PROCESS VALIDATION PROTOCOL

PARACETAMOL TABLETS BP 500mg

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1.0 APPROVAL

Prepared By	Name	Designation	Signature	Date
QUALITY ASSURANCE	P. Vadivel	Sr. Executive QA	P. Vadivel	10/11/21

Reviewed By	Name	Designation	Signature	Date
PRODUCTION	V. Dharabal	Sr. Gm		11/11/21
QUALITY CONTROL	M. Vijayakumar	AGM.		11/11/21

Approved By	Name	Designation	Signature	Date
QUALITY ASSURANCE	A. GANAPATHY	GM-QA		11/11/21

2.0 SCOPE:

This protocol is applicable for the manufacturing and sampling of Validation batches of Paracetamol Tablets BP 500mg with a batch size of 15.0 Lac tablets. In case data obtained from validation batches seem to be inadequate, further extension of the validation batches shall be done. For further confidence of efficacy and fitness till its assigned shelf life, these three batches shall be for both long term and accelerated stability study.

3.0 OBJECTIVE:

The objective of this protocol is to validate the process by establishing documented evidence for Paracetamol Tablets BP 500mg, to be manufactured at Safetab Life Science, Plot No: A-67 to 72, PIPDIC Electronic Park, Thirubuvanai, Puducherry, so that this will provide sufficient data there by the process will produce the product meeting its pre-determined specification and quality attributes in a reproducible manner.

4.0 INTRODUCTION

Paracetamol Tablets BP 500mg is a solid dosage which contains Paracetamol as active ingredient. This is being manufactured at Safetab Life Science, Puducherry, with the batch size of 15.0 Lac tablets as per Master Formula Card (MFC).

5.0 PROCESS VALIDATION APPROACH:

Prospective type of validation [Process Performance Qualification (PPQ)] approach will be adopted and the batches will be released for after verifying the compliance of validation acceptance criteria. During this validation the below mentioned process stages shall be evaluated for the controlling parameters, sequence, criticality to product quality and performance:

Note: PPQ batch will be released on concurrent approach through an interim process validation report.

- Dry Mixing
- Drying
- Blending
- Lubrication
- Compression
- Packing

Data shall be collected from executed batch manufacturing record, IPQA test data sheets and in-process/ validation sample analysis reports, for the compilation of report.

6.0 RESPONSIBILITY:

Validation Team	Responsibilities
Quality Assurance	1) Defining the manufacturing process and process parameters that impact the quality, safety, purity and efficacy of the product based on the knowledge gained through process validation.
	2) To ensure pre-requisite requirements are completed before proceeding for Process validation.
	3) Preparation of Process validation Protocol and Report.
	4) In-process monitoring and assurance of quality. Withdrawal of samples as per the sampling plan defined in this protocol.
	5) Review of batch records, analytical reports, compilation of data, evaluation of results and Process validation report.
	6) Reviewing and approving investigations and CAPA for deviations from defined manufacturing process and Process Validation protocol.
Production	1) Review of Process Validation protocol and Report.
	2) Execution of process as per the batch record and Process validation protocol and relevant operating procedures.
	3) Co-ordination with Quality Assurance for sampling.
	4) Investigating any deviations from defined manufacturing process and Process Validation protocol and identifying CAPA.
Quality Control	1) Review of Process validation protocol and report.
	2) Testing the samples drawn during Process validation study and compilation of results.
Engineering	1) Providing necessary utility as per the product requirement.
	2) Ensuring calibration of measuring devices available on process equipment and utilities and maintenance of processing equipments.
Head Quality Assurance	1) Approval of Protocol and Report. 2) To review and approve the investigations and CAPA for deviations From defined manufacturing process and protocol. 3) To take decision on further release and distribution of validation batches.

7.0 PRODUCT DETAILS:

Product Name	Paracetamol Tablets BP 500mg.
Label Claim	Each uncoated tablet contains: Paracetamol BP 500 mg
Overages (% w/w)	NA
Shelf life	36 Months
Storage Condition	Store below 30°C in a cool & dry place.
Batch Size	1500000 Tablets
Therapeutic Use	Paracetamol is a commonly used medicine that can help treat pain and reduce a high temperature (fever). Anti-inflammatory and Anti-pyretic drug.
Product Pack	Printed Foil: 202mm blister aluminum foil (0.025mm thickness). Base Foil: 206mm PVC clear foil.
Pack Style	Sales : 100x10's BLISTER PACK

PRECAUTIONS:

Maintain temperature between 23°C to 27°C and relative humidity between 45% to 55% throughout the manufacturing process. Blended material and compressed tablets should be stored in HDPE container with double lined poly bags with lids securing on and labeled accordingly.

