INTERNATIONAL JOURNAL OF DRUG DISCOVERY AND HERBAL RESEARCH (IJDDHR)
2(2): April–June: (2012), 344-364
ISSN: 2231-6078

Research Article

Process validation of multivitamin tablets filmcoated

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Abstract
Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. The present paper deals with the process validation of multivitamin film coated tablets of two batches ET100700 and ET100701.

Key-words: Validation, Tablets, Film coated.

Introduction
Quality is always an imperative prerequisite when we consider any product. It becomes important when it relates to life saving products like pharmaceuticals. Although it is mandatory from the government and regulatory bodies but it is also a fact that quality of a pharmaceutical product cannot be adequately controlled solely by Pharmacopoeial analysis of the final product. Today quality has to be built in to the product right from its inception and rigorous international environmental, safety and regulatory standards need to be followed. Validation had proven to be an important tool for quality management of pharmaceuticals.
Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control. Adequate validation is beneficial to the manufacturer in many ways. Objective of validation is to establish documented evidence that the manufacturing process of Multivitamin Tablets (Film Coated) will consistently produce a product that is safe, effective and will meet all quality specifications according to the manufacturing formula.

Manufacturing process and observations
Process Validation of Multivitamin Tablets (F/C) (Batch No: - ET100700)
Weighing of the active ingredient and excipients is done in raw material stores. The weights of all the ingredients are rechecked and noted at production floor by production chemist. The weighing balances are checked and certified regularly by State Govt. Department of weights and measures.
Preparation of Binder:
Sifting: Weighed quantity of Sodium Metabisulphite BP (0.011 kg), Sucrose BP (4.005 kg) and Gelatin BP (1.125 kg) is dissolved in about 30 L purified water in Stainless Steel vessel. Heat to boil with constant stirring till uniform solution is achieved. Sieve the solution through # 100. Sieved quantity of Maize Starch BP (8.665 kg) dispersed in about 12 L purified water in Stainless Steel Vessel to form slurry. The slurry is then sieved through the # 100. Add the slurry to the sieved boiling solution of step (i) & (ii). Stir continuously till a translucent paste is formed and then allow the paste to cool. Temperature of cooled Starch Paste: 45 °C

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Raw Material to be sifted	Sieve Size	Quantity before sifting (kg)
Maize Starch BP	# 40	8.665

Sifting of Active Ingredients & Excipients:

Excipients	Screen Size	Quantity before Sifting (kg)
Thiamine Hydrochloride BP	# 40	0.928
Riboflavin BP	# 40	0.796
Maize Starch BP	# 40	86.605

Excipients	Screen Size	Quantity before Sifting (kg)
Calcium Hydrogen Phosphate BP	# 40	52.000
Lactose BP	# 40	31.930
Microcrystalline cellulose	# 40	18.385

Mixing: Transferred bulk material of step 9.3 is mixed in the Double Cone Blender for 5 minutes. Add about 16 kg Starch of step 9.3 in the Double Cone Blender and mix for 5 minutes. Add about 32 kg Starch of step 9.3 in the Double Cone Blender and mix for 5 minutes. Add about 24.435 kg Starch (balance quantity) of step 9.3 in the Double Cone Blender and mix for 5 minutes. Blender Speed: 21 rpm, Mixing Time: 20 minutes.

Time of mixing in Double cone Blender	Sample Site	Individual content of Thiamine Hydrochloride BP of the blend (in mg)	Mean content of Thiamine Hydrochloride BP (in mg)	Relative Standard deviation
5 minutes	1, 2, 3, 4, M	0.467, 0.419, 0.433, 0.441, 0.413	0.434	4.89
10 minutes	1, 2, 3, 4, M	0.453, 0.345, 0.365, 0.355, 0.332	0.370	12.96
15 minutes	1, 2, 3, 4, M	0.467, 0.489, 0.488, 0.467, 0.409	0.464	7.02
20 minutes	1, 2, 3, 4, M	0.426, 0.410, 0.527, 0.540, 0.341	0.448	18.70

Time of mixing in Double cone Blender	Sample Site	Individual content of Riboflavin BP of the blend (in mg)	Mean content of Riboflavin BP (in mg)	Relative Standard deviation
5 minutes	1, 2, 3, 4, M	0.493, 0.567, 0.499, 0.552, 0.555	0.533	6.46
10 minutes	1, 2, 3, 4, M	0.432, 0.335, 0.426, 0.403, 0.426	0.404	9.98
15 minutes	1, 2, 3, 4, M	0.651, 0.574, 0.513, 0.540, 0.532	0.562	9.68
20 minutes	1, 2, 3, 4, M	0.565, 0.641, 0.668, 0.564, 0.529	0.593	9.85

Dry mixing: After loading of mixed material in the Rapid Mixer Granulator, mixing is done for 10 minutes at slow speed (80 rpm). In order to standardize the mixing time, samples are taken at different times and from 5 different locations of the RMG and Ampere meter reading is noted during dry mixing.

