PROCESS VALIDATION DRAFT TEMPLATES PROTOCOL FOR UN-COATED TABLETS

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1.0 PROTOCOL APPROVAL:

	Department	Name	Signature	Date
Prepared By	Quality Assurance			
Reviewed By	Production			
	Quality Control			
	Engineering			
Approved By	Head-QA			

2 . 0 INTRODUCTION:

Product shall be manufactured using the Wet Granulation Technology. The batches manufactured during the validation shall be setup for the stability study and other parameters monitored periodically and shall be reviewed by the validation Team.

3.0 OBJECTIVE:

The objective of this exercise is to develop a **PROCESS VALIDATION PROTOCOL** to validate the process and have documented evidence to ensure that critical process variables are checked during validation. Also to demonstrate the process capability of the product meets its predetermined specifications and quality attributes.

4.0 SCOPE:

This protocol for the Process validation of ***product name*** formulation defines the procedural aspects to be followed while carrying out Process validation activity that includes prerequisites before commencing the actual work like, Master formula and process, approved vendors and characteristics of raw materials. Also it defines the acceptance criteria, re-validation criteria and justification for critical process parameters.

5.0 VALIDATION CRITERIA:

- Process validation batch shall be manufactured as per process steps given in the Master Manufacturing Formula.
- The batches manufactured during process validation shall meet the criteria defined in product specification.

6.0 REVALIDATION CRITERIA:

The process shall be revalidated whenever there shall be changes in:

- Manufacturing process and the product formula.
- Manufacturing site or location.
- Change in critical equipment in manufacturing process
- Change in batch size

7.0 REASON FOR VALIDATION:

- The product ***Name*** will be manufactured as validation batch due to new product in ***Plant***,
- Transferred/change in facility from another location of Pharmadevils Pvt. Ltd.

8.0 PRODUCT PROFILE:

Name of the product : **……**

Label Claim : Each un-coated tablet contains:

API-1 (BP) ..... 12 mg

API-2 (IP) ……..…… 90 mg

API-3 (BP) ..... 100 mg

Shelf Life : 24 Months

Appearance : Biconvex, un- coated tablets having plain surface on both sides.

Storage Condition : Store in cool and dry place. Protect from light.

9.0 MASTER FORMULA

Batch size: 1000000 Tablets **MMF No.: XX/YY/ZZ/AA-01**

Sr. No.	Components	Specification	Weight/Tablet in mg
Uncoated Tablets			
Dry mixing			
1.	API-1 BP	BP	100.00
2.	Croscarmellose sodium IP	IP	51.00
3.	Microcrystalline cellulose IP (PH 112)	IP	20.00
4.	Colloidal silicon dioxide IP	IP	9.00
Binder Preparation			
5.	Povidone IP (K-30)	IP	7.20
6.	Isopropyl alcohol IHS *	IHS	210.00
Pre-Lubrication			
7.	API-3 BP	BP	79.44
8.	API-2 IP	IHS	62.7
9.	Croscarmellose sodium IP	IP	34.00
10.	Colloidal silicon dioxide IP	IP	1.00
11.	Polacrilin potassium USP	USP-NF	23.70

Lubrication			
12.	Magnesium Stearate IP	IP	4.40
		Weight of uncoated tablet	**XXX.00**

* Not considered in final weight of tablet.

10.0 RISK ANALYSIS:

The product shall be manufactured in General block with batch size of 1000000 Tablets as a validation batch. product shall be manufacturing by using wet granulation. Raw materials of approved vendor source shall be sifted, dry mixed, granulated using binder solution and dried at 50 ^{O}C ± 5 ^{O}C. Dried granules are sized (Sifted and milled) and lubricated using Magnesium stearate. An Approved lubricated granules will be compressed by using 11.5 mm diameter circular standard concave punches having plain surface on upper and lower punch.

- **Dispensing:**

Dispensing of all raw material is done by using calibrated balance, all raw material are procured from approved vendor, there is no critical parameter identified for validation during dispensing stage.

- **Granulation:**

➢ **Sifting of raw material:** Sifting of raw material is done by specified sieve under supervision of the trained personnel. Sieve integrity is verified before and after processing.

