodium(1.875Kg.) in the process area through 40 mesh and collective double polythene bag and labeled.

Granulation

Equipment must be cleared by QA before use

Dry Mixing

- Load the Sifted material in Single Pot rapid mixer granulator.
- Dry mix the material for 5 minutes at 120±10 Impeller rpm at slow speed and chopper off.

Binder Solution Preparation

Take IsoPropyl Alcohol (IPA), stir IPA (24.494lit) in a vessel to form vortex with out drawing air into liquid ,add steadily povidone(3.542kg) to vortex to get a clear solution.

Wet Granulation

- Start and run the impeller at 120±10 rpm with chopper off, add binder solution to the dry mixed material in the granulator over a period of 3min slowly, while mixing with impeller at slow speed.
- Scrap the impeller and inner walls of the bowl using a scrapper/ spatula. Continue mixing for 2 min with impeller and chopper at slow speed. Check for complete formation of granules.
- Add extra quantity of IPA(if required) and mix until the granulation end point is reach.
- Rake the material for 1 min at impeller fast and chopper slow speed.
- Record the observed parameters at the end of Granulation process.
- ✓ Total Additional Mixing Time-2 min.
- ✓ Total Mixing Time-10 min.

Drying

- Transfer the wet granular mass into a clean prelabeled Fluidized Bed Dryer(FBD) bowl check the integrity of the finger bag before use.
- Start the vacuum pump, start the Thermal resistor and set the temperature at 25 ± 5^{0}C, close the vacuum vent valve provided on the filter assembly, apply vacuum by opening the manual valve, inject air at a pressure of 15 – 20 ltr. Per min.
- Air dry the wet mass in fluid bed dryer to get the final LOD of the granules not more than 3% w/w on IR moisture analyzer.
- Rate the granules intermittently for every 10min.
- Check the LOD after every 10 Min. of drying cycle. Repeat the cycle till the LOD of the granule is within the limit of NMT 3% w/w.
- Unload the dried granules and collect in a double poly bag, weigh and labeled.

Sieving & Milling

- Ensure that the Equipment must be cleared by QA before use.
- Check the integrity of sieve and record details. (same as granulation)
- Check and ensure the temp., RH and DP. within specified limits.
- Sieve the dry granules through mesh #18 (screen size 2mm) on vibrator sifter.
- Mill the oversized dried granules using a multi mil at medium speed in forward direction and finally pass through sieve #18.
- Collect the granules in double polythene bag and labeled.

Sifting (Extra Granular Materials)

- Ensure that the Equipment must be cleared by QA before use.
- Check the integrity of sieve and record details. (same as granulation)
- Check and ensure the temp., RH and DP with in specified limits.
- Sift the extra granular material in the process area (outside isolator & transfer it to the isolator through the pass box before starting the process).
- Sift Magnesium Stearate – 7.187 Kg.
- Sodium Starch – 11.875 Kg.
- Croscarmellose Sodium – 3.750 Kg.
- Colloidal anhydrous silica -- 4.375 Kg
- Through # 40 mesh sieve and collect in double polythene bag and labeled.

Blending

- Ensure that the Equipment must be cleared by QA before use.
- Record the tare weight of Bin Blender.
- Load the granules and sifted ingredients (extra granular materials) into the Double cone blender.
- Blend the materials for 5 minutes at 10 rpm.

- Sift Lake Sunset (0.833 Kg) yellow through sieve #80 using sifter for color blend.
- Send "Request for Analysis" to QA for sampling and onward submission of samples to QC.
- Detoxify the Isolated chamber and remove bin blender from isolator and check the gross weight of bin blender.

Compression

- Ensure that the Equipment must be cleared by QA before use.
- Check and ensure the temp., RH and DP. with in specified limits.
- Set up the tablet compression machine with 12.8 mm round plain flat bevel edged lower and upper punches with correspondence dies.
- Ensure that the blend is approved for Compression.

VALIDATION PROCEDURE

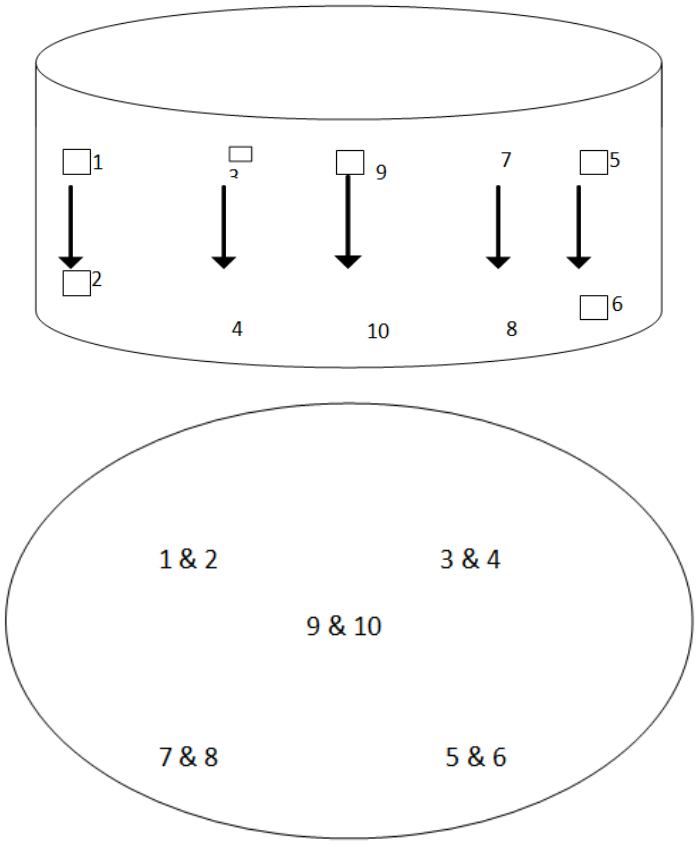
- Three batches of 12.5 Lakhs tablets batch size will be manufactured as described in the Batch manufacturing record.
- Current version of standard operating procedures to be followed
- Record the yield after blending, compression and packing.

Sampling Procedure at different stages

Dry mixing

The drying mixing step involves mixing of active ingredient with other additives using rapid mixer granulator processor. The content uniformity of Nevilast-30 has to be established during validation of dry mixing process. Determination of the content uniformity of the drug has to be done at the end of 5 minutes. The acceptance criteria for the content uniformity are 100 ± **5** % of the theoretical quantity, where as the limit for Relative Standard deviation (RSD) should be NMT± 5.0%. The sample quantity shall be between 639.5 mg to 1918.5 mg. Sampling should be done with sampling rod. Samples to be collected in Poly bags. Collect samples in to three sets. One set of sample is taken for analysis and other sets are kept as a reserve sample. In case of failure results of first sample, use reserve set otherwise discard the reserve samples.

SPP(FBD) sampling location of Dry mix



Sample No.	Location
1 & 2	Upper (left front)
3 & 4	Upper (right front)
5 & 6	Lower (right rear)
7 & 8	Lower (left front)
9 & 10	Upper (Centre)

Table no. 8: Sampling location of Dry mix

Granulation

The granulation is to be performed using SPP. The granulation step involves converting the powder into wet rough mass. The granule strength, bulk density of blend, dissolution, hardness of tablets etc are influenced by mixing time. Binding agent preparation (BAP) is being used for granulation. The granulation end point is critical process and the end point of granulation shall be checked against the amperage readings of Impeller & chopper of the SPP, which gives the co-relation to the granulation end point.

Drying

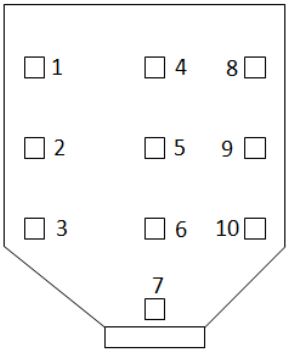
The drying of the wet granules is performed in SPP. The inlet temperature of the SPP is controlled during the process and the outlet temperature is monitored and co-related with the corresponding Loss on drying (LOD) of the granules under drying. The outlet temperature range is established which is required to attained desired LOD of the granules.

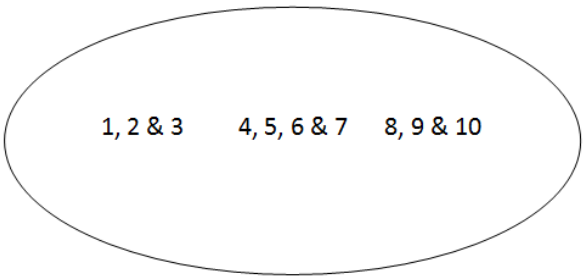
- Draw samples from different positions of the SPP bowl and make pooled Sample and check LOD. Repeat the same at different outlet temperatures.
- Once the LOD of the polled sample meets the desired range, draw samples from five different places in the S bowl and check LOD
- Record the following observations
- Inlet air temperature, outlet temperature for every 10 minutes.
- Check and record LOD of granules at different temperatures and at end of drying process.

Blending

Load the sifted materials in to the Bin blender except Magnesium stearate. Start the blender in inch mode and check for any leakage of material. On ensuring that there is no leakage, blend for 8-10 minutes. Add Magnesium stearate, Sodium starch, Croscarmellose Sodium and Colloidal anhydrous silica gel along with equal quantity of blend from octagonal blender in double polythene bags for proper mixing. Then add this lubricated material to blended material in the blender. Then blend for another 5 minutes and collect the samples from 10 locations. Sample size shall be between 700 mg to 2100 mg. All samples shall be collected in tarred vials. Collect samples in 3 sets .one set of sample is taken for analysis. Other sets are kept as reserved Sample.

Sampling locations in a cone blender





Sample No.	Location
1	Upper (left)
2	Middle (left)
3	Lower (left)
4	Upper (Centre)
5	Middle (Centre)
6	Lower (Centre)
7	Bottom (Centre)
8	Upper (right)
9	Middle (right)
10	Lower (right)

- Sample numbers to be given as 1/1 to 1/10

Check and record the following
- Sieve analysis
- Bulk density
- Content uniformity
- Assay
- LOD/Moisture content

Compression

Compression is to be carried out as per batch manufacturing record using 12.8 mm circular, plain flat, beveled edge with plain surface on upper punches, 12.8 mm circular, beveled edge with plain surface and 8 mm diameter dies set the machine at different speeds of 16, 80 rpm and check the following parameters.
- No. Of stations: 37 station compression machine
- Type of tooling type: 6.8 on lower punch and LET on upper punch
- Speed of machine from 2, 21,500 to 2, 22,000 tablets per hour.