Mixing speed of Rapid mixer granulator:

Mixing speed	Slow Speed (rpm)	Fast Speed (rpm)
Blade	80	95
Chopper	2700	3400

Ampere meter reading:

	Minutes	Ampere meter reading
Dry Mixing	0	31.2
	1	30.8
	3	30.6
	5	28.1
	7	26.2
	10	24.3

Time of mixing in Rapid Mixer Granulator	Sample Site	Individual content of Thiamine Hydrochloride BP of the blend (in mg)	Mean content of Thiamine Hydrochloride BP (in mg)	Relative Standard deviation (NMT 7%)
5 minutes	0, 1, 2, 3, M	0.652, 0.705, 0.672, 0.646, 0.774	0.689	7.60
10 minutes	0, 1, 2, 3, M	0.719, 0.788, 0.779, 0.724, 0.723	0.746	4.54

Time of mixing in Rapid Mixer Granulator	Sample Site	Individual content of Riboflavin BP of the blend (in mg)	Mean content of Riboflavin BP (in mg)	Relative Standard deviation (NMT 7%)
5 minutes	0, 1, 2, 3, M	0.532, 0.564, 0.535, 0.529, 0.481	0.528	5.65
10 minutes	0, 1, 2, 3, M	0.489, 0.460, 0.530, 0.474, 0.537	0.498	6.84

Granulation: After the addition of binder, material is mixed for 20 minutes at slow speed. Ampere meter reading should be between 39-42 and mix for 20 seconds at fast speed (2700 rpm), add more quantity of the purified water till a consistent cohesive mass is obtained. Run the rapid mixer granulator till ampere meter reading goes to 24 -27 amperes.

Ampere meter reading:

	Minutes	Ampere meter reading
Granulation at slow speed (Total time 20 minutes)	03	40.6

	07	41.0
	10	40.9
	13	35.1
	16	30.2
	18	28.3
	20	26.2
Granulation at fast Speed (Total time 20 Second)	20.10	26.0
	20.20	25.8

Semi drying: The granules made in granulation are dried in the Fluid Bed Dryer at inlet air temperature 60 °C – 70 °C and this drying operation is validated by checking the moisture content (by I.R moisture balance at 105 °C) at different intervals of time during the drying process. Samples are pooled from different locations from the bowl. outlet temperature is maintained at 40 °C – 50 °C.

Inlet and Outlet Temperature of FBD 1 & FBD 2:

Time (in Minutes)	Inlet temperature (°C)	Outlet Temperature (°C)
15 minutes	64 °C	41 °C
30 minutes	65 °C	42 °C

FBD – 1

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	17.95, 16.42, 17.07, 16.28, 16.14	16.77
30 minutes	1, 2, 3, 4, 5	12.15, 11.12, 13.27, 12.36, 12.64	12.30

FBD-2

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	16.75, 17.12, 16.47, 15.88, 16.04	16.45
30 minutes	1, 2, 3, 4, 5	11.15, 13.12, 12.47, 12.58, 11.84	12.23

Screening of semi dried granules: The material after drying of 30 minutes in Fluid bed dryer is milled through Multimill of # 8 mm screen and then dried in Fluid bed dryer for remaining time.

Milling:	
Type of mill	Multimill

Screen size	# 8 mm
Speed (rpm)	1465
Feed rate	15 kg/ min.
Configuration	Knives forward

Drying: After screening, granules are dried in the Fluid bed dryer for 45 minutes at inlet air temperature 60 °C – 70 °C. Samples are pooled from different locations from the bowl. outlet temperature is maintained at 40 °C – 50 °C.

Inlet and outlet Temperature of FBD 1 & FBD 2:

Time (in Minutes)	Inlet temperature (°C)	Outlet Temperature (°C)
15 minutes	65 °C	41 °C
30 minutes	65 °C	42 °C
45 minutes	66 °C	43 °C

FBD 1:

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	6.05, 6.04, 6.04, 6.05, 6.05	6.05%
30 minutes	1, 2, 3, 4, 5	3.23, 3.23, 3.22, 3.22, 3.23	3.23%
45 minutes	1, 2, 3, 4, 5	1.57, 1.56, 1.57, 1.56, 1.57	1.57%

FBD 2:

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	5.42, 5.43, 5.43, 5.42, 5.43	5.43%
30 minutes	1, 2, 3, 4, 5	3.49, 3.50, 3.49, 3.50, 3.50	3.50%
45 minutes	1, 2, 3, 4, 5	1.58, 1.57, 1.57, 1.58, 1.58	1.58%

Dry Screening: After complete drying, material is sifted through the screen of # 24 and then milled through the Communiting mill. After milling the material is again screened through the # 24 till all granules are sieved and then granules are stored in the labeled double polythene bag lined drums and weights are recorded.