➢ **Dry Mixing:** Dry mixing of the material is performed by laid down procedure and dry mixing uniformity was established during optimization of product, at dry mixing stage critical parameters are mixing time and speed of mixer is to be monitored. At the end of 10 minutes Samples from various locations shall be withdrawn and evaluated for mixing uniformity. Composite sample shall be withdrawn and evaluated for untapped bulk density, tapped bulk density, for record purpose as part of validation.

➢ **Binding:** At the time of binding manual monitoring is to be done for the defined mixing speed of agitator and chopper and end point of the granulation to be monitored by checking the mass intermittently for consistency and amperage load monitoring.

➢ **Drying:** At the Drying stage of the granules Inlet temperature to be monitored and sample to be withdrawn during drying and tested for LOD till the end of drying to find out rate of drying and at end

of drying sample withdrawn from seven location of bowl for checking of drying uniformity for specified LOD by using IR moisture balance.

- **Sizing of Granules:** Sizing of granules is to be milled by using Multimill, Speed of the Multimill and direction of shafts is to be monitored and sample to be withdrawn at the end of the sizing operation for the monitoring of particle size distribution, untapped bulk density, tapped bulk density and LOD at 105 ºC on IRMB for record as part of validation.

- **Lubrication:** Critical Process variable to be monitor about speed of blender and mixing time of granules and sample to be withdrawn from ten location for verification of blend uniformity and also composite sample to be withdrawn for analysis particle size distribution, untapped bulk density, tapped bulk density and for complete analysis as per QC in process specification.