Carry out the testing of content uniformity of physical parameters as mentioned in the below table. The tablets compressed at various set parameters of the specification limits should confirm as per the following:

Standard parameters

S.No.	Parameters	Standards
01	Weight of 20 tablets	14 gm ± 2%
02	Hardness	NLT 4 kp
03	*Thickness*	4.5 mm ± 0.3 mm
04	Friability	NMT 1 % w/w
05	Individual weight variation	700mg ± 2 %

Table no. 9: Standard parameters

Hopper study

To evaluate effects of vibrations during compression on blend uniformity hopper study shall be carried out. Fill the hopper completely run the compression machine. Collect tablets when powder level in the hopper is full, approx, middle hopper and when it is nearing end of the hopper.

Dissolution profile

Check the dissolution profile of 6 tablets at 10 min, 15 min, 20 min, 30 min and 45 min from the pooled sample after the completion of compression.

Note: Dissolution profile on 12 tablets shall be done in 0.1N Hydrochloric acid media, pH 4.5 acetate buffer & pH6.8 phosphate buffer using 900ml media, 50 rpm, paddle, the time points 5, 10,15,30,45 & 60min.

Container packing

Packing is to be done as per batch packing record. Before starting packing operations check the container sealing roller temperature and speed of the machine. After packing check container quality, sealing appearance and leak test.

III. Results

PROCESS VALIDATION REPORT OF TABLET DOSAGE FORMS NEVILAST 30 – 700MG

1. Dispensing

Analysis report of all the raw materials were checked and only approved raw material were used

2. Sifting

Presence of foreign particles and final and hard lumps were observed and no such materials were observed.

3. Dry mixing

Fixed Parameters

Rapid mixer Granulator rpm	: 19-21 RPM
Rapid mixer Granulator Type & Capacity	: SSPM, 400 liters
Variables Considered for Study	: Mixing Time
Time Interval Studied	: 5 minutes
Measured Response	: Description, Blend uniformity
Acceptance Criteria	: Not less than 90 % and not more

than 110 % of the label claim.

Dry mixing – blend uniformity samples (colorless layer)

DRY MIXING BLEND UNIFORMITY SAMPLES (% w/w)																	
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**															
		XXXX									**YYY**			**ZZZ**			
A.R. No.	-------	**Lot-I**			**Lot-II**			**Lot-III**			**Lot-I**			**Lot-I**			
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	
1	**90% - 110% With RSD< 5.0%**	92.4	101.4	95.0	91.29	104.59	94.69	99.92	106.59	100.21	102.95	102.01	103.18	97.58	94.73	101.12	
2		94.0	98.7	97.3	95.16	94.62	97.16	93.49	96.14	94.49	100.59	97.09	100.31	98.29	97.91	100.86	
3		94.4	99.2	97.6	94.16	98.62	97.50	105.46	108.32	106.72	100.03	97.95	100.09	98.71	95.92	101.10	
4		93.3	100.4	96.7	93.96	98.58	97.57	100.06	106.71	100.35	100.28	106.82	100.19	98.64	95.00	100.14	
5		93.4	98.9	96.4	93.76	99.20	97.06	102.09	98.76	100.70	100.63	95.34	99.28	98.27	99.78	100.64	
6		93.4	100.6	96.8	93.74	102.35	96.79	94.21	97.18	95.65	101.03	104.69	101.54	98.43	97.24	99.30	
7		94.2	99.1	97.3	90.70	102.97	94.42	97.42	100.07	98.57	100.37	97.30	100.67	98.66	97.92	100.29	
8		93.1	98.7	96.0	95.26	94.97	96.98	98.96	94.01	99.68	101.15	101.08	101.17	97.82	98.44	101.24	
9		92.4	101.6	95.1	99.54	99.27	101.40	101.91	102.24	102.56	102.60	98.57	101.37	101.14	100.02	103.25	
10		93.1	98.7	96.2	95.71	95.54	97.51	103.99	100.45	102.22	98.36	102.61	97.84	97.43	100.32	100.16	
Min.		98.7	95.0	90.7	91.2	94.42	93.49	94.01	94.49	98.36	95.34	97.84	97.84	97.43	94.73	99.3	
Max.		101.6	97.6	99.54	100.59	101.4	105.46	108.32	106.72	102.95	106.82	103.18	101.18	101.14	100.32	103.25	
MEAN		93.0	100.0	97.0	94.3	98.3	97.1	99.8	101.01	100.1	100.8	100.3	100.6	98.5	97.7	100.8	
% RSD		0.7	1.2	0.9	2.6	4.3	2.0	3.9	4.8`	3.5	1.3	3.7	1.4	1.1	2.1	1.0	

Table-13: Dry mixing – blend uniformity samples (colorless layer)

Dry mixing – blend uniformity samples (color layer)

DRY MIXING BLEND UNJIFORMITY SAMPLES (% w/w)																
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**														
		XXXX									**YYY**			**ZZZ**		
A.R. No.	-------	**Lot-I**			**Lot-II**			**Lot-III**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD< 5.0%**	95.92	96.14	98.46	94.88	95.50	96.29	99.18	106.33	103.77	100.18	103.18	104.57	100.26	97.20	103.63
2		93.30	94.29	94.97	91.88	91.43	93.87	98.93	101.0	103.55	100.12	103.13	104.71	101.94	101.36	104.34
3		94.74	95.02	97.74	103.53	102.87	105.84	98.65	106.9	102.63	95.70	106.95	99.35	103.12	99.79	105.14
4		91.25	91.04	93.41	93.74	93.80	96.60	98.93	105.73	103.07	99.04	105.91	102.56	104.04	99.71	103.57
5		92.85	93.10	95.23	95.95	96.60	97.80	98.49	107.92	103.26	96.46	104.07	100.53	103.35	104.18	102.56
6		91.87	92.54	93.54	91.78	92.53	93.10	99.68	101.85	103.38	96.34	103.94	100.44	99.91	98.64	100.71
7		97.25	96.75	99.74	97.26	97.53	99.49	99.27	104.59	102.77	99.33	106.20	102.64	103.35	101.81	100.66
8		94.37	95.03	96.14	92.26	9.79	93.81	99.51	105.11	103.69	95.72	106.98	99.31	98.35	101.50	101.49
9		94.53	94.74	97.34	94.04	94.09	96.67	101.37	107.0	103.30	9929	102.31	103.75	100.23	99.03	101.96
10		95.84	95.27	98.07	94.45	93.83	96.06	98.85	100.91	103.07	101.01	104.35	104.39	102.98	99.86	105.09
Min.		91.26	91.04	93.14	91.78	91.43	93.1	98.49	100.91	102.63	95.7	102.31	99.31	98.35	97.2	100.66
Max.		97.25	96.75	99.74	103.53	102.87	105.84	101.37	107.92	103.77	101.01	106.98	104.71	104.04	104.18	105.14
MEAN		94.2	94.4	96.5	95.0	95.1	97.0	99.3	104.8	103.3	98.3	104.7	102.2	101.8	100.3	102.9
% RSD		2.0	1.8	2.2	3.7	3.5	3.8	0.8	2.5	0.4	2.1	1.6	2.1	1.9	2.0	1.6

Table-14: Dry mixing – blend uniformity samples (color layer)

a) Dry mixing – Composite sample (Colorless layer)

Checks	**Specification/ Acceptance Criteria**	**Observations**				
		Batch No.				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
Bulk Density (gm/ml)	For information	0.471	0.496	0.477	0.462	0.497
Tapped Density (gm/ml)	For information	0.730	0.851	0.738	0.707	0.739

Table-15: Dry mixing – Composite sample (Colorless layer)

b) Dry mixing – Composite sample (Color layer)

Checks	**Specification/ Acceptance Criteria**	**Observations**				
		Batch No.				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
Bulk Density (gm/ml)	For information	0.477	0.567	0.593	0.443	0.607
Tapped Density (gm/ml)	For information	0.738	0.692	0.726	0.950	0.743

Table-16: Dry mixing – Composite sample (Color layer)

4. Wet granulation

a) Wet granulation - Composite sample (Colorless layer)

Checks	Specification/ Acceptance Criteria	Observations				
		Batch No.				
		XXX			YYY	ZZZ
		Lot-I	Lot-II	Lot-III	Lot-I	Lot-I
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	For information	4.2	9.5	7.7	8.9	6.9

Table-17: Wet granulation - Composite sample (Colorless layer)

b) Wet granulation - Composite sample (Color layer)

Checks	Specification/ Acceptance Criteria	Observations				
		Batch No.				
		XXX			YYY	ZZZ
		Lot-I	Lot-II	Lot-III	Lot-I	Lot-I
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	For information	4.2	9.5	7.7	8.9	6.9

Table-18: Wet granulation - Composite sample (Color layer)

5. Drying

Fixed Parameters

- Fluidized Type & Capacity : CLIT, 120 kg
- Bowel Temperature(^{0}C) : 25±5
- Air Pressure (L/min) : 12-14
- Fluidization : Continuous

Observed parameters

- Product temperature attained during drying : 25-28^{0}C
- Total Drying time (min) : 30
- LOD (%w/w) : NMT 3%

a) Drying Results – Rate of Drying (Colorless layer)

Percentage LOD Results for every 10 minutes (Rate of Drying)												
Checks	Specifications	Time	Observations									
			Batch No.									
			XXX						YYY		ZZZ	
			Lot-I		Lot-II		Lot-III		Lot-I		Lot-I	
			B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II
% LOD	NMT 3.0% w/w	10 min.	---	---	---	---	---	---	---	---	---	---
		20 min.	3.04	4.87	4.39	4.43	4.33	4.48	4.19	4.46	4.24	4.27
		30 min.	2.55	2.63	2.63	2.54	2.57	2.37	2.53	2.31	2.50	2.18