Sifting:	
Equipment	Mechanical Sifter
Milling:	
Type of mill	Communiting mill
Screen size	# 0.8 mm
Speed (rpm)	1500
Feed rate	12 kg/min.
Configuration	Knives forward

Sifting/ Mixing of Vitamin A (as Acetate), Colecalciferol & Excipients:

Ingredients	Screen Size	Quantity Before Sifting (kg)
Purified Talc BP	# 100	1.100

Sifted quantity of the Purified Talc BP is collect in labeled double polythene lined drums and keeps separately.Dissolve weighed quantity of Colecalciferol (13.260 g) in 0.090 kg Isopropyl Alcohol in Stainless Steel vessel and add about 1 kg of purified Talc to soak up the entire solution. Sieve soaked bulk through # 100. Rinse vessel with 0.100 kg Purified Talc and add rinse to the bulk. Transfer about 1 kg Microcrystalline cellulose and above bulk on the sifter. Sieve together on the sifter through # 40. Collect the bulk in the labeled double polythene lined drums and keep separately. Transfer about 2 kg microcrystalline cellulose and above bulk on the sifter. Sieve together on the sifter. Collect the bulk in labeled double polythene lined drum and keep separately.

Ingredients	Screen Size	Quantity Before Sifting (kg)
Vitamin A (as Acetate) BP	# 40	3.182

Sifting and mixing of Nicotinamide and Lubricants:

Excipients	Screen Size	Quantity before Screening (kg)
Nicotinamide BP	# 40	10.940
Colloidal Anhydrous Silica BP	# 40	2.520
Microcrystalline cellulose BP	# 40	2.700

After sifting, material is transferred to the Double Cone Blender and mix for 5 minutes at 21 rpm. Transfer the bulk of double cone blender in to the Octagonal blender containing dried granules of step 9.10 and mix for 30 minutes.

Sifting and mixing of Lubricants:

Excipients	Screen Size	Quantity before Screening (kg)
Purified Talc BP	# 100	2.560
Magnesium Stearate BP	# 100	2.250

Collect lubricants in labeled double polythene lined drum. Transfer the lubricants to the octagonal blender, mix the complete batch for 15 minutes. During lubrication collect the samples from 5 different locations at different interval of times.

Time of mixing in Octagonal Blender	Sample Site	Individual content of Vitamin A (as Acetate) BP of the blend (in IU)	Mean content of Vitamin A (as Acetate) BP (in IU)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	1099.617, 1165.592, 1203.521, 1022.213, 1126.242	1123.437	6.13
10 minutes	1, 2, 3, 4, M	1143.157, 1230.608, 1228.175, 1099.613, 1094.368	1159.184	5.76
15 minutes	1, 2, 3, 4, M	1142.367, 1116.531, 1041.502, 1110.047, 1186.496	1119.388	4.72

Time of mixing in Octagonal Blender	Sample Site	Individual content of Thiamine Hydrochloride BP of the blend (in mg)	Mean content of Thiamine Hydrochloride BP (in mg)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	0.589, 0.638, 0.677, 0.631, 0.629	0.632	4.95
10 minutes	1, 2, 3, 4, M	0.645, 0.651, 0.646, 0.648, 0.612	0.640	2.50
15 minutes	1, 2, 3, 4, M	0.596, 0.637, 0.645, 0.667, 0.650	0.639	4.13

Time of mixing in Octagonal Blender	Sample Site	Individual content of Riboflavin BP of the blend (in mg)	Mean content of Riboflavin BP (in mg)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	0.609, 0.575, 0.532, 0.516, 0.534	0.553	6.88
10 minutes	1, 2, 3, 4, M	0.544, 0.657, 0.631, 0.527, 0.513	0.574	11.34
15 minutes	1, 2, 3, 4, M	0.594, 0.602, 0.623, 0.637, 0.630	0.617	2.98

Time of mixing in Octagonal Blender	Sample Site	Individual content of Nicotinamide BP of the blend (in mg)	Mean content of Nicotinamide BP (in mg)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	7.84, 8.02, 8.02, 8.08, 8.09	8.01	1.25

10 minutes	1, 2, 3, 4, M	8.17, 8.21, 8.24, 8.23, 8.21	8.21	0.32
15 minutes	1, 2, 3, 4, M	8.26, 8.28, 8.27, 8.21, 8.28	8.26	0.35