8.0 RAW MATERIAL COMPONENTS:

Material Code	Ingredient	Grade	Mg/Tablet	Quantity Kg/Batch 15.0 L	Manufacture
Dry Mixing and Granulation:					
RMAP0030	Paracetamol *	BP	500.000	750.000	Bharat Chemicals, Farmson analgesics
BINDER PREPARATION					
RMEM0034	Maize Starch**	BP	30.000	45.000	Roquette India Private LTD
RMES0049	Sodium Benzoate	BP	1.000	1.500	Finar Limited
RMEM0034	Maize Starch	BP	28.000	42.000	Roquette India Private LTD
RMEP0049	Povidone K30	BP	10.000	15.000	Haungshan Bonsun Pharmaceuticals LTD
RMEP0033	Purified Water@	BP	99.000	148.500	In-House
BLENDING AND LUBRICATION					
RMEC0017	Hydrophobic colloidal anhydrous silica	BP	5.000	7.500	Wacker Chemie AG
RMET0012	Purified Talc	BP	3.000	4.500	Imerys talc Italy/Neelkanth
RMEM0033	Magnesium Stearate	BP	3.000	4.500	Nitika pharmaceutical specialties PVT.LTD
	Total weight		**580.000**	**870.000**	----------

@ Does not appear in final product evaporates during processing.
***, ** Refer calculation.**

9.0 CALCULATIONS:

9.1 Potency calculation for Paracetamol:

* The given quantity is based on 100% Assay on dried basis and without LOD.

Actual quantity to be added is calculated as:

$$\text{Actual quantity. of Paracetamol BP} = \frac{500X\ 100\ X\ 100}{\%\ \text{Assay on dried basis X (100 – LOD \%)}}\ \text{mg/tablet}$$

Quantity of Maize starch BP varies based on assay content and LOD % of Paracetamol BP for keeping the core tablet weight constant

Note: If the assay of Paracetamol BP is more than 100 %, calculation has to be done only for 100%

10.0 PACKING MATERIAL COMPONENTS:

Material code	Components	Vendor
PMP00104	202mm blister aluminum foil (0.025mm thickness).	DAGA POLY LAMINATORS (P) LTD
PMPD0013	206mm PVDC clear foil.	RAJAT VINYLS PVT LTD

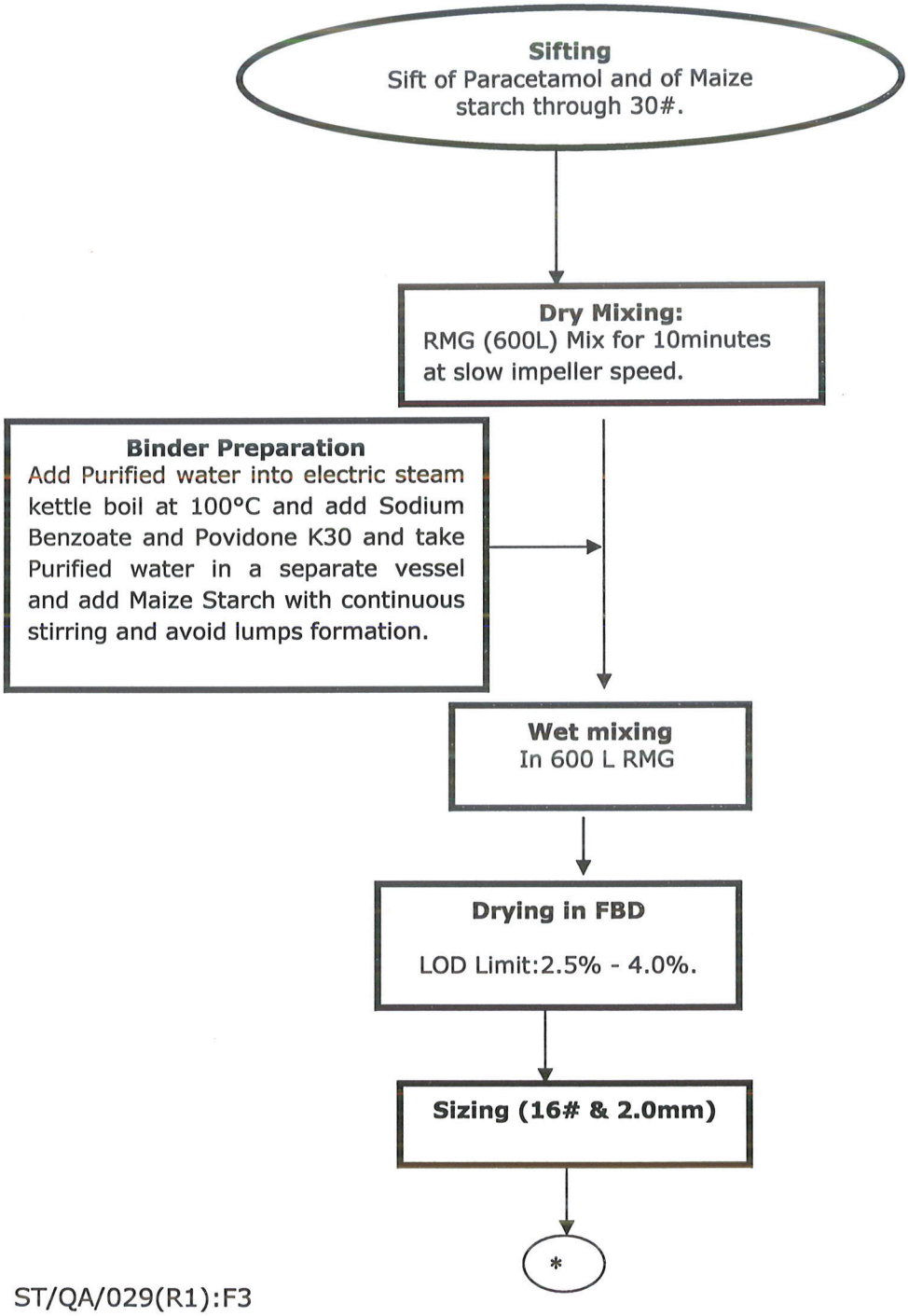
11.0 EQUIPMENT DETAILS:

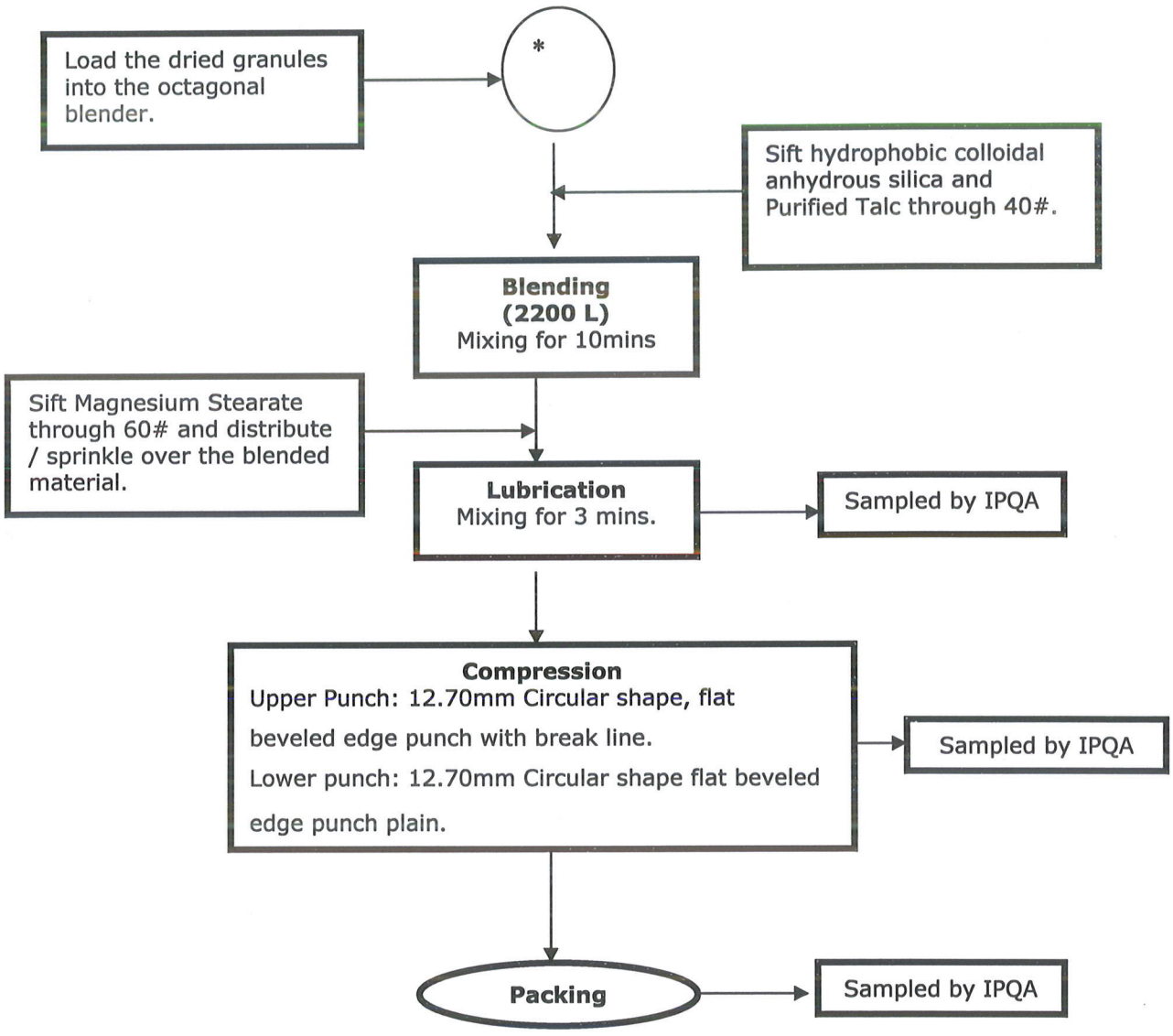
Table 1: List of major process equipment to be used in the manufacturing:

Sr. No.	Equipment	Make	Equipment No.
1.0	Weighing Balances	ESSAE TERAOKA	ST/SRWB/001, ST/SRWB/002 ST/PRWB/002, ST/PRWB/005 ST/PRWB/006, ST/WB/189 ST/WB/198, ST/WB/199 ST/WB/202
2.0	Vibratory Sifter	SARAL	ST/PRVS/001 or ST/PRVS/002 or ST/PRVS/003 or ST/PRVS/004
3.0	Fluid bed drier (250Kg)	SARAL	ST/PRFD/003
4.0	Rapid Mixer Granulator(600L)	SARAL	ST/PRRG/005
5.0	Multimill	GEM Pharma	ST/PRML/001 or ST/PRML/002
6.0	Octagonal Blender (2200L)	GEM Pharma	ST/PROB/001
7.0	Compression Machine 27/45 stn.	CADMACH	ST/PRCM/004 or ST/PRCM/005
8.0	Blister Packing Machine	RAPID PACK AX RAPID PACK 240	ST/PPB/ 001 ST/PPB2/ 001

