# PROCESS VALIDATION PROTOCOL

# PARACETAMOL, PHENYLEPHRINE HYDROCHLORIDE, CHLORPHENAMINE MALEATE AND CAFFEINE ANHYDROUS TABLETS

**TABLE OF CONTENTS**

## 1.0 APPROVAL

| Prepared By | Name | Designation | Signature | Date |
|---|---|---|---|---|
| QUALITY ASSURANCE | P.Vadivel | Sr. Executive QA | P.Vadivel | 28/07/2021 |

| Reviewed By | Name | Designation | Signature | Date |
|---|---|---|---|---|
| PRODUCTION | V. Dharabal | Sr. Gm | | 28/07/21 |
| QUALITY CONTROL | M/s Vijaya Kumar | AGM. | | 29/07/21 |

| Approved By | Name | Designation | Signature | Date |
|---|---|---|---|---|
| QUALITY ASSURANCE | K. Chandrasekar | AGM-QA | | 29/07/21 |

## 2.0 SCOPE:

This protocol is applicable for the manufacturing and sampling of Validation batches of Paracetamol 500mg, Phenylephrine Hydrochloride 5mg, Chlorphenamine Maleate 2mg and Caffeine anhydrous 30mg Tablets with a batch size of 10.0 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 500mg, Phenylephrine Hydrochloride 5mg, Chlorphenamine Maleate 2mg and Caffeine anhydrous 30mg Tablets, 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 500mg, Phenylephrine Hydrochloride 5mg, Chlorphenamine Maleate 2mg and Caffeine anhydrous 30mg Tablets is a solid dosage which contains Paracetamol, Phenylephrine Hydrochloride, Chlorphenamine Maleate and Caffeine anhydrous as active ingredient. This is being manufactured at Safetab Life Science, Puducherry, with the batch size of 10.0 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
- Wet Granulation
- Drying
- Sizing
- Blending
- 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.<br>2) To review and approve the investigations and CAPA for deviations From defined manufacturing process and protocol.<br>3) To take decision on further release and distribution of validation batches. |

## 7.0 PRODUCT DETAILS:

| | |
|---|---|
| Product Name | Paracetamol 500mg, Phenylephrine Hydrochloride 5mg, Chlorphenamine Maleate 2mg and Caffeine anhydrous 30mg Tablets. |
| Label Claim | Each Uncoated tablet contains:<br>Chlorphenamine Maleate BP 2mg<br>Phenylephrine Hydrochloride BP 5mg<br>Caffeine Anhydrous BP 30mg<br>Paracetamol BP 500mg<br>Colour: Approved colour used |
| Overages (% w/w) | NA |
| Shelf life | 36 Months |
| Storage Condition | Store in cool and dry place Protect from light and moisture. |
| Batch Size | 1000000 Tablets |
| Therapeutic Use | Used to temporarily relieve symptoms caused by the common cold, Flu, Allergies or other breathing illness. Antihistamines help to relieve watery eyes, runny nose, Sneezing. |
| Product Pack | Printed Foil: 302mm X 0.03mm Alu strip foil<br>Base Foil : 302mm X 0.03mm Alu strip foil |
| Pack Style | Sales : 1x4's Strip 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 | FUNCTION | Mg/Tablet | Quantity Kg/Batch 10.0 L | Manufacture |
|---|---|---|---|---|---|---|
| **Dry Mixing and Granulation:** | | | | | | |
| RMAC0064 | Chlorphenamine Maleate *** | BP | Antihistamine | 2.000 | 2.000 | Supriya Life Science |
| RMAP0031 | Phenylephrine Hydrochloride *** | BP | Sinusitis | 5.000 | 5.000 | Aarti Industries |
| RMAC0065 | Caffeine Anhydrous *** | BP | Central nervous system stimulant | 30.000 | 30.000 | Aarti Industries |
| RMAP0030 | Paracetamol *** | BP | Pain reliever | 500.000 | 500.000 | Bharat Chemicals |
| RMEP0046 | Pregelatinized Starch | BP | Diluent | 15.000 | 15.000 | Colorcon |
| RMEM0031 | Microcrystalline Cellulose PH 101 *** | BP | Diluent | 24.735 | 24.735 | Sigachi |
| **BINDER PREPARATION** | | | | | | |
| RMEP0045 | Povidone K90 | BP | Binder | 12.500 | 12.500 | Haungshan Bonsun Pharmaceuticals |
| RMEP0033 | Purified Water@ | BP | Vehicle | 100.000 | 100.000 | Inhouse |
| RMET0011 | Tartrazine Supra | INH | Colourant | 0.135 | 0.135 | Standardcon |
| RMEM0032 | Sodium Methyl Hydroxybenzoate | BP | Préservative | 0.500 | 0.500 | Alta Laboratories |
| **BLENDING AND LUBRICATION** | | | | | | |
| RMEP0046 | Pregelatinized Starch | BP | Diluent | 10.000 | 10.000 | Colorcon |