Time of mixing in Octagonal Blender	Sample Site	Bulk Density	Tapped Density	Angle of Repose
5 minutes	1	09534	1.2435	43.7°
	2	0.9468	1.1976	42.5°
	M	0.9305	1.1263	42.8°
	3	0.9777	1.2057	43.5°
	4	1.0181	1.1928	43.2°
10 minutes	1	0.9922	1.1167	41.3°
	2	0.9868	1..2614	40.7°
	M	0.9637	1.3008	41.8°
	3	1.0262	1.3082	42.6°
	4	0.9558	1.1896	44.2°
15 minutes	1	0.9825	1.2163	43.9°
	2	0.9937	1.1857	42.7°
	M	1.0451	1.1867	43.4°
	3	0.9952	1.1799	42.1°
	4	0.9698	1.1426	42.9°

Particle Size Distribution

Time (minutes)	Sample Site	Sample Quantity (gm)	Sample retained on # 40	Sample retained on # 100	Sample pass through # 100
15 minutes	1	100gm	38 gm	78 gm	22 gm
	2	100gm	40 gm	72 gm	28 gm
	M	100gm	32 gm	75 gm	25 gm
	3	100gm	43 gm	70 gm	30 gm
	4	100gm	41 gm	68 gm	32 gm

Moisture Content after Lubrication

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
5 minutes	1, 2, M, 3, 4	1.51, 1.50, 1.58, 1.63, 1.60	1.56
15 minutes	1, 2, M, 3, 4	1.47, 1.42, 1.50, 1.48, 1.61	1.50

Material is collected in the labeled double polythene bags lined drums and weights are recorded.

Analytical result of in process bulk:

Test Parameters	Specification	Result
	Specification No.- FT/068 M	ET100700
Description	Yellow coloured granular powder	Yellow coloured granular powder
Loss on drying (at 105 °C for 30 minutes)	Not more than 2.0% w/w.	1.44% w/w
Assay Each 170 mg of granular powder contains: Vitamin A (as Acetate) BP Thiamine Hydrochloride BP Riboflavin BP Nicotinamide BP	NLT 98% of label claim (NLT 784.0 IU) NLT 98% of label claim (NLT 0.49 IU) NLT 98% of label claim (NLT 0.49 IU) NLT 98% of label claim (NLT 7.35 mg)	1102.05 IU 0.61 mg 0.57 mg 7.91 mg

Compression: The granules are compressed initially to set the appropriate desired parameters using the required tooling. The machine is adjusted against the desired weight. After adjusting the desired weight, physical parameters viz. hardness, friability and thickness are adjusted. The following machine variables are validated in order to get the desired quality of tablet.

35 Station compression Machine	**SLOW**	**OPTIMAL**	**FAST**	**ACCEPTANCE CRITERIA**
rpm	15	25	30	
Description	Complies	Complies	Complies	Yellow coloured, round biconvex uncoated tablets
Average weight	171.22 mg	170.24 mg	169.94 mg	NLT 166 mg to NMT 173 mg
Uniformity of weight	165 mg to 178 mg	166 mg to 179 mg	162 mg to 173 mg	NLT 160 mg to NMT 180 mg
Hardness	3.0 kg/cm^2	3.5 kg/cm^2	3.5 kg/cm^2	NLT 2.5 kg/cm^2 to NMT 4.0 kg/cm^2
Diameter	8.02 mm	8.01 mm	8.02 mm	NLT 7.80 mm to NMT 8.20 mm
Thickness	2.89 mm	2.81 mm	2.85 mm	NLT 2.70 mm to NMT 3.10 mm
Friability	0.51 % w/w	0.43 % w/w	0.50 % w/w	NMT 1 % w/w
Disintegration time	7 to 8 minutes	7 to 8 minutes	9 to 10 minutes	NMT 10 Minutes
Assay Each uncoated tablet contains: Vitamin A (as Acetate) BP	1101.53 IU	1098.11 IU	1088.50 IU	NLT 776.0 IU

Thiamine Hydrochloride BP	0.62 mg	0.60 mg	0.59 mg	NLT 0.48 mg
Riboflavin BP	0.59 mg	0.58 mg	0.56 mg	NLT 0.48 mg
Nicotinamide BP	8.02 mg	7.98 mg	8.05 mg	NLT 7.27 mg

Preparation of Seal Coating Solution:

Excipients	Weights (kg)
Ethyl cellulose BP	2.165
Isopropyl Alcohol BP	58.065

Preparation of Coating Solution:

Excipients	Weights (kg)
Hypromellose BP	3.380
Isopropyl Alcohol BP	35.535
Purified Talc BP	1.130
Titanium Dioxide	1.130
Macrogol BP 6000	0.790
Macrogol BP 400	0.565
Dichloromethane BP	94.470
Colour Allura Red Lake BP	0.610