12.0 PROCESS DESCRIPTION:

12.1 Process Flow Chart




Load the dried granules into the octagonal blender.
*
Sift hydrophobic colloidal anhydrous silica and Purified Talc through 40#.
Blending (2200 L) Mixing for 10mins
Sift Magnesium Stearate through 60# and distribute / sprinkle over the blended material.
Lubrication Mixing for 3 mins.
Sampled by IPQA
Compression
Upper Punch: 12.70mm Circular shape, flat beveled edge punch with break line.
Lower punch: 12.70mm Circular shape flat beveled edge punch plain.
Sampled by IPQA
Packing
Sampled by IPQA

12.2 Brief Explanation of manufacturing process:

The steps in the manufacturing process shall be followed as per the approved batch manufacturing record. Process parameters during each unit operation shall be monitored to demonstrate that product meets the Acceptance Criteria.

The processing of Paracetamol Tablets BP 500mg comprises of following stages:

Stage	Manufacturing Procedure
1 Dispensing	Dispense the raw material as per the standard operating procedure.
2. Sifting	Sift Paracetamol and Maize starch through 30#.
3.Dry Mixing	Mix for 10 minutes at slow impeller speed.
4.Binder Preparation	Add Purified water into electric steam kettle boil at 100°C and add Sodium Benzoate and Povidone K30 and take Purified water in a separate vessel and add Maize Starch with continuous stirring and avoid lumps formation.
5. Granulation	**Granulation:(Wet mixing)** i) Binder addition: Mix for 2 minutes with slow speed impeller. ii) Racking. iii) Mixing: 3 minutes with impeller at slow speed and chopper at slow speed. iv) Mixing: Add Purified water 2 minutes with impeller at slow speed and chopper at slow speed. v) Racking. vi) Mixing: 2 minutes with at slow speed impeller to get uniform granules.
6.Drying and Sizing	Load the Wet granules into the FBD bowl and drying 60°C±5°C with intermittent racking at every 10-15 mins until LOD to reach the limit 105°C at moisture balance. LOD% limit: 2.5% - 4.0%. Sift the dried granules through 16#. Mill the retained granules through 2.0mm screen and pass through 16#.
7. Blending	Load the dried granules into the octagonal blender, Sift Hydrophobic colloidal anhydrous silica and Purified Talc through 40#.Mixing for 10mins.
8.0 Lubrication	Sift Magnesium Stearate through 60# and distribute / sprinkle over the blended material. Mix for 3minutes. Unload the final lubricated granules into the suitable container lined with double poly bag with proper status label.

Stage	Manufacturing Procedure
9.0 Compression	Set the 27/45 - station double/single rotary compression machine with Upper Punch : 12.70mm Circular shape, flat beveled edge punch with break line Lower punch: 12.70mm Circular shape flat beveled edge punch plain.

Description	White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.
Average Weight per tablet	580.000mg±3% (562.600mg to 597.400mg)
Weight of 20 tablets	11.600g±3% (11.252g to 11.948g)
Uniformity of weight	±5% of average weight (551.000mg to 609.000mg)
Thickness	*4.10mm ± 0.3mm (3.80mm to 4.40mm) (To be monitored)
Hardness	*80N-130N (To be monitored)
Disintegration time	NMT 15 mins at 37°C±2°C
Friability	NMT 1.0%w/w

10.0 Inspection	Inspect the tablets visually for removing defected tablets.
11.0 Metal detector	Tablets pass through the metal detector.
12.0 Packing	Perform packing on strip packing machine.

13.0 SAMPLING PLAN AND ACCEPTANCE CRITERIA:

13.1 CRITICAL PROCESS STAGES TO BE VALIDATED:

13.1.1 DRY MIXING STAGE

DRY MIXING PROCEDURE (Refer MFR/BMR more details)	**CRITICAL PARAMETER TO BE VALIDATED**	**SAMPLING PROCEDURE**
Sift Paracetamol and Maize starch through 30#.Mix for 10 minutes at slow impeller speed.	**MIXING TIME**	Samples shall be withdrawn from 9 different locations Collect approximately 2gm of Dry mixing powder sample. Location each in duplicate from top, middle and bottom level of the RMG (as per sampling diagram 18.1) separately using sampling thief after **10 minutes** mixing. Use these samples for blend uniformity test as per 13.2.1.1 Note: Duplicate samples to be retained for contingency.

13.1.2 Drying

DRYING PROCEDURE (Refer MFR/BMR more details)	**CRITICAL PARAMETER TO BE VALIDATED**
Loss on drying of dried granules to be evaluated using Moisture balance.	**LOD (Limit 2.5% - 4.0%)**