| | | | | | | |
|---|---|---|---|---|---|---|
| RMES0029 | Sodium Starch Glycolate | BP | Disintegrant | 17.000 | 17.000 | Roquette Riddhi Siddhi |
| RMET0012 | Purified Talc | BP | Glidant | 7.000 | 7.000 | Imerys |
| RMEC0017 | Colloidal silicon Dioxide | BP | Adsorbent | 5.000 | 5.000 | Wacker |
| RMET0013 | Tartrazine Lake | INH | Colourant | 0.130 | 0.130 | Standardcon |
| RMEM0033 | Magnesium Stearate | BP | Lubricant | 6.000 | 6.000 | Nitika |
| | | | Total weight | 635.000 | 635.000 | ---------- |

***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:

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

### 9.2 Potency calculation for Phenylephrine Hydrochloride:

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

Actual quantity to be added is calculated as:

$$\text{Actual quantity of Phenylephrine Hydrochloride} = \frac{5\ X\ 100\ X\ 100}{\%\ \text{Assay on dried basis X (100 – LOD \%)}}\ \text{mg/tablet}$$

### 9.3 Potency calculation for Chlorphenamine Maleate:

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

Actual quantity to be added is calculated as:

$$\text{Actual quantity. Of Chlorphenamine Maleate} = \frac{2\ X\ 100\ X\ 100}{\%\ \text{Assay on dried basis X (100 – LOD \%)}}\ \text{mg/tablet}$$

### 9.4 Potency calculation for Caffeine Anhydrous:

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

Actual quantity to be added is calculated as:

$$\text{Actual quantity of Caffeine Anhydrous} = \frac{30 \times 100 \times 100}{\text{\% Assay on dried basis} \times (100 - \text{LOD \%})} \text{ mg/tablet}$$

Quantity Microcrystalline cellulose PH 101 varies based on assay content of Paracetamol, Phenylephrine Hydrochloride Chlorpheniramine Maleate, Caffeine Anhydrous for keeping the core tablet weight constant.

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

## 10.0 PACKING MATERIAL COMPONENTS:

| Material code | Components | Vendor |
|---|---|---|
| PML00081 | Printed Foil: 302mm X 0.03mm Alu strip foil | Daga Poly Laminators PVT Ltd. |
| PMST0044 | Base Foil : 302mm X 0.03mm Alu strip foil | Daga Poly Laminators PVT Ltd. |

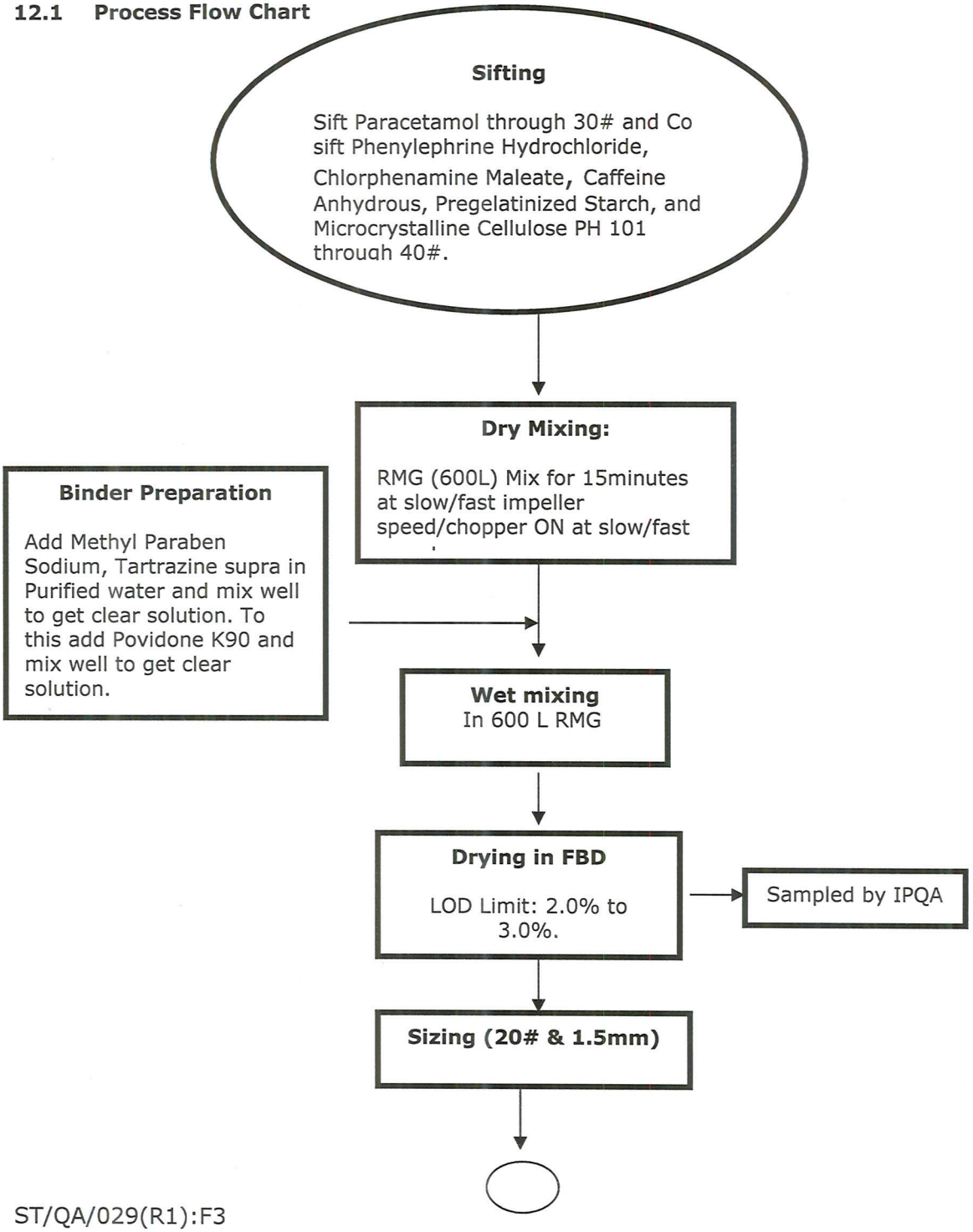
## 11.0 EQUIPMENT DETAILS:

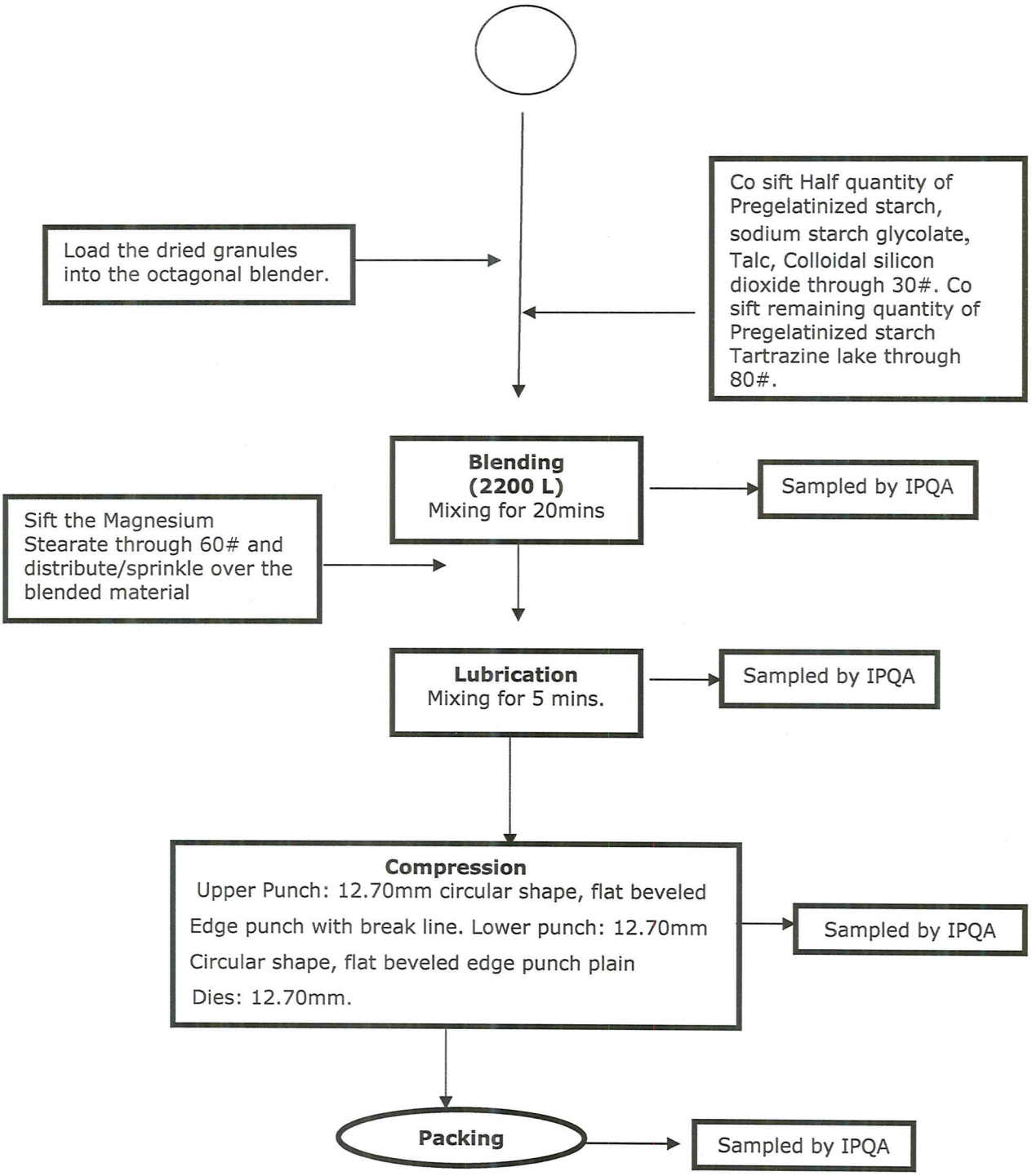
Table 1: List of major process equipment to be used in the manufacturing:

| Sr. No. | Equipment | Make | Equipment No. |
|---|---|---|---|
| 1.0 | Weighing Balances | ESSAE TERAOKA | ST/WB/189<br>ST/SRWB/001<br>ST/SRWB/002<br>ST/PRWB/009,<br>ST/PRWB/010,<br>ST/PRWB/011,<br>ST/PRWB/012,<br>ST/PRWB/013 |
| 2.0 | Vibratory Sifter | SARAL | ST/PRVS/001 or<br>ST/PRVS/002 or<br>ST/PRVS/003 or<br>ST/PRVS/004 |
| 3.0 | Fluid bed drier(250kg) | SARAL | ST/PRFD/003 |
| 4.0 | Rapid Mixer Granulator 600LTS | SARAL | ST/PRRG/005 |
| 5.0 | Dry Co Mill | SARAL | ST/PRDM/001 or<br>ST/PRDM/001 |
| 6.0 | Octagonal Blender (2200L) | SRI KARPAGA VINAYAGAR | ST/PROB/001 |
| 7.0 | Compression Machine | CADMACH | ST/PRCM/004 or<br>ST/PRCM/005 |
| 8.0 | Strip Packing Machine | VILAS ENGINEERING | ST/PRSR/001 |

## 12.0 PROCESS DESCRIPTION:

### 12.1 Process Flow Chart




Load the dried granules into the octagonal blender.
Co sift Half quantity of Pregelatinized starch, sodium starch glycolate, Talc, Colloidal silicon dioxide through 30#. Co sift remaining quantity of Pregelatinized starch Tartrazine lake through 80#.
Blending (2200 L) Mixing for 20mins
Sampled by IPQA
Sift the Magnesium Stearate through 60# and distribute/sprinkle over the blended material
Lubrication Mixing for 5 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 Dies: 12.70mm.
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, Phenylephrine Hydrochloride Chlorphenamine Maleate and Caffeine anhydrous Tablets comprises of following stages:

| Stage | Manufacturing Procedure |
|---|---|
| 1 Dispensing | Dispense the raw material as per the standard operating procedure. |
| 2. Sifting | Sift Paracetamol through 30# and Co sift Phenylephrine Hydrochloride, Chlorphenamine Maleate, Caffeine Anhydrous, Pregelatinized Starch, and Microcrystalline Cellulose PH 101 through 40#. |
| 3.Dry Mixing | Mix for 15minutes at slow/fast impeller speed/chopper ON at slow/fast speed. |
| 4.Binder Preparation | Add Methyl Paraben Sodium, Tartrazine supra in Purified water and mix well to get clear solution. To this add Povidone K90 and mix well to get clear solution. |
| 5. Granulation | **Granulation:(Wet mixing)**<br>Binder addition: 3-5 minutes mixing at slow/fast speed impeller/chopper 'ON' at slow/fast speed.<br>Kneading:<br>Mixing: 2-5 minutes mixing at slow/fast speed impeller/chopper 'ON' at slow/fast speed.<br>If required add additional Purified water and mix for 2-3mins to form a required granules. |
| 6. Drying and Sizing | Load the Wet granules into FBD and drying the granules at inlet temperature of 50°C -60°C with intermittent racking at every 10-15 mins. LOD%: limit 2.0%-3.0%. Sift the dried granules through 20#. Mill the retained granules through 1.5mm screen and pass through 20#. |
| 7. Blending | Load the dried granules into the octagonal blender. Co sift Half quantity of Pregelatinized starch, sodium starch glycolate, Talc, Colloidal silicon dioxide through 30#. Co sift remaining quantity of Pregelatinized starch Tartrazine lake through 80#. Mixing for 20mins. |
| 8.0 Lubrication | Sift the Magnesium Stearate through 60# and distribute/sprinkle over the blended material. Mix for 5minutes.<br>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 27/20 - 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 Dies: 12.70mm. |