Analysis of Coated tablets

Parameters	Observations	Acceptance Criteria
Description	Reddish pink coloured round, biconvex film coated tablets	Reddish pink coloured round, biconvex film coated tablets
Average Weight	177.08 mg	NLT 170 mg to NMT 177 mg
Uniformity of weight	174 mg to 180 mg	NLT 163 mg to NMT 184 mg
Diameter	8.21 mm	NLT 7.90 mm to NMT 8.30 mm
Thickness	3.10 mm	NLT 2.90 mm to NMT 3.20 mm
Disintegration Time	13 to 14 minutes	NMT 20 minutes

Process Validation of Multivitamin Tablets (F/C) (Batch No: - ET100701)
Sifting:

Raw Material to be sifted	Sieve Size	Quantity before sifting (kg)
Maize Starch BP	# 40	8.665

Sifting of Active Ingredients & Excipients:

Excipients	Screen Size	Quantity before Sifting (kg)
Thiamine Hydrochloride BP	# 40	0.928
Riboflavin BP	# 40	0.796
Maize Starch BP	# 40	86.605

Excipients	Screen Size	Quantity before Sifting (kg)
Calcium Hydrogen Phosphate BP	# 40	52.000
Lactose BP	# 40	31.930
Microcrystalline cellulose	# 40	18.385

Mixing:

Time of mixing in Double cone Blender	Sample Site	Individual content of Thiamine Hydrochloride BP of the blend (in mg)	Mean content of Thiamine Hydrochloride BP (in mg)	Relative Standard deviation
5 minutes	1, 2, 3, 4, M	0.321, 0.727, 0.554, 0.547, 0.711	0.572	28.63
10 minutes	1, 2, 3, 4, M	0.674, 0.615, 0.597, 0.673, 0.682	0.648	6.04
15 minutes	1, 2, 3, 4, M	0.658, 0.691, 0.683, 0.777, 0.826	0.727	9.79
20 minutes	1, 2, 3, 4, M	0.778, 0.919, 0.757, 0.872, 0.838	0.832	8.00

Time of mixing in Double cone Blender	Sample Site	Individual content of Riboflavin BP of the blend (in mg)	Mean content of Riboflavin BP (in mg)	Relative Standard deviation
5 minutes	1, 2, 3, 4, M	0.319, 0.497, 0.594, 0.635, 0.569	0.522	23.84
10 minutes	1, 2, 3, 4, M	0.577, 0.536, 0.542, 0.685, 0.633	0.594	10.69
15 minutes	1, 2, 3, 4, M	0.671, 0.622, 0.648, 0.667, 0.685	0.658	3.70
20 minutes	1, 2, 3, 4, M	0.675, 0.768, 0.593, 0.573, 0.697	0.661	12.03

Mixing speed of Rapid mixer granulator:

Mixing speed	Slow Speed (rpm)	Fast Speed (rpm)
Blade	80	95
Chopper	2700	3400

Ampere meter reading:

	Minutes	Ampere meter reading
Dry Mixing	0	31.4
	1	31.0
	3	30.8

	5	28.3
	7	26.4
	10	24.7

Time of mixing in Rapid Mixer Granulator	Sample Site	Individual content of Thiamine Hydrochloride BP of the blend (in mg)	Mean content of Thiamine Hydrochloride BP (in mg)	Relative Standard deviation (NMT 7%)
5 minutes	0, 1, 2, 3, M	0.650, 0.639, 0.652, 0.663, 0.650	0.650	1.31
10 minutes	0, 1, 2, 3, M	0.709, 0.689, 0.722, 0.703, 0.698	0.704	1.75

Time of mixing in Rapid Mixer Granulator	Sample Site	Individual content of Riboflavin BP of the blend (in mg)	Mean content of Riboflavin BP (in mg)	Relative Standard deviation (NMT 7%)
5 minutes	0, 1, 2, 3, M	0.535, 0.507, 0.542, 0.534, 0.538	0.531	2.61
10 minutes	0, 1, 2, 3, M	0.495, 0.572, 0.499, 0.568, 0.551	0.537	6.96

Granulation: Ampere meter reading:

	Minutes	Ampere meter reading
Granulation at slow speed (Total time 20 minutes)	03	40.8
	07	41.2
	10	40.8
	13	35.3
	16	30.5
	18	28.5
	20	26.3
Granulation at fast Speed (Total time 20 Second)	20.10	26.4
	20.20	26.1

Semi drying:
Inlet and Outlet Temperature of FBD 1 & FBD 2:

Time (in Minutes)	Inlet temperature (°C)	Outlet Temperature (°C)
15 minutes	64 °C	41 °C
30 minutes	64 °C	42 °C

FBD – 1

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	15.55, 16.78, 17.35, 15.75, 16.44	16.37
30 minutes	1, 2, 3, 4, 5	11.08, 10.82, 12.17, 12.45, 12.95	11.89

FBD – 2

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	16.45, 15.32, 16.87, 15.48, 17.04	16.23
30 minutes	1, 2, 3, 4, 5	11.64, 12.40, 12.10, 12.75, 11.14	12.00

Drying: Inlet and outlet Temperature of FBD 1 & FBD 2:

Time (in Minutes)	Inlet temperature (°C)	Outlet Temperature (°C)
15 minutes	64 °C	43 °C
30 minutes	65 °C	43 °C
45 minutes	66 °C	44 °C

FBD 1:

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	6.09, 6.24, 6.34, 6.45, 6.15	6.25
30 minutes	1, 2, 3, 4, 5	3.43, 3.33, 3.12, 3.22, 3.63	3.34
45 minutes	1, 2, 3, 4, 5	1.77, 1.66, 1.79, 1.56, 1.47	1.65

FBD 2:

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
15 minutes	1, 2, 3, 4, 5	5.62, 5.73, 5.93, 5.52, 5.63	5.68
30 minutes	1, 2, 3, 4, 5	3.89, 3.54, 3.69, 3.70, 3.52	3.66
45 minutes	1, 2, 3, 4, 5	1.68, 1.57, 1.77, 1.68, 1.58	1.65

Dry Screening:

Sifting:	
Equipment	Mechanical Sifter
Screen Size	# 24
Milling:	
Type of mill	Communiting mill
Screen size	# 0.8 mm
Speed (rpm)	1500
Feed rate	12 kg/min.
Configuration	Knives forward

Sifting/ Mixing of Vitamin A (as Acetate), Colecalciferol & Excipients:

Ingredients	Screen Size	Quantity Before Sifting (kg)
Purified Talc BP	# 100	1.100

Ingredients	Screen Size	Quantity Before Sifting (kg)
Vitamin A (as Acetate) BP	# 40	3.182

Sifting and mixing of Nicotinamide and Lubricants:

Excipients	Screen Size	Quantity before Screening (kg)
Nicotinamide BP	# 40	10.940
Colloidal Anhydrous Silica BP	# 40	2.520
Microcrystalline cellulose BP	# 40	2.700

Sifting and mixing of Lubricants:

Excipients	Screen Size	Quantity before Screening (kg)
Purified Talc BP	# 100	2.560

Magnesium Stearate BP	# 100	2.250

Time of mixing in Octagonal Blender	Sample Site	Individual content of Vitamin A (as Acetate) BP of the blend (in IU)	Mean content of Vitamin A (as Acetate) BP (in IU)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	881.276, 1024.641, 836.942, 997.846, 1102.006	968.542	11.16
10 minutes	1, 2, 3, 4, M	1042.641, 1019.730, 1063.539, 1095.125, 1053.520	1054.911	2.63
15 minutes	1, 2, 3, 4, M	1154.783, 1108.252, 1156.638, 1131.880, 1201.740	1150.658	3.01

Time of mixing in Octagonal Blender	Sample Site	Individual content of Thiamine Hydrochloride BP of the blend (in mg)	Mean content of Thiamine Hydrochloride BP (in mg)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	0.675, 0.666, 0.655, 0.656, 0.648	0.660	1.59
10 minutes	1, 2, 3, 4, M	0.669, 0.658, 0.688, 0.697, 0.647	0.671	3.08
15 minutes	1, 2, 3, 4, M	0.679, 0.677, 0.702, 0.730, 0.696	0.696	3.08

Time of mixing in Octagonal Blender	Sample Site	Individual content of Riboflavin BP of the blend (in mg)	Mean content of Riboflavin BP (in mg)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	0.573, 0.538, 0.628, 0.657, 0.531	0.585	9.47
10 minutes	1, 2, 3, 4, M	0.593, 0.610, 0.613, 0.577, 0.530	0.584	5.78
15 minutes	1, 2, 3, 4, M	0.552, 0.545, 0.604, 0.593, 0.606	0.580	5.04

Time of mixing in Octagonal Blender	Sample Site	Individual content of Nicotinamide BP of the blend (in mg)	Mean content of Nicotinamide BP (in mg)	Relative Standard deviation (NMT 6%)
5 minutes	1, 2, 3, 4, M	7.83, 8.03, 8.02, 8.01, 8.05	7.98	1.12
10 minutes	1, 2, 3, 4, M	8.15, 8.18, 8.24, 8.15, 8.21	8.18	0.47
15 minutes	1, 2, 3, 4, M	8.26, 8.25, 8.19, 8.23, 8.23	8.23	0.32