13.1.3 BLENDING AND LUBRICATION STAGE

BLENDING AND LUBRICATION PROCEDURE (Refer MFR/BMR more details)	**CRITICAL PARAMETER TO BE VALIDATED**	**SAMPLING PROCEDURE**
Step-1 Load the dried granules into the octagonal Sift Hydrophobic colloidal anhydrous silica and Purified Talc through 40#.Mix for 10mins.	**1. Mixing time (Pre-lubricated blend uniformity)**	**Step- 1: PRE - LUBRICATION:** Samples shall be withdrawn from 10 different locations Collect approximately 2gm of blend sample location each in duplicate from top, middle and bottom level of the Octagonal blender (as per sampling diagram 18.2) separately into the tarred using sampling thief after **10 minutes** mixing. Use these samples for blend uniformity test as per 13.2.2.1
Step - 2 Sift Magnesium Stearate through 60# and distribute / sprinkle over the blended material. Mix for 3minutes.	**2. Mixing time (Lubricated blend uniformity)**	**Step- 2: AFTER LUBRICATION:** Samples shall be withdrawn from 10 different locations Collect approximately 2gm of lubrication blend sample location each in duplicate from top, middle and bottom level of the Octagonal blender (as per sampling diagram 18.3) separately using sampling thief after **3 minutes** mixing. Use these samples for blend uniformity test as per 13.2.2.2 **For first batch only:** After **3** minutes mixing of lubricated blend, collect a pooled sample – about 250g total from three different sampling locations viz; top, middle and bottom of the Octagonal blender. Use this pooled sample for evaluation of physical parameters as per 13.2.2.2