Table-19: Drying Results – Rate of Drying (Colorless layer)

b) Drying Results – Rate of Drying (Color layer)

Percentage LOD Results for every 10 minutes (Rate of Drying)												
Checks	Specifications	Time	Observations									
			Batch No.									
			XXX						YYY		ZZZ	
			Lot-I		Lot-II		Lot-III		Lot-I		Lot-I	
			B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II	B-I	B-II
% LOD	NMT 3.0% w/w	10 min.	---	---	---	---	---	---	---	---	---	---
		20 min.	3.89	3.77	2.85	3.94	3.44	3.78	3.83	3.77	3.34	3.29
		30 min.	2.03	1.39	1.73	2.81	1.44	1.94	1.87	1.70	1.16	1.73

Table-20: Drying Results – Rate of Drying (Color layer)

c) Drying results (Drying Uniformity) (Colorless layer)

BOWL-I

Percentage LOD results (Drying Uniformity)								
Checks		**Specification**	**Observations**					
Batch Number		---	**Batch No.**					
			XXX			**YYY**	**ZZZ**	
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**	
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---	
	1		1.2	0.8	1.3	0.9	1.0	
	2		1.3	1.0	1.8	0.6	0.9	
	3		1.2	0.8	1.5	0.5	1.0	
	4		1.2	0.9	1.3	0.2	0.9	
	5		0.5	1.1	1.4	0.4	0.8	
	6		0.6	1.2	1.4	1.1	0.6	

Table-21: Drying results (Drying Uniformity) (Colorless layer)

BOWL-II

Percentage LOD results (Drying Uniformity)							
Checks		**Specification**	**Observations**				
Batch Number		---	**Batch No.**				
			XXX			**YYY**	**ZZZ**
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---
	1		1.5	1.0	1.2	1.0	0.6
	2		1.3	0.8	1.3	0.9	0.9
	3		1.2	1.0	1.5	0.7	1.2
	4		1.4	1.3	1.1	1.0	1.3
	5		1.2	0.8	1.6	1.2	1.1
	6		0.9	1.1	1.2	1.0	1.2

Table-22: Drying results (Drying Uniformity) (Colorless layer)

d) Drying results (Drying Uniformity) (Color layer)

BOWL-I

Percentage LOD results (Drying Uniformity)								
Checks		**Specification**	**Observations**					
Batch Number		---	**Batch No.**					
			XXX			**YYY**	**ZZZ**	
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**	
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---	
	1		1.4	1.1	0.4	1.2	0.9	
	2		1.3	1.1	0.5	1.2	0.9	
	3		1.5	1.0	0.1	1.0	0.8	
	4		1.1	1.0	0.6	0.9	0.7	
	5		0.9	1.0	0.5	0.9	0.8	
	6		0.7	0.7	0.5	1.0	0.8	

Table-23: Drying results (Drying Uniformity) (Color layer)

BOWL-II

Percentage LOD results (Drying Uniformity)								
Checks		**Specification**	**Observations**					
Batch Number		---	**Batch No.**					
			XXX			**YYY**	**ZZZ**	
			Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**	
%LOD of Dried granules (%m/m) after completion of drying	**Location**	**NMT 3.0%**	---	---	---	---	---	
	1		1.0	0.5	0.6	1.3	0.9	
	2		1.1	0.6	0.7	1.2	0.7	
	3		1.6	0.4	0.7	1.3	0.9	
	4		1.2	0.6	0.6	1.2	0.8	
	5		1.0	0.5	1.0	1.2	0.8	
	6		1.0	0.1	0.6	1.0	1.0	

Table-24: Drying results (Drying Uniformity) (Color layer)

e) Drying results - composite sample (Colorless layer)

BOWL-1

Percentage LOD results (Drying Uniformity) – BOWL-I						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.7	1.1	1.6	1.0	1.7
Residual solvents analysis (IPA Content)	NMT 5000 ppm	113	329	620	758	711

Table-25: Drying results - composite sample (Colorless layer)

BOWL-2

Percentage LOD results (Drying Uniformity) – BOWL-II						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.4	0.8	1.1	1.3	1.8
Residual solvents analysis (IPA Content)	NMT 5000 ppm	138	607	1048	705	587

Table-26: Drying results - composite sample (Colorless layer)

f) Drying results - composite sample (Color layer)

BOWL-1

Percentage LOD results (Drying Uniformity) – BOWL-I						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.0	1.9	0.8	1.1	1.5
Residual solvents analysis (IPA Content)	NMT 5000 ppm	348	135	121	352	1974

Table-27: Drying results - composite sample (Color layer)

BOWL-II

Percentage LOD results (Drying Uniformity) – BOWL-II						
Checks	**Specification**	**Observations**				
---	---	**Batch No.**				
		XXX			**YYY**	**ZZZ**
		Lot-I	**Lot-II**	**Lot-III**	**Lot-I**	**Lot-I**
LOD by moisture analyzer in an auto mode at 105ºC (%w/w)	NMT 3.0% w/w	1.5	0.9	0.9	0.9	1.2
Residual solvents analysis (IPA Content)	NMT 5000 ppm	146	109	160	372	1186

Table-28: Drying results - composite sample (Color layer)

6. Sifting / milling dried granules

Fixed Parameters

Equipment : Multimill
Screen Size : 2 mm (2000µ)
Sieve No. : 18

Percentage of Granules Retained & Passed

After milling through Multimill			
%of Granules retained on #18 mesh	4.2	3.5	3.7
%of Granules passed through #80esh	89.5	89.4	90.0

Table-29: Percentage of Granules Retained & Passed

7. Blending

Fixed parameters

Blender rpm : 9 ±1 rpm
Variables considered for study : blending time
Time interval studied : 5 minutes
Acceptance criteria : NLT90 % and not morethan110 % of the label claim
Measured response : Content Uniformity and RSD

a) Lubrication (Colorless layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	92.32	91.03	92.80	97.02	99.33	97.64	92.36	94.76	95.65
2		99.70	95.72	100.44	99.28	99.57	98.92	94.15	97.69	97.60
3		94.54	93.85	94.92	97.44	97.59	97.04	92.37	95.64	95.858
4		92.14	90.35	92.30	98.30	98.78	98.67	90.42	91.62	94.49
5		92.77	91.97	93.16	98.67	98.71	98.32	91.23	92.00	93.88
6		98.59	101.18	100.58	100.43	100.50	100.02	98.83	101.18	99.62
7		96.43	96.74	97.41	98.70	99.26	99.08	97.06	92.19	98.16
8		98.75	97.86	99.52	97.63	97.28	97.24	100.46	99.72	101.92
9		102.38	97.93	101.74	101.56	101.81	101.07	100.24	103.11	103.44
10		100.42	98.44	100.86	96.98	99.30	97.41	101.60	104.26	104.72
Min.		92.14	90.34	92.3	96.98	97.59	97.04	90.42	91.62	93.88
Max.		102.38	101.18	101.74	101.56	101.81	101.07	101.6	104.26	104.72
MEAN		96.8	95.5	97.4	98.6	99.3	98.5	95.9	97.2	98.5

Table-30: Lubrication (Colorless layer)

b) Lubrication - Sample from Containers (Colorless layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	91.40	90.08	92.28	101.90	94.62	99.67	99.90	102.25	104.26
2		94.11	93.29	94.72	101.70	99.74	100.91	97.69	92.76	98.46
3		100.58	102.96	101.91	99.51	102.65	99.97	90.20	93.23	94.17
4		98.47	98.81	99.25	101.23	102.89	101.69	90.24	91.39	94.60
5		100.32	96.26	100.81	99.49	99.16	98.80	96.15	96.79	98.86
6		96.13	94.76	96.80	99.54	99.17	98.83	101.70	100.99	103.17
7		97.78	96.89	98.51	100.83	102.33	101.06	98.27	101.11	101.41
8		95.06	90.72	94.99	99.31	102.54	99.67	98.06	98.97	99.13
9		92.73	91.98	93.25	100.14	92.95	98.0	98.05	100.50	100.17
10		99.98	97.39	100.13	101.27	99.14	100.25	95.43	90.72	96.21
Min.		91.5	90.08	92.28	99.31	92.95	98.0	90.2	90.72	94.17
Max.		100.58	102.96	101.91	101.9	102.89	101.69	101.7	102.25	104.26

MEAN		96.7	95.3	97.3	100.5	99.5	99.9	96.6	96.9	99.0

Table-31: Lubrication - Sample from Containers (Colorless layer)

c) Lubrication - Sample from Containers (Color layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	96.42	103.27	100.46	96.13	103.23	99.99	96.24	98.20	96.10
2		97.68	99.48	101.93	95.01	102.48	99.55	94.26	98.41	95.15
3		96.12	103.73	99.60	98.37	105.87	102.03	96.86	103.89	100.76
4		94.27	100.64	97.85	96.53	104.20	100.73	97.31	103.26	99.65
5		97.14	106.19	101.54	95.91	100.23	98.86	97.20	101.36	99.20
6		94.93	96.93	98.18	95.83	102.46	99.48	97.49	103.52	99.70
7		96.12	101.39	98.14	95.43	102.84	99.54	96.92	103.85	100.45
8		95.86	103.75	99.29	96.23	100.67	99.0	94.36	98.57	95.16
9		98.89	104.53	99.62	95.31	101.77	98.59	97.12	99.19	96.45
10		96.22	98.27	100.23	95.54	102.97	99.72	96.54	100.73	98.71
Min.		94.27	96.93	97.85	95.01	100.23	98.59	94.26	98.2	95.15
Max.		98.89	106.19	101.93	98.37	105.87	102.03	97.49	103.89	100.76
MEAN		96.4	101.8	99.7	96.0	103.0	99.8	96.4	101.1	98.1
% RSD		1.4	2.9	1.4	1.0	1.6	1.0	1.2	2.4	2.2

Table-32: Lubrication - Sample from Containers (Color layer)

d) Lubrication - Sample from Containers (Color layer)