| | |
|---|---|
| Description | Light yellow coloured flat round beveled edged tablet with break line on one side and plain on another side. |
| Average Weight per tablet | 635mg±3% (615.950mg to 654.050mg) |
| Weight of 20 tablets | 12.700±3% (12.319g to 13.081g) |
| Uniformity of weight | ±5% of average weight (603.25mg to 666.75mg) |
| Thickness | 4.30mm ± 0.2mm (4.10mm to 4.50mm) |
| Hardness | 100N-250N |
| 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 through 30# and Co sift Phenylephrine Hydrochloride, Chlorphenamine Maleate, Caffeine Anhydrous, Pregelatinized Starch, and Microcrystalline Cellulose PH 101 through 40#. Mix for 15minutes at slow/fast impeller speed/chopper ON at slow/fast speed.<br><br>**# Dry mixing is carried out in 4 similar lots. So the first lot shall be validated with extensive sampling positions and analysis as per this protocol, Since all the four lots dry mixing are processed in similar manner and time. Only 1st lot shall be validated.**<br>**Similarly the dry mixing validation shall be carried out for next two batches.** | **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 18.1) separately using sampling thief after 15 **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** | **SAMPLING PROCEDURE** |
|---|---|---|
| Loss on drying of dried granules to be evaluated using Moisture balance. | **DRYING** | Samples of the dried granules shall be withdrawn from FBD bowl from 5 random locations (as per 18.2). |