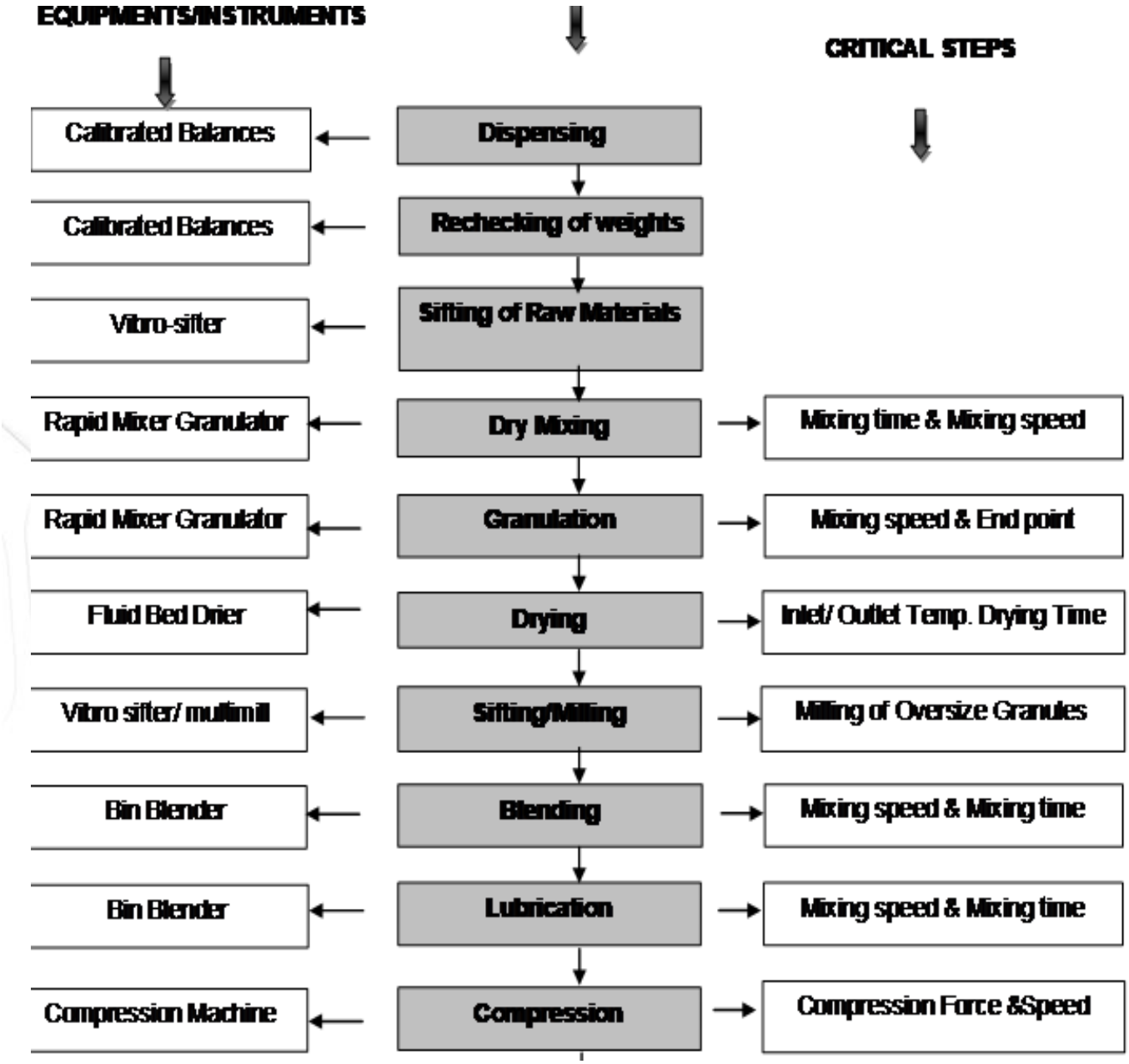
- **Compression:**

  During compression stages physical parameter, assay and dissolution as per sample summary of tablet to be checked at different challenges, at maximum/minimum speed, at maximum/minimum hardness, at optimum speed and optimum hardness during – initial/ full of hopper stage, middle stage and end/ half of hopper stage of compression process. This process will cover critical process variables such as effect of speed and compression force. After completion of compression process composite sample to be withdrawn for analysis as per QC in-process specification.

11.0 SAMPLING PROCEDURE:

- All validation samples except unit dose blend samples shall be placed in clean container and labeled.
- **Unit dose blend sample** shall be taken in accordance with SOP for **"Procedure for cleaning and operation of sampling thief".** The samples shall be placed in container or sampling poly bag and labeled.

12.0 FLOW DIAGRAM (PROCESS):



13.0 MANUFACTURING PROCEDURE:

13.1 Sifting of raw material:

- Sift API-1 through s.s. sieve # 60 ASTM (250 µ) on a vibro sifter.

- Co-sift Microcrystalline cellulose (PH 112) and Colloidal silicon dioxide through s.s. sieve # 40 ASTM (425 µ) on a vibro sifter.
- Sift Lactose Monohydrate through s.s. sieve # 40 ASTM (425 µ) on a vibro sifter.

13.2 Dry Mixing:

- Transfer the material of step 10.1 to RMG and mix for 10 minutes at slow speed.

13.3 Binder Preparation:

- Dissolve Povidone (K-30) in Isopropyl alcohol under stirring to form a clear solution.

13.4 Granulation:

- Add the binder solution obtained in step 10.3 to the dry mix of step 10.2 and granulate to obtain dough mass of required consistency. Continue mixing till the desired dough mass is obtained. If required add additional quantity of Isopropyl alcohol to get the desired dough mass and note down the same.

13.5 Drying:

- Air-dry the granules in FBD for 30 minutes. Reshuffle the granules.
- Air-dry the granules in FBD for 10 minutes. Reshuffle the granules.
- Dry the granules at an inlet temperature of 50 ^{O}C ± 5 ^{O}C, till the desired LOD (Limit: 3.0 % - 4.0 % w/w at 105 ^{O}C on IRMB) is achieved.

13.6 Sifting and Milling:

- Sift the dried granules through sieve # 24 on a vibro sifter.
- Mill the granules retained on # 24 through 1.5 mm screen fitted on multimill; at medium speed knives forward direction and pass the granules through # 24.

13.7 Pre-Lubrication:

- Co-sift API-2 and API-3 geometrically through s.s. sieve # 40 ASTM (425 µ) on a vibro sifter.
- Co-sift the materials of step 10.7.1 with the dried granules of step 10.6 geometrically through s.s. sieve # 24 on a vibro sifter.
- Sift Croscarmellose sodium through s.s. sieve # 40 ASTM (425 µ) on a vibro sifter.
- Sift Colloidal silicon dioxide through s.s. sieve # 40 ASTM (425 µ) on a vibro sifter.
- Sift Polacrilin potassium through s.s. sieve # 40 ASTM (425 µ) on a vibro sifter.
- Transfer the sifted materials of step 10.7.2, 10.7.3, 10.7.4 and 10.7.5 into the blender and mix for 15 minutes.