LUBRICATION BLEND UNIFORMITY SAMPLES (% w/w)										
Sampling Point Location	**Specification/ Acceptance Criteria**	**Batch No.**								
		XXXX			**YYY**			**ZZZ**		
A.R.No.	-------	**Lot-I**			**Lot-I**			**Lot-I**		
		L	**S**	**N**	**L**	**S**	**N**	**L**	**S**	**N**
1	**90% - 110% With RSD<5.0%**	92.10	98.56	97.62	94.78	101.79	99014	94.4	104.11	100.78
2		93.22	98.55	98.87	99.78	105.81	103.83	98.75	100.08	99.25
3		92.70	98.23	98.36	96.84	100.87	100.54	95.48	103.10	102.00
4		91.90	98.97	97.88	95.77	98.99	99.33	94.32	104.94	98.80
5		92.59	99.24	99.37	94.25	99.51	98.03	93.49	102.44	100.23
6		91.97	99.32	98.36	94.19	99.35	98.03	94.39	104.86	98.90
7		92.33	99.14	98.54	95.21	98.42	98.78	93.63	102.69	100.47
8		91.07	97.41	96.47	95.76	99.78	99.41	94.39	102.41	101.01
9		91.51	96.77	96.75	94.21	101.04	98.28	98.45	99.79	98.90
10		92.50	99.96	98.70	98.75	104.76	102.87	94.42	104.05	100.77
Min.		91.07	96.77	96.47	94.12	98.42	98.03	93.49	99.79	98.8
Max.		93.22	99.96	99.37	99.78	105.81	103.83	98.75	104.94	102.0
MEAN		92.2	98.6	98.1	96.0	101.0	99.8	95.2	102.9	100.1
% RSD		0.7	1.0	0.9	2.0	2.5	2.0	2.0	1.7	1.1

Table-33: Lubrication - Sample from Containers (Color layer)

Blend pooled sample Results

Parameter	**XXX**	**YYY**	**ZZZ**
Sieve analysis			
1. Retains on # 16	3.94 % w/w	3.96% w/w	3.92 % w/w
2. Retains on # 30	5.783 % w/w	5.661 % w/w	5.714 % w/w
3. Retains on # 40	17.613 % w/w	16.518 % w/w	17.500 % w/w
4. Retains on # 60	34.281 % w/w	34.910 % w/w	35.134 % w/w
5. Retains on # 80	89.15 % w/w	89.42% w/w	90.2 % w/w
6. Retains on # 100	57.320 % w/w	58.921 % w/w	59.222 % w/w
7. Passing through # 100	39.674 % w/w	39.479 % w/w	39.518 % w/w
Untapped density (g/ml)	0.592	0.555	0.576
Tapped density (g/ml)	0.721	0.654	0.696

Angle or repose (°)	30 – 35	30 – 35	30 – 35
Compressibility index (%)	17.910	15.150	17.187
Hausner's ratio	1.218	1.180	1.207

Table-34: Blend pooled sample Results

The water contents and Assay of Blend as follows

Batch No.	Specification	XXX	YYY	ZZZ
Water content (%) (Limit: NMT 4.5%)	NMT 5% w/w	3.6	3.31	3.6
Assay (mg)				
Lamivudine	NLT 90% & NMT 110%	99.3%	100.0%	98.8%
Stavudine		101.6%	101.2%	97.8%
Nevirapine		100%	100.8%	100%

Table-35: The water content and Assay of Blend

8. Compression

Fixed parameters

Number of station : 37

Type of tooling : D type

Variables considered for study : Optimum Speed

MEASURED RESPONSE	ACCEPTANCE CRITERIA
Appearance	Two layered, flat, circular, bevel edged uncoated tablets, one layer with white color and the other layer with Orange color.
Individual weight variation	700 mg ± 2% (686mg-714 mg)
Thickness	4.5 ± 0.30mm (4.2mm – 4.8 mm)
Hardness	Not less than 4.0 Kp
Friability	NMT 1.0% w/w
Disintegration time	NMT 15 minutes
Content Uniformity RSD	90.0% to 110.0% NMT 5.0%
Dissolution	NLT 85.0% in 30 min.

Table-36: Compression parameters

a) Group weight variation

The target speedof the compression machine is 18-20 rpm.The speed is decreased by 3 rpm and the group weight variation is checked.

Approximate sample size **Acceptance criteria**

20 tablets 7.00 gm ± 2% (6.86gms - 7.14gms)

S.No	GROUP WEIGHT VARIATION (grams)		
	XXX	YYY	ZZZ
01	7.0415	7.0355	7.0148
02	7.0157	7.0014	6.9806
03	7.0245	7.0212	7.0180
04	7.0083	7.0009	7.0012
05	7.0232	7.0415	7.0293
06	7.0012	6.9819	6.9913
07	7.0415	7.0325	7.0120
08	6.9809	7.0010	6.9723
09	6.9982	7.0147	6.9969
10	6.9805	7.0134	7.0030
11	7.0169	6.9911	7.0357
12	6.9715	7.0425	7.0013
13	7.0018	7.0230	7.0294
14	7.0432	7.0512	6.9816
15	7.0245	7.0089	7.0207
16	7.0011	7.0320	7.0136
17	7.0537	7.0037	7.0073
18	7.0130	7.0215	7.0231
19	7.0256	7.0534	6.9865
20	7.0431	7.0123	7.0380
Avg	**7.0155**	**7.0192**	**7.0078**

Min	**6.9805**	**6.9911**	**6.9723**
Max	**7.0431**	**7.0534**	**7.0380**

Table-37: Group weight variation

TREND CHART FOR GROUP WEIGHT VARIATION

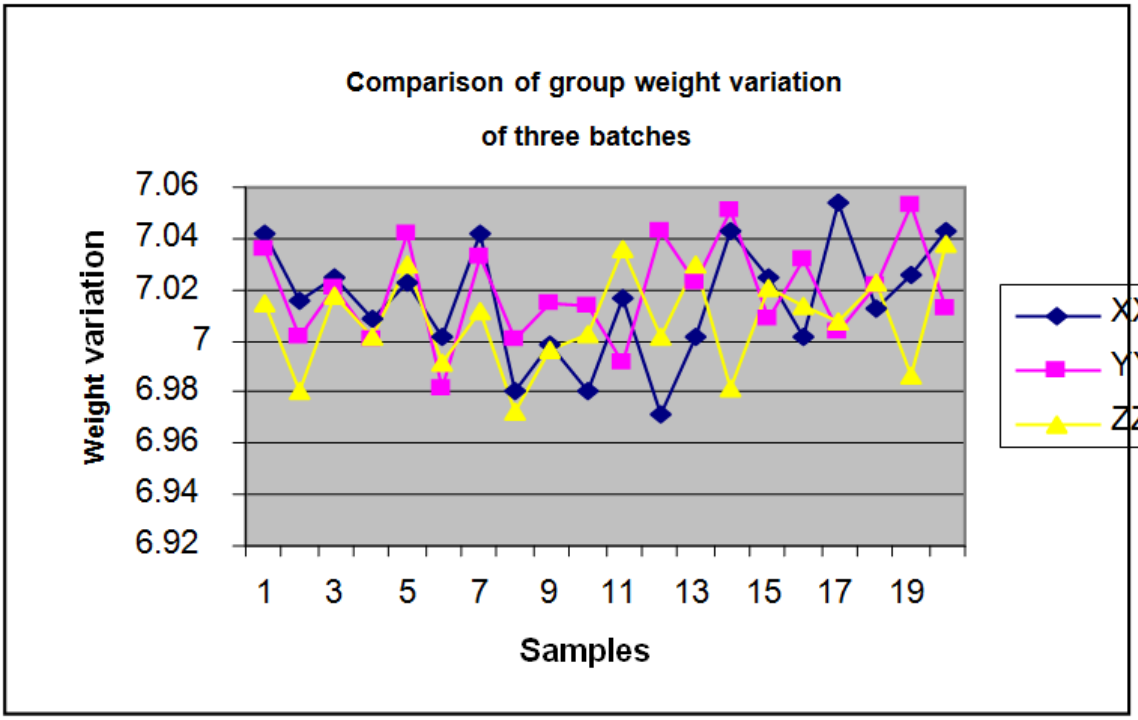


Figure-1

b) Individual weight variation:
Approx. sample size: 20 tablets **Acceptance criteria:** 700mg+/-2 % (686mg -714 mg)

S.No	INDIVIDUAL WEIGHT VARIATION (mg)		
	XXX	YYY	ZZZ
01	702.2	691.3	706.6
02	694.9	690.4	706.9
03	708.3	709.8	702.1
04	698.2	706.7	694.8
05	701.3	711.5	711.7
06	698.3	698.8	703.9
07	699.3	694.7	695.2
08	698.6	706.7	702.5
09	705.4	699.2	696.4
10	709.2	713.0	697.9
11	697.6	698.5	700.9
12	693.8	697.6	698.9
13	690.2	704.9	713.4
14	700.4	705.9	701.4
15	704.6	709.1	703.3
16	694.0	707.7	703.8
17	691.1	710.7	709.3
18	704.2	705.1	689.4
19	703.5	703.5	701.2
20	701.5	689.5	707.2
Avg	**699.83**	**702.73**	**702.34**
Min	**690.2**	**690.4**	**689.4**
Max	**705.4**	**713.0**	**713.4**