**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: Dried granules shall be loaded into Octagonal blender and Co sift Half quantity of Pregelatinized starch, sodium starch glycolate, Talc, Colloidal silicon dioxide through 30#. Co sift remaining quantity of Pregelatinized starch Tartrazine lake through 80#. Mixing for 20mins. | **1. Mixing time (Pre-lubricated blend uniformity)** | **Step- 1: PRE - LUBRICATION:** Samples shall be withdrawn from 10 different locations Collect approximately 2 g of blend sample. Location each in duplicate from top, middle and bottom level of the Octagonal blender (as per 18.3) and Use these samples for blend uniformity test as per 13.2.2.1 |
| Step - 2: Sift the Magnesium Stearate through 60# and distribute/sprinkle over the blended material. Mix for 5minutes. | **2. Mixing time (Lubricated blend uniformity)** | **Step- 2: AFTER LUBRICATION:** Samples shall be withdrawn from 10 different locations Collect approximately 2 g of lubrication blend sample. Location each in duplicate from top, middle and bottom level of the Octagonal blender (as per 18.2) and Use these samples for blend uniformity test as per 13.2.2.2<br><br>**For first batch only:** After 5 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:** | Individual sample values between 85% to 115% & RSD: NMT 5 % Average value between 90% to 110%. | Specification and test procedure no: FGSTSL022-02 FGTTSL022-00 |
| **13.2.2** | **BLENDING & LUBRICATION PROCESS:** | | |
| **13.2.2.1** | **BLENDING – PRE LUBRICATION:** | | |
| **1** | **Blend uniformity:** | Individual sample values between 85% to 115% & RSD: NMT 5 % Average value between 90% to 110%. | Specification and test procedure no: FGSTSL022-02 FGTTSL022-00 |
| **13.2.2.2** | **LUBRICATION:** | | |
| **1** | **Appearance** (pooled sample) | White granular powder | Specification and test procedure no: FGSTSL022-02 FGTTSL022-00 |
| **2** | **Blend uniformity:** | Individual sample values between 85% to 115% & RSD: NMT 5 % Average value between 90% to 110%. | |
| **3** | **Bulk density** (Weight of 100 ml -pooled sample) | For information only | NA |
| **4** | **Tap density** (pooled sample) | For information only | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| **13.2.3** | **COMPRESSION PROCESS:** | | | |
| **13.2.3.1** | **COMPRESSION FORCE**<br>To find out the hardness range, the following procedure to be adopted.<br>**To fix minimum compression force:**<br>Adjust the compression force to achieve the thickness at higher limit **4.50mm** and run the machine. Record the minimum compression force. Collect about 200 tablets and perform tests as per Specification and Test Procedure given at right side.<br>**To fix standard compression force:**<br>Adjust the compression force to achieve the thickness at standard limit **4.30mm** and run the machine. Record the optimum compression force. Collect about 200 tablets and perform tests as per Specification and Test Procedure given at right side.<br>**To fix maximum compression force:**<br>Adjust the compression force to achieve the thickness at lower limit **4.10mm** and run the machine. Record the maximum compression Force. Collect about 200 tablets and perform tests as per Specification and Test Procedure given at right side.<br>**This challenge study is applicable for first validation batch only.**<br>**Fixed compression forces shall be verified in next two consecutive validation batches.** | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | Specification and test procedure no: IMSL00117-02 IMTL00117-00 |
| | | **Average weight** (20 tablets) | 635.000mg±3% (615.95mg to 654.05mg) | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than ±5%. | |
| | | **Thickness** (Average 10 tablets) | 4.30mm ± 0.2mm (4.10mm to 4.50mm) | |
| | | **Friability** | Not more than 1.0% w/w | |
| | | **Hardness** (Average of 10 tablets) | 100N-250N | |
| | | **Disintegration time** | Not more than 15 minutes | |
| | | **Dissolution** | Not less than 80% of stated amount released in 45 minutes | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| **13.2.3.2** | **Compression Rate (RPM -Challenge)** | | | |
| | **For first batch only:**<br><br>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 200 tablets during each speed individually.<br><br>**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 12rpm. 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. | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | Specification and test procedure no: IMSL00117-02 IMTL00117-00 |
| | | **Average weight** (20 tablets) | 635.000mg±3% (615.95mg to 654.05mg) | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than ±5%. | |
| | | **Thickness** (Average 10 tablets) | 4.30mm ± 0.2mm (4.10mm to 4.50mm) | |
| | | **Friability** | Not more than 1.0% w/w | |
| | | **Hardness** (Average of 10 tablets) | 100N-250N | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| | **To fix the Maximum Speed:** Similarly check on the last sample collected at 35 rpm. If all the results are satisfactory fix the same as the maximum speed. If not, check on the previous sample collected at 18rpm. 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.** | **Disintegration time** | Not more than 15 minutes | Specification and test procedure no: IMSL00117-02 IMTL00117-00 |
| **13.2.3.3** | **Hopper Level (Hopper level - Challenge)** | | | |
| | **<u>For first batch only:</u>** Collect about 200 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)** | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | Specification and test procedure no: IMSL00117-02 IMTL00117-00 |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| | 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<br><br>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. If the results are not satisfactory, repeat the same with samples collected at **full** hopper level also. | **Average weight** (20 tablets) | 635.000mg±3% (615.95mg to 654.05mg) | Specification and test procedure no: IMSL00117-02 IMTL00117-00 |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5%. | |