13.2 TEST PROGRAM AND ACCEPTANCE CRITERIA FOR VALIDATION:

S.No.	MEASURED PARAMETERS	ACCEPTANCE CRITERIA	TEST PROCEDURE
13.2.1	**GRANULATION PROCESS :**		
13.2.1.1	**Dry Mixing:**		
1	**Blend uniformity:** (Paracetamol)	Individual sample values between 85% to 115% of label claim & RSD: NMT 5 % Average value between 95.0% to 105.0%.	Specification and test procedure no: IMSP00135-01 IMTP00135-01
13.2.2	**BLENDING & LUBRICATION PROCESS:**		
13.2.2.1	**BLENDING – PRE LUBRICATION:**		
1	**Blend uniformity:** (Paracetamol)	Individual sample values between 85% to 115% of label claim & RSD: NMT 5 % Average value between 95.0% to 105.0%.	Specification and test procedure no: IMSP00135-01 IMTP00135-01
13.2.2.2	**LUBRICATION:**		
1	**Appearance** (pooled sample)	White granular powder	Specification and test procedure no: IMSP00135-01 IMTP00135-01
2	**Blend uniformity:** (Paracetamol)	Individual sample values between 85% to 115% of label claim & RSD: NMT 5 % Average value between 95.0% to 105.0%.	
3	**Bulk density** (pooled sample)	For information only	NA
4	**Tap density** (pooled sample)	For information only	
5	**Particle size** (Cumulative retains in %)	For information only	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.2.3	**COMPRESSION PROCESS:**			
13.2.3.1	**Compression Force (Hardness -Challenge)**			
	To find out the hardness range, the following procedure to be adopted. **To fix minimum compression force:** Adjust the compression force to achieve the thickness at higher limit **4.40** mm and run the machine. Record the minimum compression force. Collect about 100 tablets and perform tests as per Specification and Test Procedure given at right side. **To fix standard compression force:** Adjust the compression force to achieve the thickness at standard limit **4.10** mm and run the machine. Record the optimum compression force. Collect about 100 tablets and perform tests as per Specification and Test Procedure given at right side. **To fix maximum compression force:** Adjust the compression force to achieve the thickness at lower limit **3.80** mm and run the machine. Record the maximum compression force. Collect about 100 tablets and perform tests as per Specification and Test Procedure given at right side.	**i) Appearance**	White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	Specification and test procedure no: IMSP00134-00 IMTP00134-00
		ii) Average weight	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by 5%.	
		iv) Thickness (Average 10 tablets)	*4.10mm ± 0.3mm (3.80mm to 4.40mm)	
		v) Friability (10 tablets)	Not more than 1.0% w/w	
		vi) Hardness (Average of 10 tablets)	*80N-130N	
		vii)Disintegration time	Not more than 15 minutes	
		Viii) Assay Each uncoated tablets. Paracetamol BP 500mg	95.0% to 105.0% of the label claim.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	This challenge study is applicable for first Validation batch only. Fixed compression forces shall be verified in next two consecutive Validation batches. **Note:** * To be monitored	**ix) Dissolution** Paracetamol BP 500mg	Not less than 70.0% (Q) of the stated amount of Paracetamol dissolved in 45 mins.	Specification and test procedure no: IMSP00134-00 IMTP00134-00
13.2.3.2	**Compression Rate (RPM -Challenge)**			
	<u>For first batch only:</u> Start compressing the lubricated blend at constant optimum compression force parameters, hopper level – (not at nearly-empty) and at minimum to maximum compression speeds starting from **10rpm, 15 rpm, 20rpm, 25rpm, 30rpm, & 35rpm,** Collect about 100 tablets during each speed individually. **To fix the Minimum Speed:** Initially check the physical parameters of the tablets collected at 10 rpm. If all the physical parameters comply with the acceptance criteria, fix 10rpm as the minimum speed. If any physical parameter does not comply with the acceptance criteria, repeat the same procedure to the next sample collected at 15rpm. Repeat this procedure at different speeds as mentioned above (in an increasing order) and fix the minimum speed on which all the test results are satisfactory.	**i) Appearance**	White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	Specification and test procedure no: IMSP00134-00 IMTP00134-00
		ii) Average weight (20 tablets)	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by 5%.	
		iv) Thickness (Average 10 tablets)	*4.10mm ± 0.3mm (3.80mm to 4.40mm)	
		v) Friability (10 tablets)	Not more than 1.0% w/w	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	To fix the Maximum Speed: Similarly check on the last sample collected at 35rpm. If all the results are satisfactory fix the same as the maximum speed. If not, check on the previous sample collected at 30rpm. Repeat this procedure at different speeds as mentioned above (in a decreasing order) and fix the maximum speed on which all the test results are satisfactory. **This challenge study is applicable for first Validation batch. Fixed compression machine speeds shall be verified in next two consecutive Validation batches.** **Note:** * To be monitored	**vi) Hardness** (Average of 10 tablets)	*80N-130N	Specification and test procedure no: IMSP00134-00 IMTP00134-00
		vii)Disintegration time	Not more than 15 minutes	
		Viii) Assay Each uncoated tablets. Paracetamol BP 500mg	95.0% to 105.0% of the label claim.	
		ix) Dissolution Paracetamol BP 500mg	Not less than 70.0% (Q) of the stated amount of Paracetamol dissolved in 45 mins.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.2.3.3	**Hopper Level (Hopper level - Challenge)**			
	For first batch only: Collect about 100 tablets while running the machine at optimum setting parameters and at three different levels of blend in the hopper. **(Full, Half-full** and **Nearly - empty)** Initially check the physical parameters (other than assay and dissolution) for all the samples collected at three different hopper levels. If any physical parameter does not comply with the acceptance criteria for any sample, raise an unplanned deviation report as per ST/QA/005(R2):F3. If all the test results are well within the acceptance criteria for all the hopper levels, perform the assay and dissolution for the samples collected at **nearly-empty level**. If assay and dissolution tests also comply with the acceptance criteria, conclude that process complies at all the blend levels in the hopper. If assay and / or dissolution test for the samples collected at **nearly-empty** level does not comply to the acceptance criteria, raise an unplanned deviation report as per ST/QA/005(R2):F3 and perform the assay and dissolution tests on the samples collected at **half-full** hopper level.	**i) Appearance**	White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	Specification and test procedure no: IMSP00134-00 IMTP00134-00
		ii) Average weight (20 tablets)	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by 5%.	
		iv) Thickness (Average 10 tablets)	*4.10mm ± 0.3mm (3.80mm to 4.40mm)	
		v) Friability (10 tablets)	Not more than 1.0% w/w	
		vi) Hardness (Average of 10 tablets)	*80N-130N	
		vii)Disintegration time	Not more than 15 minutes	
		Viii) Assay Each uncoated tablets. Paracetamol BP 500mg	95.0% to 105.0% of the label claim.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	If the results are not satisfactory, repeat the same with samples collected at **full** hopper level also. If assay and dissolution tests for the samples collected at **half –full** hopper level comply with the acceptance criteria, the assay and dissolution tests are not necessarily to be carried out for the Samples at **full hopper level.** **This challenge study is applicable for first validation batch.** **Near empty level shall be verified in next two consecutive validation batches** **Note:** * To be monitored	**ix) Dissolution** Paracetamol BP 500mg	Not less than 70.0% (Q) of the stated amount of Paracetamol dissolved in 45 mins.	Specification and test procedure no: IMSP00134-00 IMTP00134-00
13.2.3.4	**COMPOSITE SAMPLE FOR COMPRESSION**			
	Samples to be collected at the end of the process for 100 tablets.	**i) Appearance**	White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	Specification and test procedure no: IMSP00134-00 IMTP00134-00
		ii) Average weight (20 tablets)	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by 5%.	
		iv) Thickness (Average 10 tablets)	*4.10mm ± 0.3mm (3.80mm to 4.40mm)	
		v) Friability (10 tablets)	Not more than 1.0% w/w	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	Samples to be collected at the end of the process for 100 tablets. **Note:** * To be monitored	**vi) Hardness** (Average of 10 tablets)	*80N-130N	Specification and test procedure no: IMSP00134-00 IMTP00134-00
		vii)Disintegration time	Not more than 15 minutes	
		Viii) Assay Each uncoated tablets. Paracetamol BP 500mg	95.0% to 105.0% of the label claim.	
		ix) Dissolution Paracetamol BP 500mg	Not less than 70.0% (Q) of the stated amount of Paracetamol dissolved in 45 mins.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.2.3.5	**Packing**			
13.2.3.5.1	Sealing Temperature	a)195°C to 210°C.	i) No Foil Damage. ii) No broken Tablets. iii) No melting of tablets observed. iv) Over printed details are legible.	SOP.NO ST/QA/056
		b) Leak test.	No Strip should fail in leak test.	
13.2.3.5.2	Forming Temperature	a) 140°C to 175°C.	i) No Foil Damage. ii) No pin holes observed in foil. iii) No white patches / colour change in PVDC. iv) Over printed details are legible.	
		b) Leak test.	No Strip should fail in leak test.	
13.2.3.5.3	Blister Packing Machine Speed	a) Different speed 25, 30, & 35 Stroke and verify the strip quality.	No Foil Damage, No broken Tablets, No Tablets Sticking to Foil, No ink lifting shall be observed, Strip should have proper cutting and knurling, Free flowing of tablets from hopper to guide track, Over printed details are legible.	
		b) Leak test.	No Strip should fail in leak test.	
13.2.3.5.4	Verification of optimum sealing temperature and optimum speed range.	a) Strip quality.	Cutting should be uniform on all sided without any angular cuts over printing should be visible and Readable and knurling should be proper.	
		b) Leak test.	No Strip should fail in leak test.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.2.3.5.5	Verification of optimum forming temperature and optimum speed range.	a) Strip quality.	Cutting should be uniform on all sided without any angular cuts over printing should be visible and Readable and knurling should be proper.	SOP.NO ST/QA/056
		b) Leak test.	No Strip should fail in leak test.	
13.2.3.5.6	Efficiency Of Tablet Feeder	a) Chipping, breaking, & overlapping of tablets	Tablets feeding should be smooth without Chipping, breaking, & overlapping of tablets.	
		b) Flow of tablets from hopper through chute to forming roller. c) Effective of feeder level sensor	Proper flow of the tablet should be observed and all formed pockets should be filled. When the tablets reaches below the minimum feeder level the vibrator should switched on automatically and the tablets should be filled in the feeder.	
13.2.3.5.7	**Impact assessment** After completion of first run packaging blister to be de-blistered by de-blistered machine. The tablets are collected and inspected. Similarly the de-blistering process is shall be performed for 2nd run and 3 rd run.	i) De blistered tablets.	Assay test to be performed when meet with the specification. Perform 3rd Re-Striping analysis first. If the 3rd Re-Striping analysis is meet the acceptance criteria, no need to perform the 1st and 2nd Re-Striping analysis.	
		ii) Leak test.	No Strip should fail in leak test	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.2.3.5.8	At the end of operation switch off the main, wait for 3 minutes and again switch on the main and start the packing.	i) power failure	Observe for physical parameter of the tablets.	SOP.NO ST/QA/056
		ii) Leak test.	No Strip should fail in leak test.	
13.2.3.5.9	Blister Inspection system	a) Black spots detector	Blister with black spots tablet should be detected and rejected.	
		b) Shaped tablet detector	Blister with different shape tablet should be detected and rejected.	
		c) Foreign tablet detector	Blister with foreign tablet should be detected and rejected.	
		d) Half tablet detector	Blister with half tablet should be detected and rejected.	
		e) Non filled detector	Blister with non filled pack should be detected and rejected.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.2.3.6	**FINISHED PRODUCT:**			
13.2.3.6.1	**Initial stage of operation** collect for 3 strips	**i) Appearance**	White coloured White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	Specification and test procedure no: FGSTSP027-00 FGTTSP027-00
		ii) Average weight (20 tablets)	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by more than 5%.	
13.2.3.6.2	**MIDDLE stage of operation** collect for 3 strips	**i) Appearance**	White coloured White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	
		ii) Average weight (20 tablets)	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by more than 5%.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.2.3.6.3	**FINAL stage of operation** collect for 3 strips.	**i) Appearance**	White coloured White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	Specification and test procedure no: FGSTSP027-00 FGTTSP027-00
		ii) Average weight (20 tablets)	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by more than 5%.	
13.2.3.6.4	Composite sample to be collected to represent entire batch (6 strips).	**i) Appearance**	White coloured White coloured, Circular shaped flat beveled edge uncoated tablet with score on one side and plain on other side.	
		ii) Average weight (20 tablets)	580.000mg±3% (562.600mg to 597.400mg)	
		iii) Weight Variation (20 tablets)	Not more than 2 of the individual masses deviate from the average mass by more than 5%.	