Table-38: Individual weight variation

Trend Chart For Individual Weight Variation

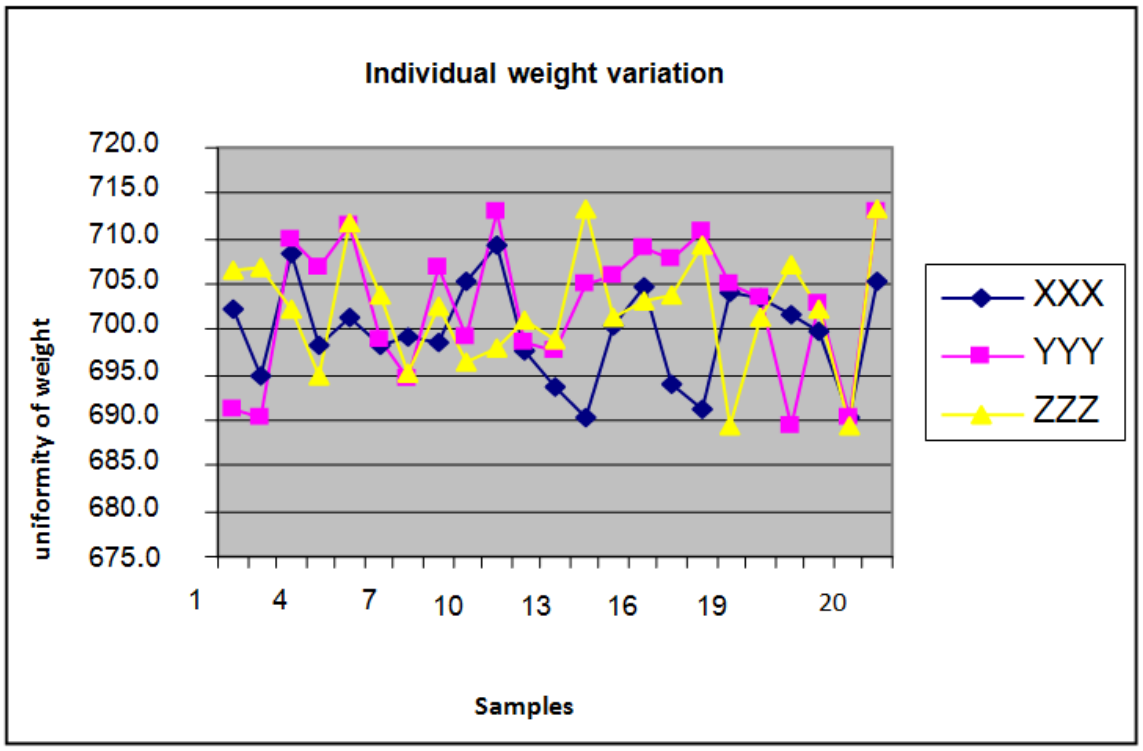


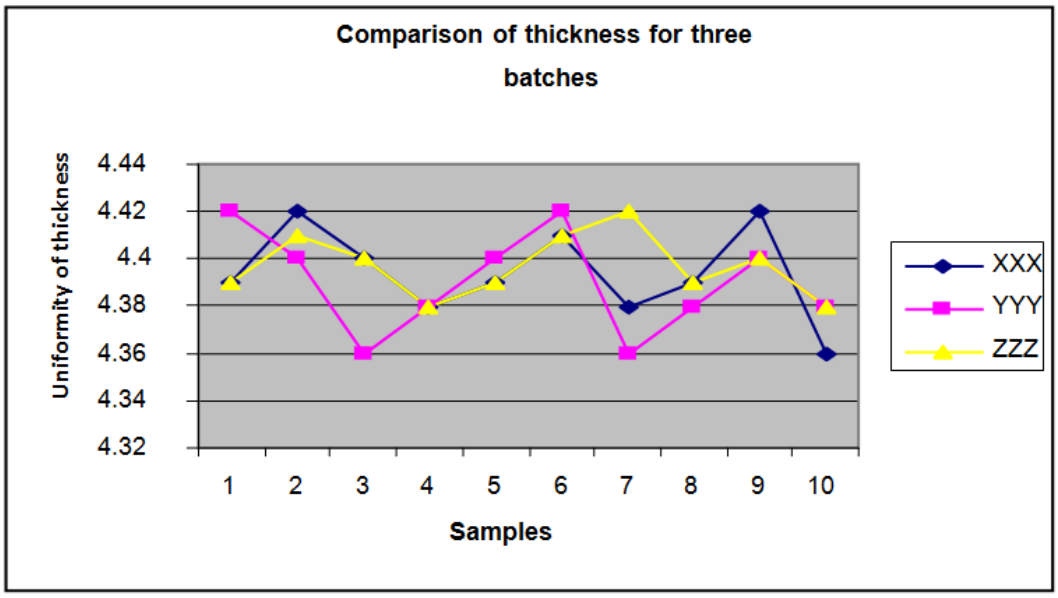
Figure-2

c) Thickness & Hardness studies for three batches

Average Thickness **Acceptance criteria :**
Approx. sample size : 6 Tablets 4.50 mm ± 0.30 mm
Average Hardness **Acceptance criteria**
Approx. sample size : 6 Tablets NLT 4.0 Kp

S.No	Thickness (4.50 mm ± 0.30 mm) Batch number			Hardness (NLT 4.0 Kp) Batch number		
	XXX	YYY	ZZZ	XXX	YYY	ZZZ
01	4.39	4.42	4.39	10.9	12.2	12.8
02	4.42	4.40	4.41	11.2	12.8	11.6
03	4.40	4.36	4.40	12.1	14.5	13.2
04	4.38	4.38	4.38	10.9	13.8	12.8
05	4.39	4.40	4.39	11.6	12.8	11.2
06	4.41	4.42	4.41	12.3	12.2	12.9
07	4.38	4.36	4.42	11.2	13.8	13.2
08	4.39	4.38	4.39	12.9	13.5	12.8
09	4.42	4.40	4.40	11.2	13.5	11.6
10	4.36	4.38	4.38	12.8	13.8	12.2
Avg	**4.39**	**4.39**	**4.39**	**11.71**	**13.29**	**12.43**
Min	**4.36**	**4.36**	**4.38**	**10.9**	**12.2**	**11.2**
Max	**4.42**	**4.42**	**4.42**	**12.8**	**14.5**	**13.2**

Table-39: Thickness & Hardness studies for three batches



Trend chart for thickness

Trend chart for Hardness

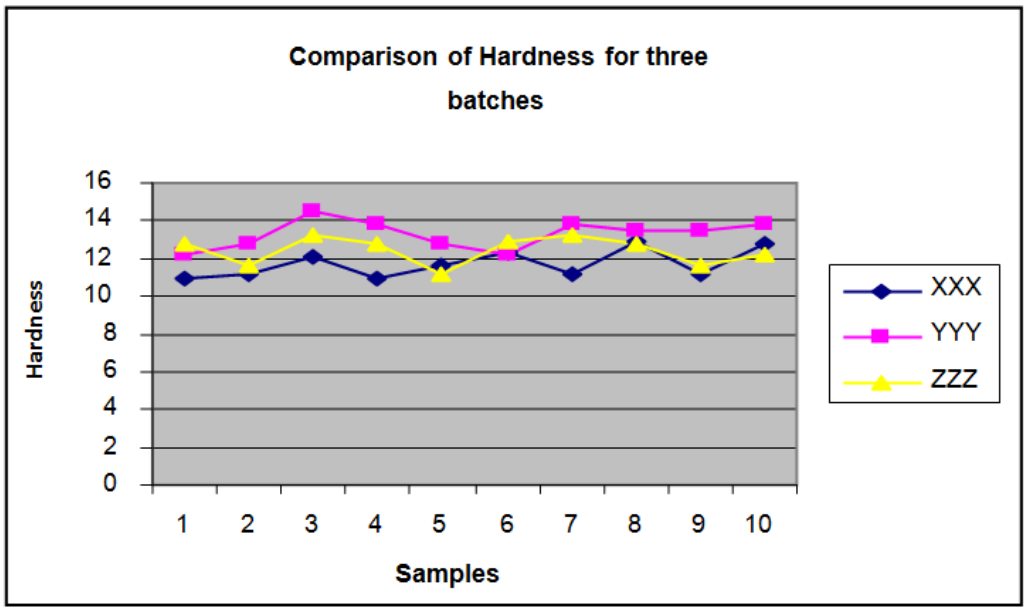


Figure-4

d) Friability:

Approx. sample size : Acceptance criteria: 20 Tablets NMT 1%

Batch no	Friability (%) w/w
XXX	0.16
YYY	0.12
ZZZ	0.21

Table-40: Friability

e) Dissolution and content uniformity studies at different rpm

Dissolution:

Approx. sample size :

3x6 Tablets

Acceptance criteria
NLT 85% in 30 minutes

Content uniformity in %(NEVILAST 30)

S.No.	CONTENT UNIFORMITY STUDIES AT DIFFERENT RPM								
	BATCH NO: XXX								
	12RPM			25 RPM			18 RPM		
	L	S	N	L	S	N	L	S	N
01	101.03	101.37	101.75	97.90	98.34	99.67	100.15	96.93	101.40
02	99.38	99.81	100.36	97.95	98.98	99.36	99.41	96.09	100.35
03	99.55	98.38	100.49	98.04	97.02	99.17	98.49	95.05	99.31
04	102.84	103.31	103.24	98.88	99.94	100.04	99.48	95.08	100.55
05	99.16	100.22	100.49	99.34	98.17	100.18	100.46	95.92	100.18
06	96.81	98.87	99.11	99.62	99.64	100.90	101.34	97.99	102.14
07	97.13	99.23	99.51	100.85	101.00	102.14	99.69	99.73	102.79
08	98.38	98.67	100.03	99.66	100.60	100.66	100.54	97.12	101.44
09	99.32	99.63	100.92	96.07	98.17	98.48	99.91	96.67	100.34
10	97.91	99.03	99.52	95.80	97.85	98.17	10.94	97.65	102.05
Min	**96.81**	**98.38**	**99.11**	**95.80**	**97.02**	**98.17**	**98.49**	**95.05**	**99.31**
Max	**102.84**	**103.31**	**103.24**	**100.85**	**101.00**	**102.14**	**101.34**	**99.73**	**102.79**
Mean	**99.2**	**99.9**	**100.5**	**98.4**	**99.0**	**99.9**	**100**	**96.9**	**101.1**
RSD	**1.8**	**1.5**	**1.2**	**1.6**	**1.3**	**1.2**	**0.8**	**1.3**	**1.1**

Table-41: Content uniformity in %(NEVILAST 30)