13.8 Lubrication:

- Sift Magnesium stearate through s.s. sieve # 60 ASTM (250 µ) on a vibro sifter.
- Transfer the sifted Magnesium stearate to the blender and mix for 3 minutes.

13.9 Blend Analysis:

- Intimate the Quality Control department for analysis of blend as per current in process specifications.

13.10 Compression:

- Compress the approved blend on rotary compression machine as per in process specification.

13.11 Finished Product Analysis:

- Intimate the Q.C. for analysis of finished product as per current Finished Product Specifications.

14.0 CALIBRATION/QUALIFICATION:

All equipment utilized in conducting the Validation activity shall be within calibration / qualification. Calibration/qualification shall be conducted in-house in accordance with approved SOPs or by an external body. All standards used in calibration shall be traceable to a national standard and shall remain within calibration for the duration of the Validation exercise.

15.0 SAMPLE SUMMARY:

Stage	Location	Sample Size	Sample Type	Frequency	Tests	Acceptance Criteria
$Dry Mixing	10 position from RMG	Draw samples equivalent to between 1-3 unit dose (XX mg to XX mg)*	Unit dose sample	After 10 minutes of dry mixing	Mixing Uniformity**	As per specification / To record
	Composite sample from the Top, middle and bottom level of RMG	Approximately 20 gm *	Composite sample		Untapped bulk density Tapped bulk density	
$Drying	Fluid bed drier	Approximately 2 gm	Composite sample	During drying operation	LOD at 105° C/ IR Balance	Till the desired LOD achieved as per BMR
		Approximately 2 gm each	6 locations	At the end of drying	LOD	As per BMR
$ Milled granules	Blender	Approximately 50 g *	Composite	At the end of milling operation	LOD Particle Size Distribution (20#,40#,60#,80#and 100#) Untapped Bulk Density Tapped Bulk Density	As per BMR To record To record To record
Pre-lubrication	10 position from Blender	Draw samples equivalent to between 1-3 unit dose (XX mg to XX mg) *	Unit dose sample	After 10 minutes of pre-lubrication	Blend Uniformity**	As per specification / To record
lubrication	10 position from Blender	Draw samples equivalent to between 1-3 unit dose (XX mg to XX mg) *	Unit dose sample	After 3 minutes of lubrication	Blend Uniformity	As per specification
	Composite sample from the top, middle and bottom level of Blender	50 g*	Composite		1) Particle size distribution* (20,40,60,80 & 100#) 2) Untapped bulk density*, 3) Tapped bulk density* 4) LOD*	For record For record For record
					5) For complete analysis	As per blend specification

Average weight during lubrication : 400.0 mg

* Sample shall be withdrawn and sent to QC along with test requisition.

** Duplicate sample to be retained by QA for reference purpose till testing.

$ Sample from each lot.

For unit dose sampling during Lubrication stage use 1.0 CC covette.

Sample shall be withdrawn at the depth of Approx 20 % from top layer of blend using sampling thief and about Approx .0.6 feet from wall of the Bin Blender.

Sample shall be withdrawn at the depth of Approx 50 % from top layer of blend using sampling thief and about Approx. 0.6 feet from wall of the Bin Blender.

Sample shall be withdrawn at the depth of Approx 80 % from top layer of blend using sampling thief and about approx. 0.6 feet from wall of the Bin Blender.

Stage	Location	Sample Size	Sample Type	Frequency	Tests	Acceptance Criteria
Compression #	Direct from Compression Machine	100** Tablets	Individual Tablets	1) At maximum hardness 2) At minimum hardness	1) Appearance* 2) Group Weight 3) Avg. Weight 4) Uniformity of weight 5) Thickness 6) Hardness 7) Disintegration time 8) Friability	As per Specification
					Capability index	NLT 1.33
		100+(20*)** Tablets		3) At maximum speed 4) At minimum speed 5) At optimum speed & hardness a) Initial stage/ Full Hopper b) Middle stage c) End stage/ Half Hopper	1) Appearance* 2) Group Weight 3) Avg. Weight 4) Uniformity of weight 5) Thickness 6) Hardness 7) Disintegration time 8) Friability 9) Assay*	As per Specification
					Capability index	NLT 1.33
		100 Tablets	Individual Tablets	At regular interval as per BMR	1) Appearance 2) Group Weight 3) Avg. Weight 4) Uniformity of weight 5) Thickness 6) Hardness 7) Disintegration time 8) Friability	As per Specification (To be recorded in BMR)
	Pooled Tablet Container	100 Tablets*	Composite sample	End of Compression	For complete analysis*	As per QC specification