| | | **Thickness** | 4.30mm ± 0.2mm (4.10mm to 4.50mm) | |
| | | **Friability** | Not more than 1.0% w/w | |
| | | **Hardness** (Average of 10 tablets) | 100 N to 250 N | |
| | | **Disintegration time** | Not more than 15 minutes | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| | 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** | **Assay** Each uncoated tablet contains. 1.Chlorphenamine Maleate BP 2mg 2.Phenylehrine Hydrochloride BP 5mg 3.Paracetamol BP 500mg 4.Caffeine (anhydrous) BP 30mg | 90.0% to 110.0% of the labelled claim. | Specification and test procedure no: IMSL00117-02 IMTL00117-00 |
| | | **Dissolution** | Not less than 80% of stated amount released in 45 minutes | |
| **13.2.3.4** | Composite Sample (100 NO'S) to be collected to represent entire batch. | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | |
| | | **Average weight** (20 tablets) | 635.000mg±3% (615.95mg to 654.05mg) | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5%. | |
| | | **Thickness** (Average 10 tablets) | 4.30mm ± 0.2mm (4.10mm to 4.50mm) | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| | Composite Sample (100 NO'S) to be collected to represent entire batch. | **Friability** | Not more than 1.0% w/w | Specification and test procedure no: IMSL00117-02 IMTL00117-00 |
| | | **Hardness** (Average of 10 tablets) | 100 N to 250 N | |
| | | **Disintegration time** | Not more than 15 minutes | |
| | | **Assay** Each uncoated tablet contains. 1.Chlorphenamine Maleate BP 2mg 2.Phenylehrine Hydrochloride BP 5mg 3.Paracetamol BP 500mg 4.Caffeine (anhydrous) BP 30mg | NLT 90.0% and NMT 110.0%. | |
| | | **Dissolution** | Not less than 80% of stated amount released in 45 minutes | |
| | | **Related substance**<br>i) Single maximum unknown purity.<br>ii) Total impurities | <br>Not more than 0.20%.<br>Not more than 0.50% | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| **13.2.4** | **PACKING** | | | |
| **13.2.4.1** | Sealing Temperature | a) 100°C to 120°C<br><br>b) Leak test. | i) No Foil Damage.<br>ii) No broken Tablets.<br>iii) No melting of tablets observed.<br>iv) Over printed Details are legible.<br>No Strip should fail in leak test. | SOP.NO ST/QA/056 |
| **13.2.4.2** | Strip Packing Machine Speed | a) Different speed 20,25, 30, & 40 Stroke and verify the strip quality.<br><br>b) Leak test. | 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.<br>No Strip should fail in leak test. | |
| **13.2.4.3** | Verification of optimum sealing temperature and optimum speed range. | a) Strip quality.<br><br>b) Leak test. | Cutting should be uniform on all sided without any angular cuts over printing should be visible and Readable and knurling should be proper.<br><br>No Strip should fail in leak test. | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| **13.2.4.4** | Efficiency of Tablet Feeder | a) Chipping, breaking, & overlapping of tablets<br><br>b) Flow of tablets from hopper through chute to forming roller.<br>c) Effective of feeder level sensor | Tablets feeding should be smooth without Chipping, breaking, & overlapping of tablets.<br>Proper flow of the tablet should be observed and all formed pockets should be filled.<br><br>When the tablets reaches below the minimum feeder level the vibrator should switched on automatically and the tablets should be filled in the feeder. | SOP.NO ST/QA/056 |
| **13.2.4.5** | **Impact assessment**<br>After completion of first run packaging strip to be de-striped. The tablets are collected and inspected. Similarly the de-striping process is shall be performed for 2nd run and 3 rd run. (Each run collect for 12 strips) | i) De striped tablets.<br><br>Leak test. | Assay and Dissolution test to be performed when Related Substances meet with the specification.<br>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.<br>No Strip should fail in leak test | |
| **13.2.4.6** | At the end of operation switch off the main, wait for 3 minutes and again switch on the main and start the packing. | ii) power failure<br><br>Leak test. | Observe for physical parameter of the tablets.<br><br>No Strip should fail in leak test. | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| **13.2.5** | **FINISHED PRODUCT:** | | | |
| **13.2.5.1** | **Initial stage of operation** collect for 8 strips | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | Specification and test procedure no: FGSTSL022-02 FGTTSL022-00 |
| | | **Average weight** (20 tablets) | 635.00mg±3% (615.95mg to 654.05mg) | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5%. | |
| **13.2.5.2** | **MIDDLE stage of operation** collect for 8 strips | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | |
| | | **Average weight** (20 tablets) | 635.00mg±3% (615.95mg to 654.05mg) | |
| | | **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 PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| **13.2.5.3** | **FINAL stage of operation** collect for 8 strips. | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | Specification and test procedure no: FGSTSL022-02 FGTTSL022-00 |
| | | **Average weight** (20 tablets) | 635.00mg±3% (615.95mg to 654.05mg) | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5%. | |
| **13.2.5.4** | Composite sample to be collected to represent entire batch (6 strips). | **Appearance** | Light yellow coloured flat, round beveled edged uncoated tablet with break line on one side and plain on another side. | |
| | | **Average weight** (20 tablets) | 635.00mg±3% (615.95mg to 654.05mg) | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5%. | |
| | | **Microbiological parameter** | i) Total viable aerobic count.<br>a) Total aerobic microbial count.<br>b) Total yeast and mould count.<br>ii) Pseudomonas aeruginosa.<br>iii) Salmonella species.<br>iv) Escherichia coli.<br>v) staphylococcus aureus. | |