Trend chart for content uniformity at different RPM for XXX

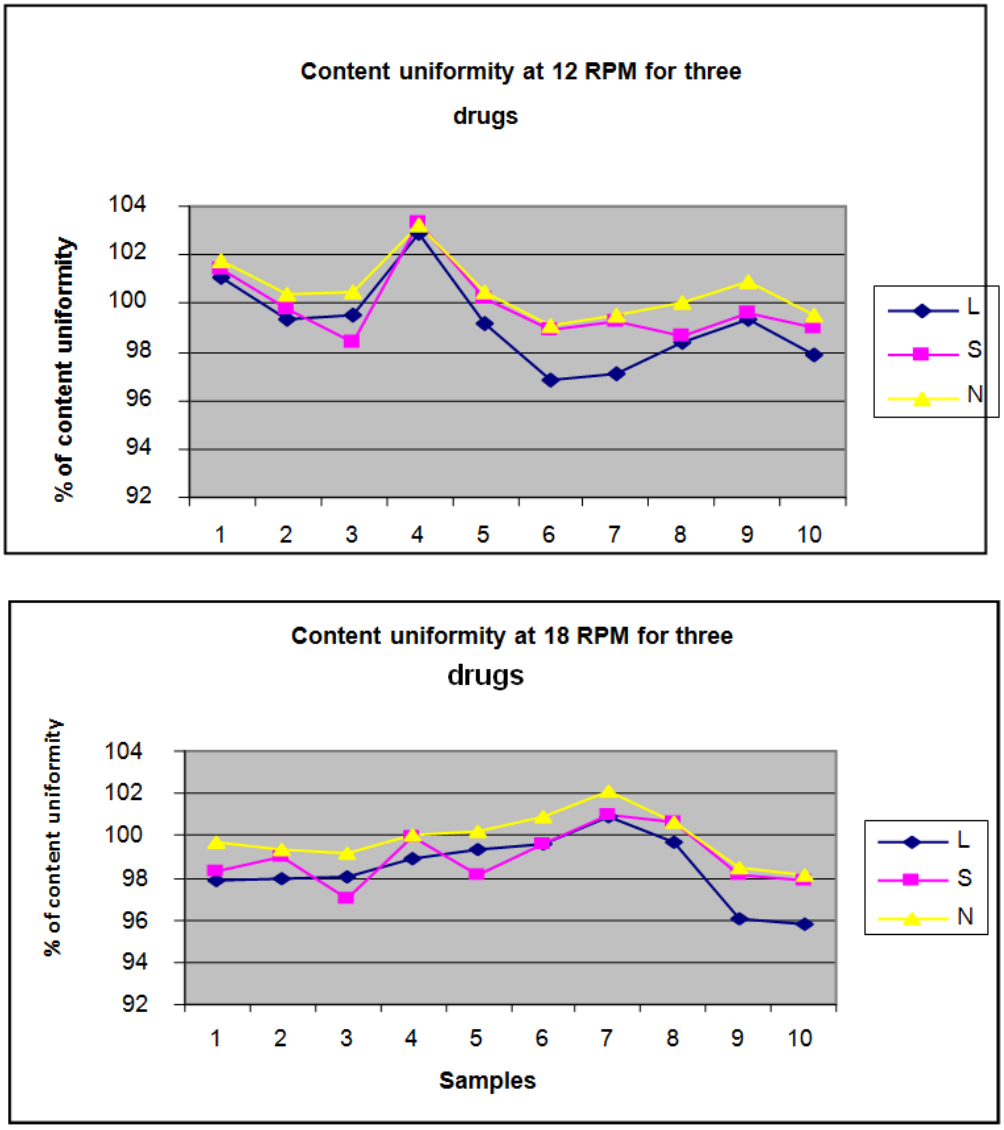


Figure-6

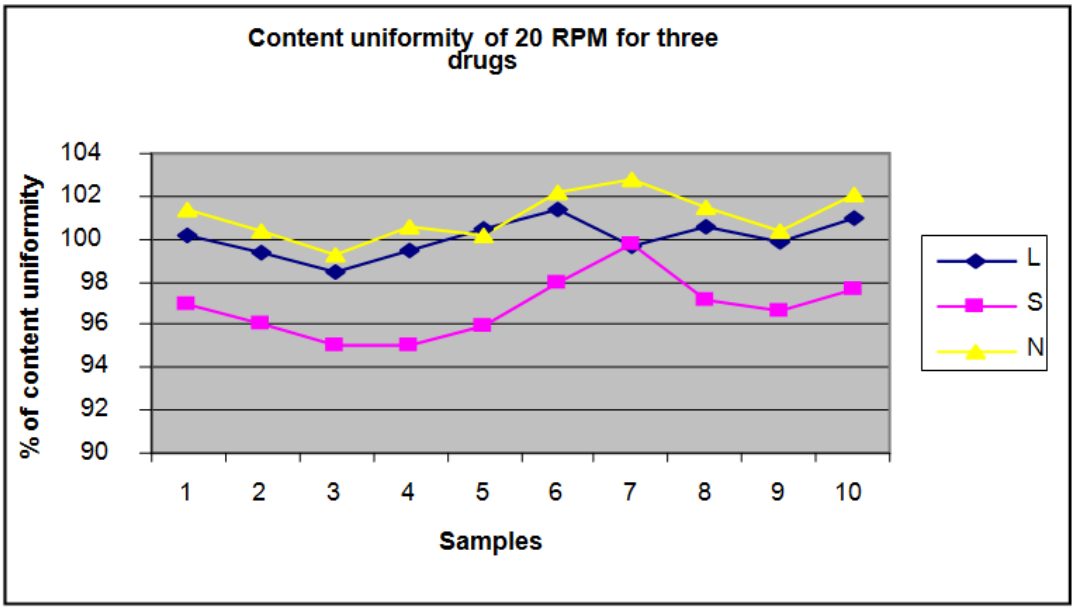


Figure-7

f) Hopper study

The hopper study is conducted at different stages of hopper like full hopper, middle hopper, and end hopper. In this hopper study content uniformity of **NEVILAST 30** are studied.

Full hopper study for three batches

Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

S.No.	Content uniformity results								
	Batch Number								
	XXX			YYY			ZZZ		
	L	S	N	L	S	N	L	S	N
01	98.0	96.2	99.8	97.0	99.2	98.7	98.3	94.9	96.8
02	93.4	93.5	90.7	98.9	101.9	100.8	94.6	95.7	97.7
03	101.8	100.1	103.8	91.4	95.5	89.2	94.6	93.9	95.1
04	95.1	96.1	93.3	100.3	100.5	100.0	98.8	93.5	95.1
05	95.8	92.8	96.9	91.3	95.4	89.1	97.9	95.7	97.6
06	98.1	94.5	99.2	98.7	102.0	100.7	99.3	94.9	96.8
Min	**93.4**	**92.8**	**90.7**	**91.3**	**95.4**	**89.1**	**94.6**	**93.5**	**95.1**
Max	**101.8**	**100.1**	**103.8**	**100.3**	**102.0**	**100.8**	**99.3**	**95.7**	**97.7**

Table-42: Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

Trend chart for content uniformity at Full hopper study

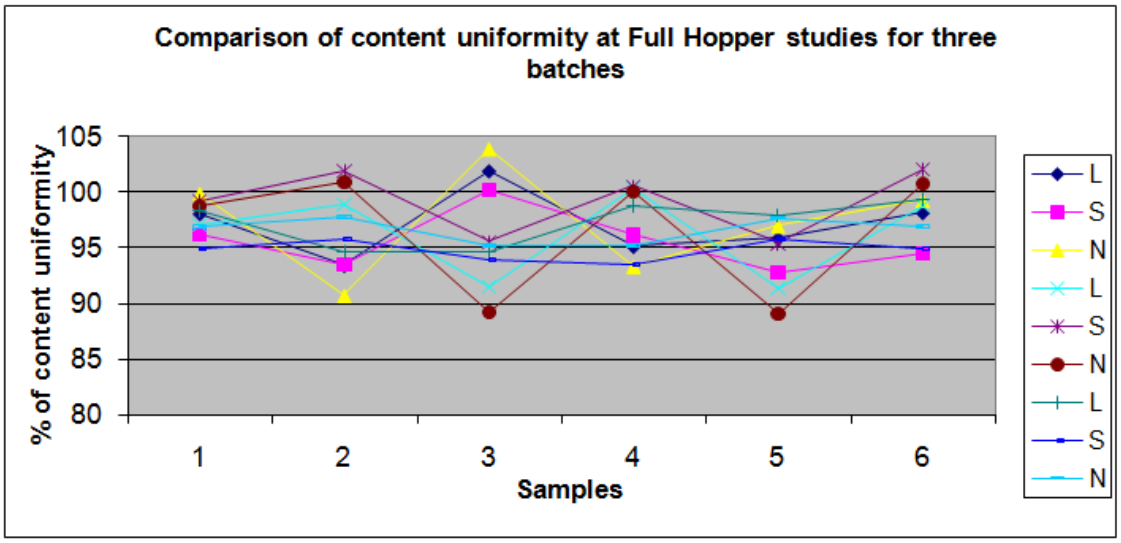


Figure-8

Middle hopper study for three batches
Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

S.No.	Content uniformity results								
	Batch Number								
	XXX			YYY			ZZZ		
	L	S	N	L	S	N	L	S	N
01	98.6	95.0	99.6	87.1	89.2	87.8	100.9	101.6	100.1
02	97.9	96.1	99.8	89.9	93.7	91.0	103.9	104.1	103.1
03	98.1	96.3	100.0	87.1	89.0	87.7	103.7	104.0	102.5
04	96.4	95.3	97.7	94.7	97.3	92.0	96.3	97.0	95.4
05	97.5	96.2	98.0	89.9	93.4	90.8	96.5	97.2	95.7
06	97.5	96.2	98.8	99.9	102.3	97.9	100.9	101.6	100.1
Min	**96.47**	**95.0**	**98.0**	**87.1**	**89.0**	**87.7**	**96.3**	**97.0**	**95.4**
Min	**98.6**	**96.2**	**100.0**	**99.9**	**102.3**	**97.9**	**103.9**	**104.1**	**103.1**