S.No.	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	Composite sample to be collected to represent entire batch (6 strips).	**iv)Microbiological parameter**		Specification and test procedure no: FGSTSP027-00 FGTTSP027-00
		i) Total viable aerobic count.		
		a) Total aerobic microbial count	NMT 1000 cfu/g.	
		b) Total yeast and mould count	NMT 100 cfu/g).	
		ii) Pseudomonas aeruginosa	Should be absent /g).	
		iii) Salmonella species	Should be absent/10g.	
		iv) Esherichia coli	Should be absent/g).	
		v) staphylococcus aureus	Should be absent/g).	

14.0 PROCESS PARAMETERS:

Manufacturing Process Stages	Critical Process Parameters	Set-Point
Dry Mixing	Mixing Time	10 min
Drying	LOD	2.5%-4.0%
Blending	Mixing Time	10 min
Lubrication	Lubrication Time	3 min
Compression	Compression Machine Speed	10 – 35 rotation/min ***
	Hardness	80N-130N ***
Packing	Sealing temperature	195°C to 210°C ***
	Speed of blister packing machine	25-35 strokes/min ***

NOTE: ***Test shall be monitored to first 3 batches.

15.0 YIELD (%):

Yield details shall be captured in process validation report as per the batch record.

16.0 DEVIATIONS:

Any deviation from the protocol related to manufacturing process, raw materials, equipments used, sampling, in-process controls and analytical methods should be authorized and documented in the batch manufacturing record as well as the validation report.

17.0 EVALUATION OF RESULTS AND CONCLUSION:

A Process validation report shall be prepared to summarise the results of the batch validation studies and process parameters shall be established and reflected in the validation summary sheet which shall be attached to the protocol after the completion of validation batches. On the basis of evaluation of results, a conclusion shall be drawn to state the adequacy of the process to carry out the manufacturing of Paracetamol Tablets BP 500mg.