* Sample shall be withdrawn and sent to QC along with test requisition.
** Duplicate sample to be retained by QA for reference purpose till testing.
*** Results to be recorded in PVR.
@ For Microbial analysis.
# Samples to be collected from L.H.S and R.H.S separately and sent to QC as per sample summery.

16.0 RAW MATERIALS RATIONALE:

The raw materials shall be tested to ensure that the materials are of the acceptable quality prior to their use in the manufacturing. All the API and excipients shall be tested as per the respective Pharmacopoeial monograph. The details of reference monographs, vendor and analytical reference number are to be written in validation report.

17.0 SPECIFICATIONS:

Specifications for Uncoated Tablets: (As per BMR/MMF*)

Sr. No.	Parameter	Specification
1.	Appearance	Light yellow circular, biconvex uncoated tablet having plain surface on both sides.
2.	Weight of 20 tablets	8.0 g ± 2.5%
3.	Average weight	400.0 mg ± 2.5 %
4.	Uniformity of weight	400.0 mg ± 5.0 %
5.	Thickness	4.4 ± 0.30 mm
6.	Hardness	NLT 6 kg/cm^2
7.	Friability	NMT 1.0 % w/w
8.	Disintegration time	NMT 15 minutes

Specifications for Coated Tablets: (As per BMR/MMF*)

Sr. No.	Parameter	Specification
1.	Appearance	Reddish orange coloured, circular, biconvex, enteric coated tablets having plain surface on both sides.
2.	Weight of 20 tablets	9.020 g □ 2.5 %
3.	Average weight	451.0 mg ± 2.5 %
4.	Uniformity of weight	451.0 mg □ 5.0 %
7.	Thickness	4.6 ± 0.30 mm
8.	Disintegration time	As per IP monograph for enteric coated tablets.

Note:-

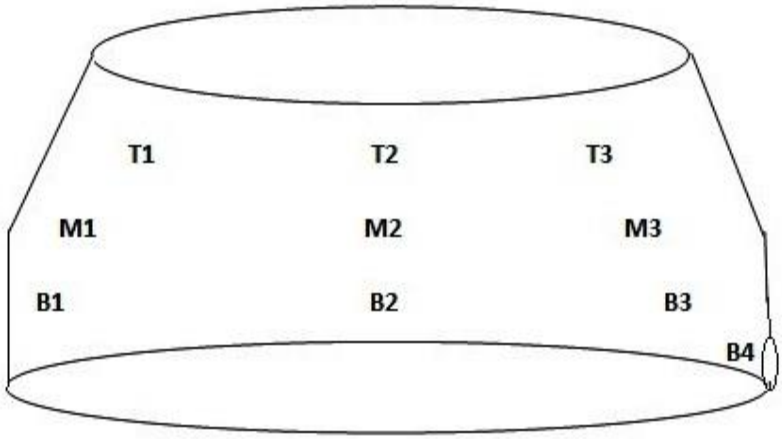
- Uncontrolled Copy of Raw material specification attached*:_____
- Uncontrolled Copy of Inprocess specification for Lubricated blend and core tablets attached*:_____
- Uncontrolled Copy of Finished product specification attached*:_____

***Current version shall be followed**

❖ **DRY MIXING:**

As specified in the BMR, dry mix the material for 10 minutes. Withdraw about 20 gm of sample after 10 minutes of dry mixing as specified in BMR, from the centre position of Top, middle and bottom layer of dry mixed granules in rapid mixer granulator for determination as test given in sample summary.