Table-43: Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

Trend chart for content uniformity at Middle Hopper study for three batches

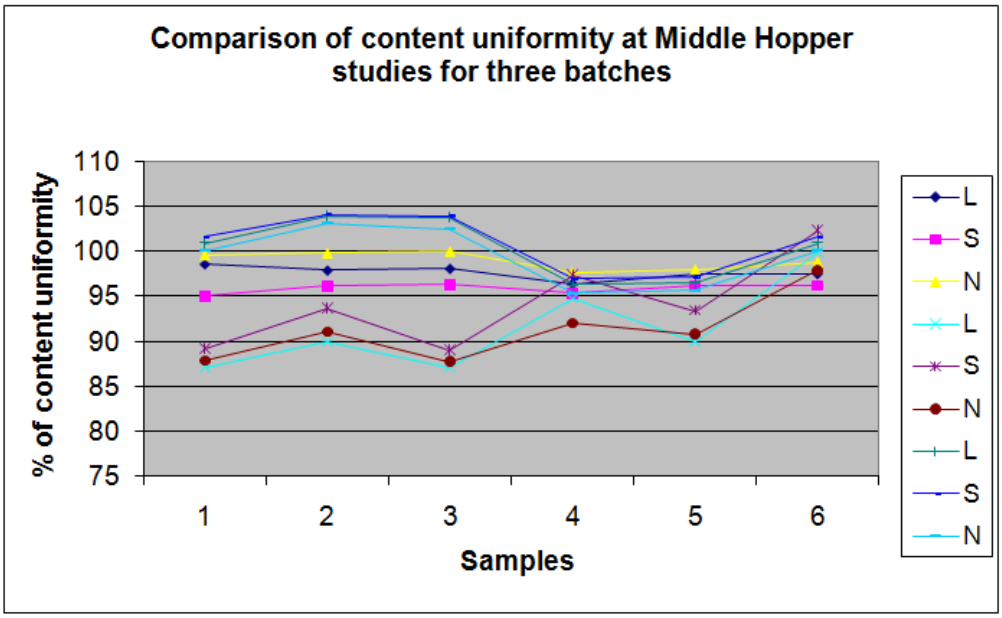


Figure-9

End hopper study for three batches:
Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

S.No.	Content uniformity results								
	Batch Number								
	XXX			YYY			ZZZ		
	L	S	N	L	S	N	L	S	N
01	96.9	95.7	97.4	100.3	100.5	100.0	98.9	98.4	98.2
02	97.9	96.4	98.9	97.5	97.9	95.3	99.0	98.2	98.3
03	94.5	92.7	96.1	101.0	101.6	100.3	105.2	105.8	104.3
04	93.4	92.1	95.3	100.6	101.3	99.8	105.2	105.6	104.4
05	90.5	93.9	93.3	98.7	98.9	99.8	105.3	95.8	98.8
06	87.8	89.4	91.2	98.2	98.4	99.4	98.8	95.4	98.4
Min	**87.8**	**89.4**	**91.2**	**97.5**	**97.9**	**95.3**	**98.8**	**95.4**	**98.2**
Max	**97.9**	**96.4**	**98.9**	**101.0**	**101.6**	**100.3**	**105.3**	**105.8**	**104.4**

Table-44: Content uniformity (NEVILAST 30) is NLT 85% in 30 min.

Trend chart for content uniformity at end Hopper study for three batches

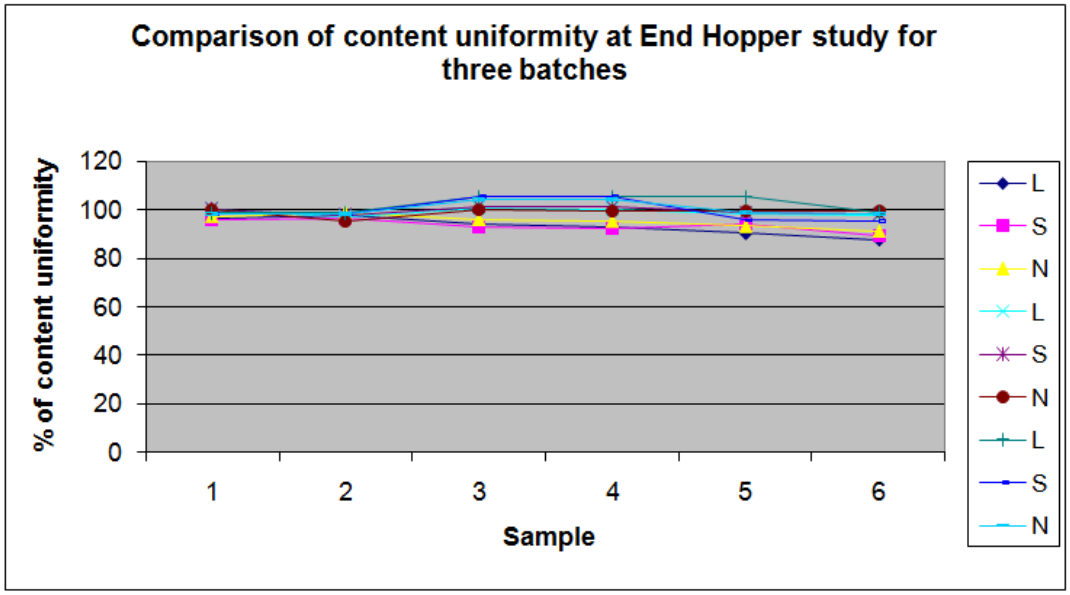


Figure-10

a) Content uniformity, Dissolution of NEVILAST 30 in compressed tablets at different Hardness during compression (Expressed in%)

Low Hardness Tablets: content uniformity in %(NEVILAST-30)

Batch No.	**XXX**					
	Acceptance criteria	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
A)Lamivudine USP	NLT 85% in 30 minutes	10	65.6	80.4	73.9	8.07
		15	85.5	92.4	89.5	2.65
		20	93.9	98.1	96.7	1.52
		30	97.0	101.2	99.7	1.64
		45	96.2	101.1	98.8	1.91
B)Stavudine USP	NLT 85% in 30 minutes	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
		10	65.2	80.4	72.5	8.33
		15	87.5	93.9	90.5	2.48
		20	94.7	100.5	98.0	2.08
		30	97.5	102.6	100.7	2.00
		45	97.7	103.7	100.7	2.29
C)Nevirapine USP	NLT 85% in 30 minutes	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
		10	72.4	82.4	78.3	5.42
		15	87.5	93.1	91.6	2.06
		20	94.7	98.4	96.9	1.23
		30	97.5	100.9	99.3	1.58
		45	97.7	102.4	99.5	1.86

Table -46: Low Hardness Tablets: content uniformity in %(NEVILAST-30)

High Hardness Tablets: Content uniformity in %(NEVILAST 30)

	% of Nevilast 30					
Batch No.	**XXX**					
	Acceptance criteria	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
A)Lamivudine USP	NLT 85% in 30 minutes	10	65.4	79.2	73.4	7.81
		15	85.2	91.8	88.9	2.59
		20	94.3	98.9	96.6	1.66
		30	85.7	101.0	96.3	5.72
		45	97.2	100.8	99.3	1.54
B)Stavudine	NLT 85% in 30	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**

USP	minutes	10	66.3	77.3	73.7	8.18
		15	88.6	94.8	91.6	2.34
		20	96.1	102.4	99.0	2.32
		30	88.3	104.3	98.6	5.64
		45	99.0	103.7	101.4	1.93
C)Nevirapine USP	NLT 85% in 30 minutes	**Time(min)**	**MIN.**	**MAX.**	**MEAN**	**%RSD**
		10	70.6	81.3	76.9	5.86
		15	87.2	92.5	91.0	2.11
		20	95.3	98.5	96.8	1.50
		30	85.5	101.4	96.3	5.92
		45	97.3	101.3	99.1	1.54

Table-47: High Hardness Tablets: Content uniformity in %(NEVILAST 30)

Dissolution profile of NEVILAST 30:

Batch No.	Dissolution Profile	LAMIVUDINE				STAVUDINE				NEVIRAPINE			
		Min	**Max**	**Mean**	**%RSD**	**Min**	**Max**	**Mean**	**%RSD**	**Min**	**Max**	**Mean**	**%RSD**
XXX	10Min	58.5	83.3	69.0	15.96	57.0	92.2	68.0	16.58	65.1	92.4	72.98	12.17
	15 Min	70.9	94.4	85.0	9.42	69.9	94.7	85.0	9.97	76.3	93.7	86.42	7.15
	20 Min	94.0	98.6	97.0	1.71	93.2	98.0	96.0	1.65	89.8	97.7	95.08	2.72
	30 Min	95.2	102.0	99.0	2.17	93.4	100.1	98.0	2.21	90.4	101.9	97.09	3.59
	45 Min	96.5	106.8	101.0	2.73	95.4	101.5	99.0	2.47	94.7	102.9	99.14	2.79
YYY	10 Min	61.1	89.2	71.0	13.40	62.0	87.7	72.0	11.76	67.1	86.7	74.0	9.73
	15 Min	90.1	95.1	93.0	2.30	92.8	96.3	94.0	1.39	92.2	96.1	94.0	1.41
	20 Min	90.6	99.7	95.0	3.15	90.4	103.0	97.0	4.32	90.7	100.6	96.0	3.77
	30 Min	91.3	99.2	95.0	2.60	90.9	102.0	96.0	3.87	92.3	101.1	96.0	2.83
	45 Min	92.2	99.4	96.0	2.45	91.6	104.6	97.0	4.70	93.2	101.4	97.0	2.83
ZZZ	10 Min	50.3	84.2	69.0	18.26	47.8	81.1	66.0	18.55	55.8	80.7	69.0	12.66
	15 Min	80.2	101.6	91.0	8.08	77.5	97.3	88.0	7.92	79.6	99.9	90.0	7.97
	20 Min	93.0	104.5	98.0	4.29	89.3	100.1	93.0	4.02	92.0	103.7	96.0	4.34
	30 Min	94.3	103.8	98.0	2.33	91.0	98.9	93.0	2.18	25.2	97.6	90.0	22.72
	45 Min	94.3	105.1	99.0	3.39	89.7	98.8	93.0	2.98	93.6	104.3	98.0	3.36

Table-45: Dissolution profile of NEVILAST 30

Acceptance criteria: NLT 85% in 30 min

7. Yield

STAGE	Limit	%Yield								
		XXX			YYY			ZZZ		
		L	S	N	L	S	N	L	S	N
Blending Color less	**98.50 – 100.0%**	99.3	101.6	100.0	99.0	101.2	100.8	98.8	97.8	100.0
Color		99.8	101.9	100.3	100.0	100.5	100.2	98.1	98.9	99.6
Compression	**96-100%**	97.47			98.04			98.12		
Packing	**95-100%**	99.95			99.80			99.85		

Table-48: % Yield of blending, compression, packing

Trend chart for Yield at different stages.