Time of mixing in Octagonal Blender	Sample Site	Bulk Density	Tapped Density	Angle of Repose
5 minutes	1	09545	1.2468	42.7°
	2	0.9445	1.1964	44.5°
	M	0.9335	1.1278	42.8°
	3	0.9745	1.2048	43.5°
	4	1.0115	1.1915	43.2°
10 minutes	1	0.9945	1.1457	44.3°
	2	0.9868	1..2124	42.7°
	M	0.9648	1.3158	41.8°
	3	1.0249	1.3452	43.6°
	4	0.9585	1.1986	42.2°
15 minutes	1	0.9845	1.2753	42.9°
	2	0.9968	1.1147	41.7°
	M	1.0478	1.1487	44.4°
	3	0.9978	1.1689	43.1°
	4	0.9648	1.1256	40.9°

Particle Size Distribution:

Time (minutes)	Sample Site	Sample Quantity (gm)	Sample retained on # 40	Sample retained on # 100	Sample pass through # 100
15 minutes	1	100gm	36 gm	72 gm	28 gm
	2	100gm	41 gm	70 gm	30 gm
	M	100gm	36 gm	73 gm	27 gm
	3	100gm	48 gm	76 gm	24 gm
	4	100gm	42 gm	69 gm	31 gm

Moisture Content after Lubrication:

TIME	SAMPLE SITE	MOISTURE CONTENT AT DIFFERENT LOCATION	MEAN OF MOISTURE CONTENT (%)
5 minutes	1, 2, M, 3, 4	1.53, 1.57, 1.52, 1.43, 1.70	1.55
15 minutes	1, 2, M, 3, 4	1.48, 1.45, 1.61, 1.58, 1.63	1.55

Analytical result of in process bulk:

Test Parameters	Specification	Result
	Specification No.- FT/068 M	ET100701
Description	Yellow coloured granular powder	Yellow coloured granular powder

Loss on drying (at 105 °C for 30 minutes)	Not more than 2.0% w/w.	1.47% w/w
Assay Each 170 mg of granular powder contains: Vitamin A (as Acetate) BP Thiamine Hydrochloride BP Riboflavin BP Nicotinamide BP	NLT 98% of label claim (NLT 784.0 IU) NLT 98% of label claim (NLT 0.49 IU) NLT 98% of label claim (NLT 0.49 IU) NLT 98% of label claim (NLT 7.35 mg)	1100.29 IU 0.62 mg 0.55 mg 7.88 mg

Compression:

45 Station compression Machine	**SLOW**	**OPTIMAL**	**FAST**	**ACCEPTANCE CRITERIA**
rpm	15	25	30	
Description	Complies	Complies	Complies	Yellow coloured, round biconvex uncoated tablets
Average weight	171.40 mg	170.32 mg	171.04 mg	NLT 166 mg to NMT 173 mg
Uniformity of weight	164 mg to 176 mg	168 mg to 175 mg	163 mg to 177 mg	NLT 160 mg to NMT 180 mg
Hardness	3.0 kg/cm^2	3.5 kg/cm^2	3.5 kg/cm^2	NLT 2.5 kg/cm^2 to NMT 4.0 kg/cm^2
Diameter	8.05 mm	8.04 mm	8.10 mm	NLT 7.80 mm to NMT 8.20 mm
Thickness	2.86 mm	2.82 mm	2.83 mm	NLT 2.70 mm to NMT 3.10 mm
Friability	0.53 % w/w	0.42 % w/w	0.52 % w/w	NMT 1 % w/w
Disintegration time	7 to 8 minutes	7 to 8 minutes	8 to 9 minutes	NMT 10 Minutes
Assay **Each uncoated tablet contains:** **Vitamin A (as Acetate) BP** **Thiamine Hydrochloride BP** **Riboflavin BP** **Nicotinamide BP**	 1106.41 IU 0.63 mg 0.57 mg 8.07 mg	 1107.61 IU 0.59 mg 0.56 mg 7.89 mg	 1112.04 IU 0.61 mg 0.52 mg 8.11 mg	 NLT 776.0 IU NLT 0.48 mg NLT 0.48 mg NLT 7.27 mg

Preparation of Seal Coating Solution:

Excipients	**Weights (kg)**
Ethyl cellulose BP	2.165
Isopropyl Alcohol BP	58.065

Preparation of Coating Solution:

Excipients	Weights (kg)
Hypromellose BP	3.380
Isopropyl Alcohol BP	35.535
Purified Talc BP	1.130
Titanium Dioxide	1.130
Macrogol BP 6000	0.790
Macrogol BP 400	0.565
Dichloromethane BP	94.470
Colour Allura Red Lake BP	0.610