18.0 SAMPLING LOCATION DIAGRAM:

18.1Sampling Plan Diagram of RMG:

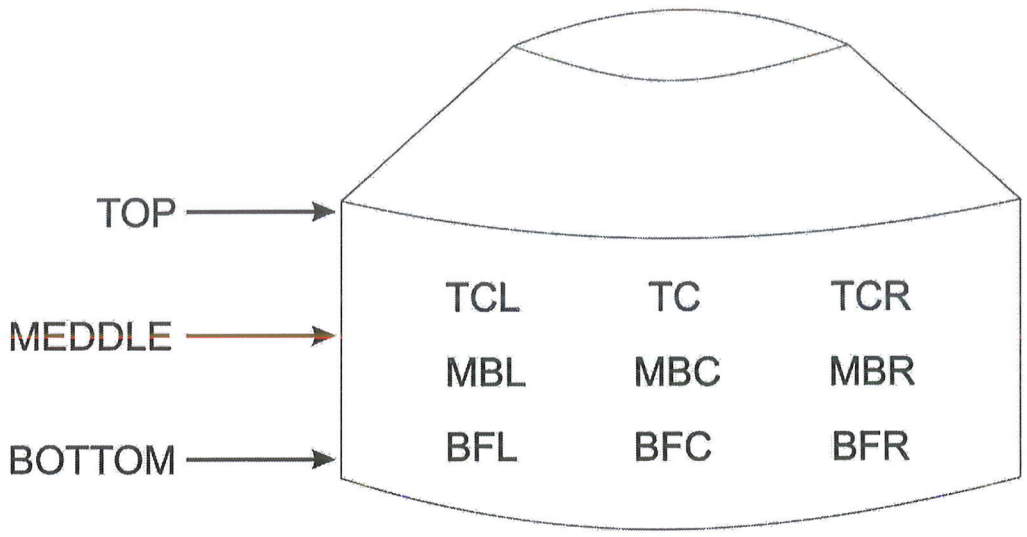


Fig. No.1

TCL – Top center left
TC - Top center
TCR – Top center right
MBL – Middle back left
MBC – Middle back center
MBR – Middle back right
BFL – Bottom front left
BFC – Bottom front center
BFR – Bottom front right

18.2 Sampling Plan Diagram of Octagonal Blender:

SIDE VIEW

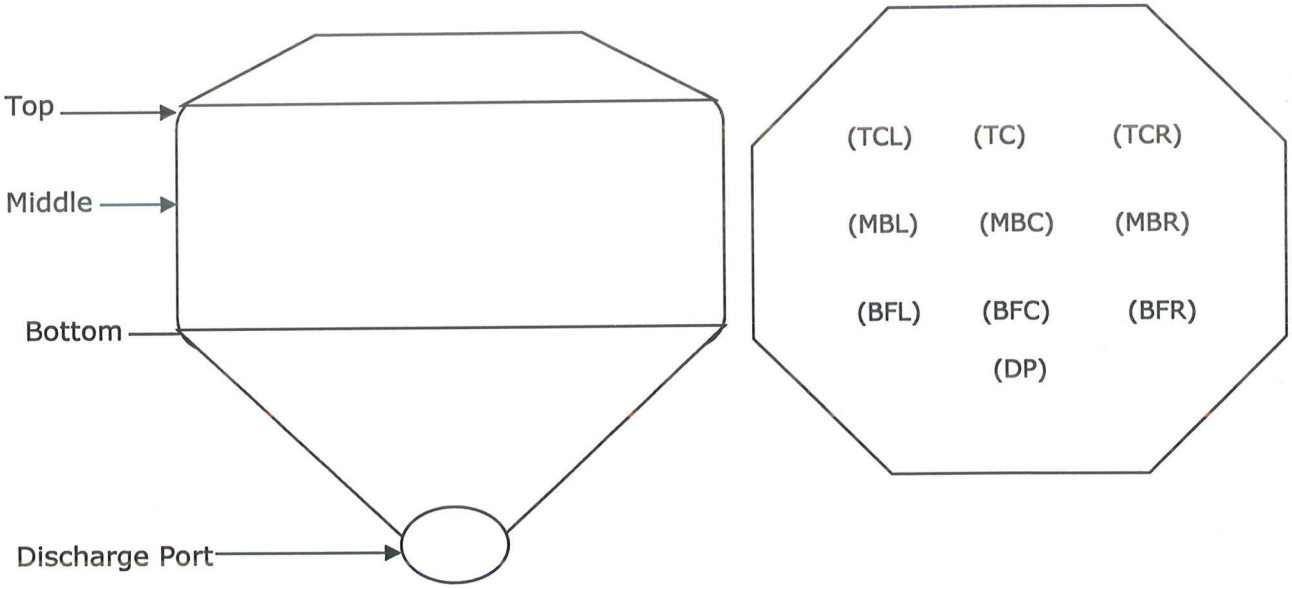


Fig-2

Samples are to be drawn from 10 different positions as follows:

TCL –	Top center left
TC -	Top center
TCR –	Top center right
MBL –	Middle back left
MBC –	Middle back center
MBR –	Middle back right
BFL –	Bottom front left
BFC –	Bottom front center
BFR –	Bottom front right
DP -	Discharge port