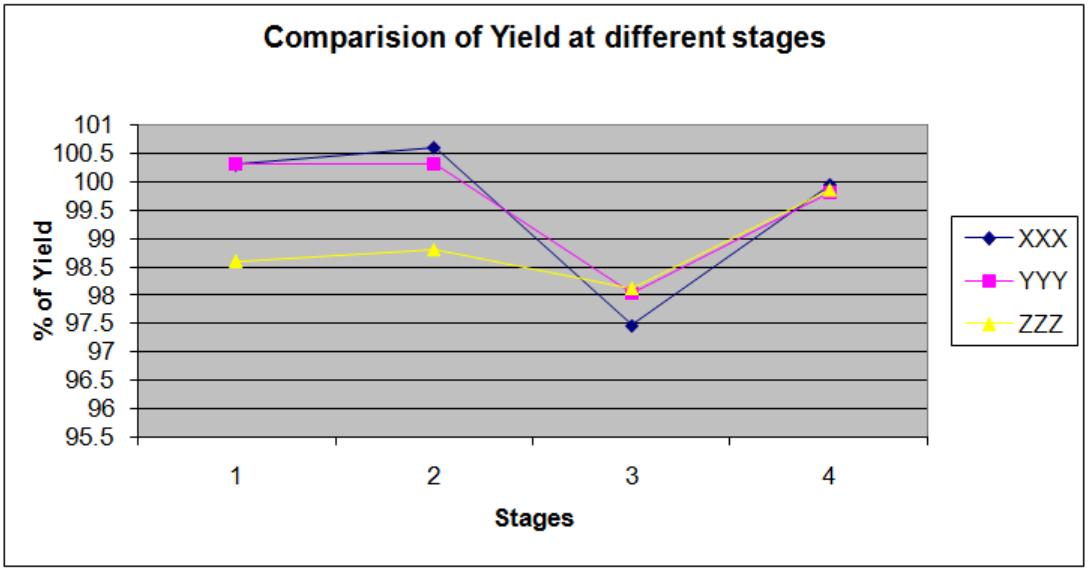


Figure-11

IV. Discussions

PROCESS VALIDATION REPORT OF TABLET DOSAGE FORMS NEVILAST 30 – 700MG

1. Dispensing

As per the analysis report all the raw materials were checked and reported that materials are approved as per specifications for use.

2. Sifting

Presence of foreign particles and hard lumps were observed and such materials are sifted as per specification and reported the material for use.

3. Dry Mixing

After dry mixing blend uniformity of drug for colour & colourless layers of three validation batches as shown in Table-15 & 16 is specified that the results are with in the acceptance criteria.

4. Granulation

Wet granulation: At this stage %LOD for both color and colorless layers of the drug is specified with in the limits of acceptance criteria as per the specification which are mention in Table-17 & 18.

5. Drying

%LOD of the drug of 3lots for both color and colorless layer parts shown in Tables.19-28 for 3three validation batches are specified that the results are with in the acceptance criteria as per specification.

6. Milling

After milling % of granules retained on #16 and #80 mesh in 3lots results are specified that with in the accepted limits. Hence the granulation is similar in three lots.

8. Blending

a) Lubrication

The % of blend uniformity of color and colorless layers of the drug shown in Tables.31-33 for three validation batches are specified with in the limits of acceptance criteria.

b) Blend pooled samples:

Seive analysis, untapped density, tapped density, angle of repose, compressibility index and hausner's ratio shown in Table-19 for three validated batches are specified with in the limits of acceptance criteria.

c) Water content
It is observed that the moisture content of the drug for3 validated batches are with in the acceptance criteria shown in Table-35.

d)Assay
The assay value of lamuvidine, stamudine, nevarupine (NEVILAST-30) in Table-20 are specified with in the limits of acceptance criteria and comparision of trend charts for three batches shown in Figure-1.

9. Compression
a) Group weight variation
The group weight variation is checked for 20 tablets shown in Table-37 for 3 validated batches are within the limits of acceptable criteria and comparision of trend charts for three batches shown in Figure-1.

b) Individual weight variation
It is specified that for each tablet in Table-38 , the individual weight variation are with in the limits of acceptable criteria for three validated batches of the drug and comparision of trend charts for three batches shown in Figure-2.

c) Thickness and Hardness
The checked individual thickness and hardness in Table-39 for 10 tablets are specified with in the limits for 3 validated batches of the drug and comparision of trend charts for three validated batches shown in Figure-3 and 4.

d) Friability
The friability is checked for 20 tablets for 3 validated batches are within the limits of acceptance criteria shown in Table-40.

e) Content uniformity at different RPM
The content uniformity of the drug for 3 validation batches at different RPM i.e., 12, 18, 20rpm are shown in Table-26 well specified and it is in the limits of acceptance.

f) Hopper study
Content uniformity of drug is studied at different levels of the hopper i.e., full, middle and end of the hopper shown in Table-42, 43 and 44 are within the limits of acceptable criteria as per the specification and trend charts for three validated batches shown in Figure-8,9, and 10.

g) Hardness during compression
At different hardness like low and high hardness during compression, it is reported that the content uniformity of the drug for 3 validated batches are specified with in the limits of acceptance criteria. The results were given in table- 46, 47.

h) Dissolution profile:
The dissolution for NEVILAST-30 is shown in TABLE-45. It is reported that the dissolution profile of the drug for three validated batches are specified within the limits of acceptance criteria.

9. Yield
% of yield at different stages of blending, compression and packing are accepted and the results are in tablulated which are specified within the acceptance limits shown in trend chart.

V. Conclusion

This project involves Process validation of NEVILAST-30 which is carried out in Hetero Drugs Ltd. The data provided by trail and executive batches was studied extensively to understand product behaviour and drug verified cessability and available steps of facilities and equipments. These validation batches of commercial scale were taken successfully and setup the inprocess critical parameters for commercial batches.NEVILAST-30 were prepared with in specific for resulting all quality attributes.

The overall successful three consecutive validation batches of NEVILAST-30 verified all predetermined limits and it assure the process to use for production of tablet and it meets the goals. Hence the process is validated.

References

[1]. Aiken, J., "Panel criticizes FDA inspections of imported drugs".
[2]. Aarnoutse,R.E., Verweij-van Wissen, C.P.W.G.M., Underberg, W.J.M. Kleinnijenhuis,
[3]. J. Hekster, Y.A., Burger, D.M., "High-performance liquid chromatography of HIV protease inhibitors in human biological matrices. Journal of Chromatography B, 2001, **764**: 363–384.
[4]. 3. Alnouti, Y., White, C.A., Bartlett, M.G, "Simultaneous determination of stavudine and lamivudine from rat plasma, amniotic fluid and tissues by HPLC", J.Biomed Chromatog*r*,2004, **18** (9):641.
[5]. Antiretroviral drug content in products from developing countries.HIV/AIDs: 38.
[6]. Antimicrob. Agents Chemother. **42**: 2656.
[7]. Allan H.Goroll, "Primary care medicine".Office evaluation and management of drugs, 2009 562-570.
[8]. Aurag Singh Rathore, "Process validation in manufacturing of biopharmaceuticals", 2005, 514-522. Aservice of U.S department of Health and Human services (2005) Lamivudine: AIDSinformation. http://WWW.aidsinfo.nih.gov
[9]. Beijnen,J.H., " Simultaneous quantitative determination of the HIV protease inhibitors amprenavir, indinavir, nelfinavir, ritonavir and saquinavir in human plasma by ion-pair high-performance liquid chromatography with ultraviolet detection". J. Chromatogr B,1998, 719: 159–168.
[10]. Bounine, J.P., " Development and validation of a high performance validation", 1999.
[11]. Burke A.Cauha, "Infectious diseases in critical care medicine", 4th edition, 2006, 420-429.
[12]. 10. Bakshi, M., Singh. S., "Development of validated stability indicating", assaymethods.J.Phrm.Biomed.Anal,2001, 28:1011-1040.
[13]. Balfour, H.H., JR., M.D (1999) Antiviral drugs. Drug Therapy, volume340 (16): 1255
[14]. Becher, F., Pruvost, A., Goujard, C., Guerreiro, C., Delfraissy, J.F., Grassi, J., Enech,H, "Improved method for the simultaneous determination of d4T, 3TC and ddl intracellular phosphorylated anabolites in human peripheral-blood mononuclear cells using high-performance liquid chromatography/tandem mass spectrometry". Rapid Commun Mass Spectrom.16,2001, (6):555.
[15]. FDA Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics. Food and Drug Administration, Rockville, MD. (1987).
[16]. FDA, Guidance for Industry: Stability Testing of Drug Substances and DrugProducts (Draft guidance), Food and Drug Administration, Rockville, MD., Floery, K., "Analytical profile of Drug Substances", Vol.8 Academic Press.London.UK, (1998), (1979) , pp 49-223.
[17]. Gail Skowron, "Reverse transcriptase inhibitors in HIV/AIDS therapy", 2006, 330-335.
[18]. James P.Agalloco, "Validation of pharmaceutical processes", 2007, 710.
[19]. Kenney, K.B., Wring, S.A., Carr, R.M., Wells, G.N., Dunn, J.A., "Simultaneous determination of zidovudine and lamivudine in human serum using HPLC with tandem mass spectrometry". J. Pharm. Biomed. Anal. 22: (2000) ,967.
[20]. Leon shargel, "Generic drug product development". Solid dosage forms, 2005, 95-102.
[21]. Moyer, T.P., Temesegen, Z., Enger, R., Estes, L., Charlson,J., Oliver,L., Wright.A,"Drug monitoring of antiretroviral therapy for HIV-1 infection". Method validation and results of a pilot study. Clinical chemistry.45 (9): (1999)1465.

IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) is UGC approved Journal with Sl. No. 5012, Journal no. 49063.

Thejovathi B. " In Process Validation of Nevilast-30. " IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 14.3 (2019): 44-69.