Analysis of Coated tablets

Parameters	Observations	Acceptance Criteria
Description	Reddish pink coloured round, biconvex film coated tablets	Reddish pink coloured round, biconvex film coated tablets
Average Weight	176.34 mg	NLT 170 mg to NMT 177 mg
Uniformity of weight	175 mg to 182 mg	NLT 163 mg to NMT 184 mg
Diameter	8.20 mm	NLT 7.90 mm to NMT 8.30 mm
Thickness	3.08 mm	NLT 2.90 mm to NMT 3.20 mm
Disintegration Time	12 to 13 minutes	NMT 20 minutes

Reports
Analytical Result of Core Tablets:

S. No.	Test Parameters	Specification	Report	Report
		Specification No.- FT/070 M	Batch No.- ET100700	Batch No.- ET100701
1.	Description	Yellow coloured, round, biconvex uncoated tablets.	Yellow coloured, round, biconvex uncoated tablets.	Yellow coloured, round, biconvex uncoated tablets.
2.	Average Weight	170.0 mg ± 3.0%	171.3 mg	172.2 mg
3.	Disintegration time	Not more than 10 minutes.	7-8 minutes.	8-9 minutes.
4.	*Friability	Not more than 1.0% w/w.	0.25% w/w.	0.28% w/w.
5.	*Hardness	2.5 to 4.0 kg/cm^2	3.0 kg/cm^2	3.5 kg/cm^2
6.	*Loss on drying (at 105 °C for 30 minutes)	Not more than 2.0% w/w.	1.56 % w/w.	1.45 % w/w.

7.	Assay Each uncoated Tablet contains: Vitamin A(as Acetate) BP Colecalciferol BP Thiamine Hydrochloride BP (Vitamin B_1) Riboflavin BP (Vitamin B_2) Nicotinamide BP	NLT 97% of label claim (NLT 776.0 IU) NLT 97% of label claim (NLT 194.0 IU) NLT 97% of label claim (NLT 0.48 mg) NLT 97% of label claim (NLT 0.48 mg) NLT 97% of label claim (NLT 7.27 mg)	798.2 IU 205.6 IU 0.53 mg 0.56 mg 7.54 mg	799.7 IU 204.9 IU 0.55 mg 0.54 mg 7.65 mg
8.	*Microbial contamination Total bacterial count Total Fungal Count *E-Coli*	Not more than 1000 CFU per g Not more than 100 CFU per g Should be absent.	875 CFU per g 75 CFU per g absent	778 CFU per g 72 CFU per g Absent

***** Additional test

Analytical Result of Release Coated Tablets:

Test Parameters	**Specification** **Specification No.- FT/069 M**	**Report** **Batch No.- ET100700**	**Report** **Batch No.- ET100701**
Description	Reddish pink coloured, round, biconvex, film coated tablets.	Reddish pink coloured, round, biconvex, film coated tablets.	Reddish pink coloured, round, biconvex, film coated tablets.
Average Weight	174.0 mg ± 3.0%	175.3 mg	174.9 mg
Disintegration time	Not more than 20 minutes.	15-16 minutes	15-16 minutes
*Loss on drying (at 105 °C for 30 minutes)	Not more than 2.0% w/w.	1.54 % w/w.	1.65 % w/w.
Assay Each Film Coated Tablet contains: Vitamin A(as Acetate) BP Colecalciferol BP Thiamine Hydrochloride BP (Vitamin B_1) Riboflavin BP (Vitamin B_2) Nicotinamide BP	NLT 97% of label claim (NLT 776.0 IU) NLT 97% of label claim (NLT 194.0 IU) NLT 97% of label claim (NLT 0.48 mg) NLT 97% of label claim (NLT 0.48 mg) NLT 97% of label claim (NLT 7.27 mg)	797.2 IU 207.3 IU 0.55 mg 0.57 mg 7.69 mg	796.5 IU 206.5 IU 0.58 mg 0.58 mg 7.76 mg

*Microbial contamination Total bacterial count Total Fungal Count *E-Coli*	Not more than 1000 CFU per g Not more than 100 CFU per g Should be absent.	876 CFU per g 65 CFU per g absent	854 CFU per g 76 CFU per g absent

***** Additional test

Discussion

Analytical parameters at various critical steps were strictly found to be under control. The bulk and release data for three different batches manufactured by said procedure were found to be comparable (Attached)**.** The titrimetric method (USP specification) for ferrous sulphate were found to be under control.

Conclusion

On the basis of statistical analysis of critical process involved in manufacture and comparison of three batches, it is concluded that the manufacture process is Robust and hence stands validated.

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