DIAGRAM AND SAMPLING LOCATION FOR R.M.G :



T1 = Top left T2 = Top middle T3 = Top right

M1 = Middle left M2 = Middle centre M3 = Middle right

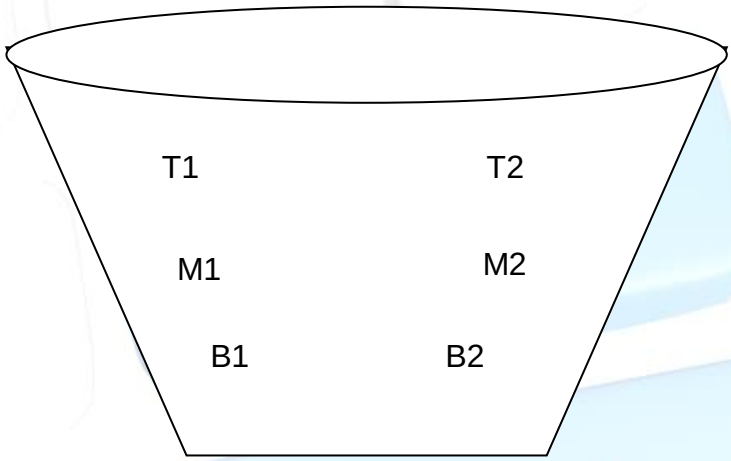
B1 = Bottom left B2 = Bottom middle B3 = Bottom right

B4 = Discharge chute

❖ **DRYING:**

Dry the granules at inlet temperature defined in BMR. Withdraw the composite sample during drying to till the end of drying to get the desired LOD and after the completion of drying withdraw samples from seven locations to determine the uniformity of drying in FBD as defined in sample summary.

DIAGRAM OF FLUID BED DRYER BOWL WITH SAMPLING POINTS:



Where,

T1	=	Top Left	**M2**	=	Middle Right
T2	=	Top Right	**B1**	=	Bottom Left
M1	=	Middle Left	**B2**	=	Bottom Right

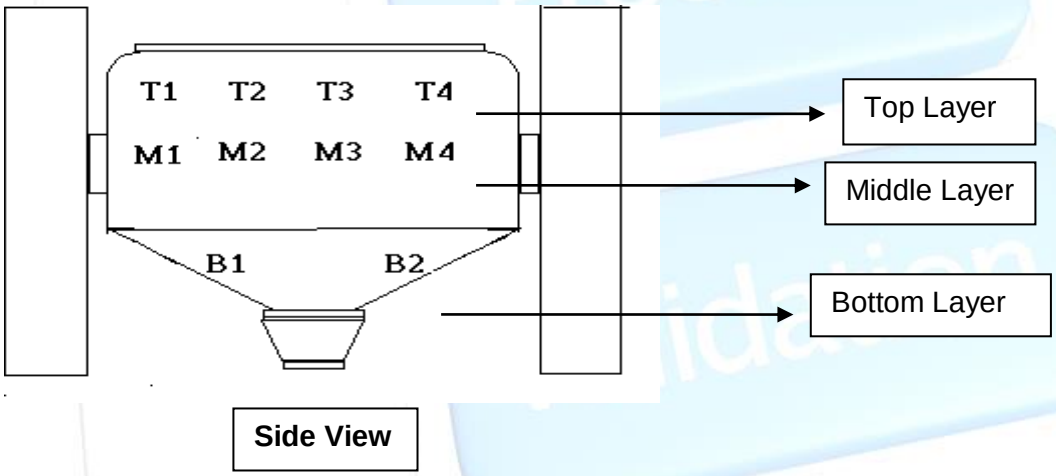
❖ LUBRICATION:

As specified in the BMR, blend the material for 20 minutes for pre-lubrication. Withdraw the samples equivalent to between 1 – 3 unit dose (395.60 – 1216.80) mg, in duplicate separately from 10 locations as per defined sampling location; determine the blend uniformity of granules.

As specified in the BMR, blend the material for 03 minutes for lubrication. Withdraw the samples equivalent to between 1 – 3 unit dose (400.0 – 1230.0) mg, in duplicate separately from 10 locations as per defined sampling location; determine the blend uniformity of granules.

Withdraw about 50 gm of sample after 03 minutes of blending as specified in BMR, from the centre position of Top, middle and bottom layer of blend in Bin bender for determination of test given in sample summary.