## 14.0 PROCESS PARAMETERS:

| Manufacturing Process Stages | Critical Process Parameters | Set-Point |
|---|---|---|
| **Dry Mixing** | Mixing Time | 15 min |
| **Drying** | LOD | 2.0 to 3.0% |
| **Sizing** | Sifter Screen | 20# |
| | Miller Screen | 1.5mm |
| **Blending** | Mixing Time | 20 min |
| **Lubrication** | Mesh size | 60# |
| | Lubrication Time | 5 min |
| **Compression** | Compression Machine Speed | 10 – 35 rotation/min *** |
| | Hardness | 100N-250N *** |
| **Packing** | Sealing temperature | 100°C to 120°C *** |

**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 500mg, phenylephrine hydrochloride 5mg, chlorphenamine maleate 2mg and caffeine anhydrous 30mg tablets.

**18.0 SAMPLING LOCATION DIAGRAM:**

**18.1 Sampling Plan Diagram of RMG:**

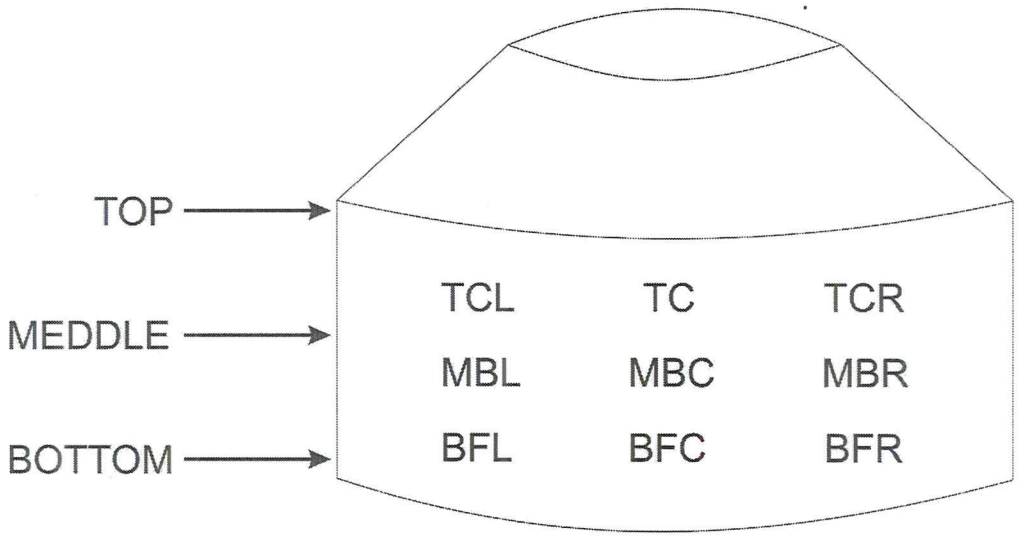



**Fig. No.1**

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 FBD:**

**SIDE VIEW**

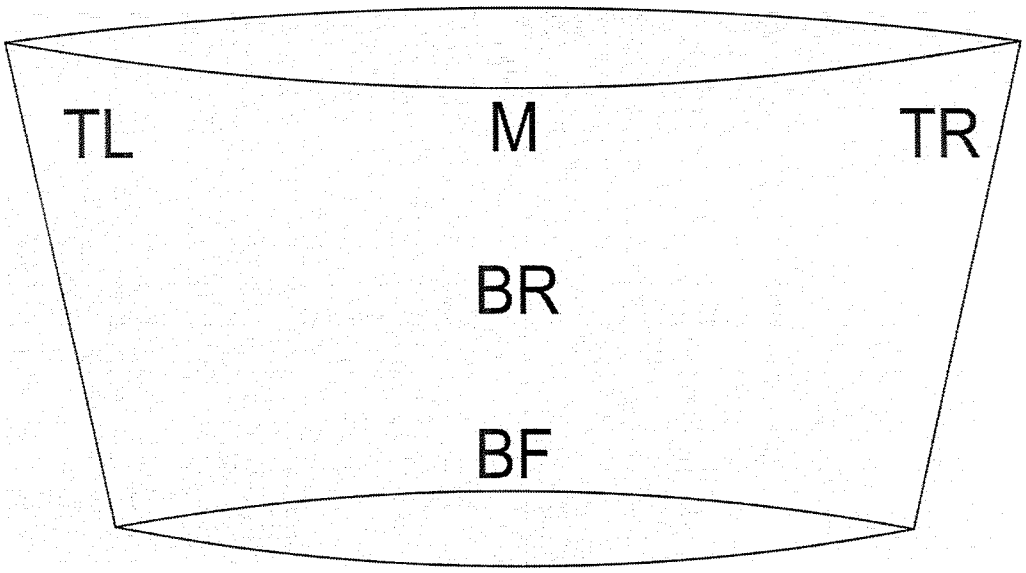



**Fig. No.2**

TL – Top Left
TR – Top Right
M – Middle
BF – Bottom Front
BR – Bottom Rear

**18.3 Sampling Plan Diagram of Octagonal Blender:**

**SIDE VIEW**

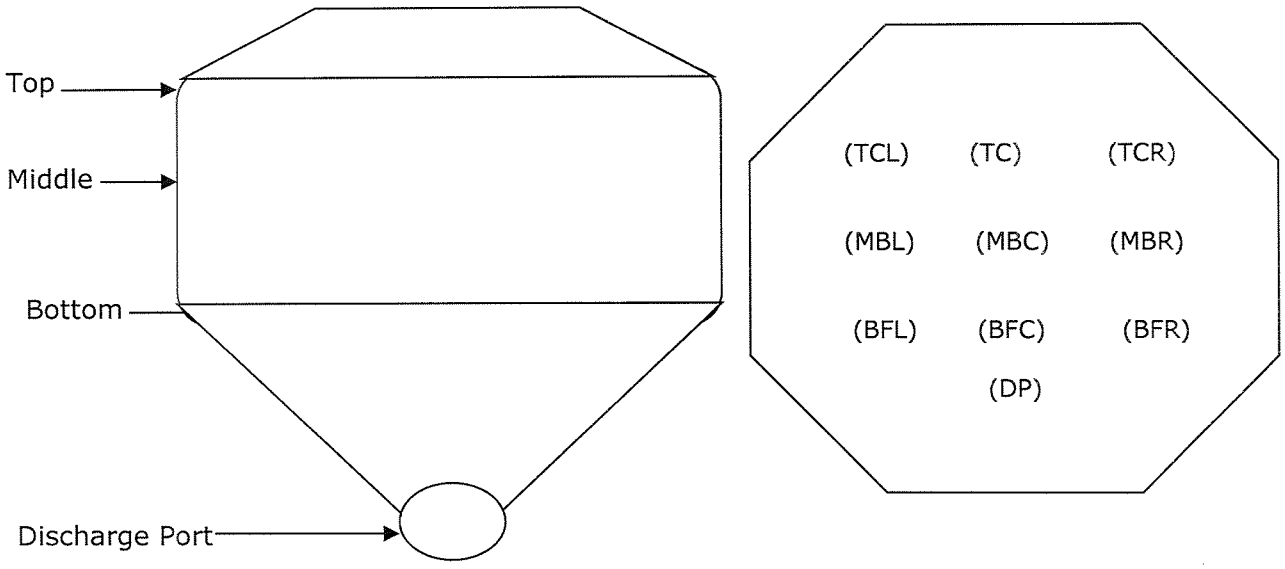



**Fig. No.3**

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