DIAGRAM OF BIN BLENDER WITH SAMPLING LOCATIONS:



Side View

Where,

T1	=	Top Left	**M2**	=	Middle Front
T2	=	Top Front	**M3**	=	Middle Rear
T3	=	Top Rear	**M4**	=	Middle Right
T4	=	Top Right	**B1**	=	Bottom Left
M1	=	Middle Left	**B2**	=	Bottom Right

❖ **COMPRESSION:**

On release of the lubricated granules by QA, the granules are taken up for compression. During tablet compression stage, the homogeneous granules are compressed on a tableting machine. To validate the tableting process for ***product***, the compression machine is run on maximum / minimum hardness, maximum / minimum speed and on optimum hardness / speed - at initial run, middle run, end of the run. Samples are collected for analysis as defined in the sample summary. The in-process testing shall be carried out at regular intervals during the machine run. These validation samples shall be tested as per the sample summary, to meet the acceptance criteria specified therein.

➢ **PROCEDURE**

Appropriately label the sample containers and collect samples as follows:

Set the machine, and adjust the compression parameters. After stabilization of the compression machine, the parameters mentioned below are checked and recorded in the respective BMR and report.

	Parameters of Evaluation		
1.	Appearance	5.	Disintegration Time
2.	Hardness	6	Group Weight
3.	Thickness	7.	Average Weight
4.	Friability	8.	Uniformity of Weight

After the start of compression operation, set the compression machine -

AT OPTIMUM HARDNESS AND MAXIMUM SPEED:

Set the compression machine at optimum hardness and maximum limit of speed and collect the tablets as per the sample summary. Maximum speed to be recorded in validation report.

AT OPTIMUM HARDNESS AND MINIMUM SPEED:

Set the compression machine at optimum hardness and minimum limit of speed and collect the tablets as per the sample summary. Minimum speed to be recorded in validation report.

AT OPTIMUM SPEED AND MAXIMUM HARDNESS:

Set the compression machine at optimum speed and higher limit of hardness range and collect the tablets as per the sample summary. Target hardness and thickness to be recorded in validation report.

AT OPTIMUM SPEED AND MINIMUM HARDNESS:

Set the compression machine at optimum speed and lower limit of hardness range and collect the tablets as per the sample summary. Target hardness and thickness to be recorded in validation report.

OPTIMUM RUN:

Set the compression machine at optimum speed / hardness and collect the tablets as per the sample summary Optimum speed to be recorded in validation report.

AT INITIAL /FULL HOPPER RUN

MIDDLE RUN

END/HALF HOPPER OF RUN

Collect tablets at regular intervals till the end of the compression cycle as per the Batch Manufacturing Record and sample summary. Record the sample details in validation report and Batch Manufacturing Record. About 100 tablets in a container labelled, as 'POOLED SAMPLE' shall be collected throughout the compression operation. The tablet for Inprocess analysis shall be taken from the pooled sample for Inprocess Product Analysis as per specification.

18.0 DESTRUCTION OF REMAINING VALIDATION SAMPLES:

All remaining samples of the validation batch shall be destroyed as per respective SOP, details to be recorded in validation report.

19.0 SUMMARY, CONCLUSION AND APPROVAL:

Record the summary of the validation study with special emphasis on physical parameter, chemical parameter and evaluation of data obtained in validation report. Details of out of specification / deviation if any should be recorded in validation report. Record the recommendations or suggestions based on the implementations of the results in validation report. It should include the approval of quality assurance, quality control and production head.

20.0 ABBREVIATIONS:

QA	: Quality Assurance
QC	: Quality Control
OOS	: Out of Specification
SOP	: Standard Operating Procedure
LOD	: Loss on Drying
BMR	: Batch Manufacturing Record
MMF	: Master Manufacturing Formula
A.R. No.	: Analytical Report Number
NLT	: Not Less Than
NMT	: Not More Than
FBD	: Fluid Bed Dryer
RMG	: Rapid Mixer Granulator
PVR	: Process validation report
ASTM	: American Society for Testing and Materials
IRMB	: Infra Red Moisture Balance
API	: Active Pharmaceutical Ingredient

REVISION CARD

Sr. No.	PPV No.	RPV No.	Reason for Revision	Change Control No.
1			New	-----