# PROCESS VALIDATION PROTOCOL

# IBUPROFEN BP 400mg AND PARACETAMOL BP 500mg TABLETS

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## 1.0 APPROVAL

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| Reviewed By | Name | Designation | Signature | Date |
|---|---|---|---|---|
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| QUALITY CONTROL | T. Vijayakumar | AGM. | | 01/06/21 |

| Approved By | Name | Designation | Signature | Date |
|---|---|---|---|---|
| QUALITY ASSURANCE | K. Chandrasekar | AGM- | | 01/06/21 |

## 2.0 SCOPE:

This protocol is applicable for the manufacturing and sampling of Validation batches of **IBUPROFEN BP 400mg and PARACETAMOL BP 500mg** tablets with a batch size of 8.0 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, this batch shall be charged for stability studies.

## 3.0 OBJECTIVE:

The objective of this protocol is to validate the process by establishing documented evidence for **IBUPROFEN BP 400mg and PARACETAMOL BP 500mg** tablets, to be manufactured at Safetab Life Science, Plot No: A-67-72, 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:

**IBUPROFEN BP 400mg and PARACETAMOL BP 500mg tablets** is a solid dosage which contains Ibuprofen BP and Paracetamol BP as active ingredient. This is being manufactured at Safetab Life Science, Puducherry, with the batch size of 8.0 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 | Ibuprofen and Paracetamol Tablets |
| Label Claim | Each Uncoated tablet contains:<br>Ibuprofen BP 400mg<br>Paracetamol BP 500mg<br>Colour: Approved Colour used |
| Overages (% w/w) | NA |
| Shelf life | 36 Months |
| Storage Condition | Store at a temperature below 30°C. Protect from light. |
| Batch Size | 800000 Tablets |
| Therapeutic Use | For the treatment of Patient with NSAIDs work by reducing pain, reducing swelling and lowering high temperatures. Paracetamol is an analgesic which works in a different way from ibuprofen to relieve pain and fever. Of non-serious arthritis, cold and flu symptoms, sore throat and fever. |
| Product Pack | Printed Foil: 172X0.04 mm sales printed foil.<br>Base Foil: 176mm PVC Clear film. |
| Pack Style | Sales: (1X10)x10 Tablets |

**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 8.0 L | Vendor |
|---|---|---|---|---|---|---|
| **Dry Mixing and Granulation:** | | | | | | |
| RMAP0030 | Paracetamol *** | BP | Pain killer | 500.000 | 400.000 | Bharat Chemicals |
| RMAI0015 | Ibuprofen *** | BP | NSAID | 400.000 | 320.000 | IOL Chemicals and Pharmaceuticals Pvt Ltd. |
| RMEM0034 | Maize Starch *** | BP | Diluent | 55.920 | 44.736 | Roquette, Riddhi Siddhi |
| RMEP0044 | Povidone K 90 | BP | Binder | 26.000 | 20.800 | Haungshan Bonsun Pharmaceuticals |
| RMEP0048 | Sodium Propyl Hydroxybenzoate | BP | Preservative | 0.440 | 0.352 | Rasula Pharmaceuticals and Fine Chemicals |
| RMES0030 | Sunset Yellow supra | INH | Colourant | 0.140 | 0.112 | Neelkanth |
| RMEP0033 | Purified Water @ | BP | vehicle | 175.000 | 140.000 | Inhouse |
| RMEP0032 | Pregelatinized Starch 1500 | BP | Diluent | 40.000 | 32.000 | Colorcon |
| RMES0029 | Sodium Starch Glycolate | BP | Disintegrant | 15.000 | 12.000 | Roquette Riddhi Siddhi |
| RMEM0033 | Magnesium Stearate | BP | Lubricant | 2.500 | 2.000 | Nitika |
| | | | Total | 1040 | 832.000 | --------- |

***Refer Calculation**

**@ Does not appear in final product, Evaporate during the processing.**

## 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:

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

### 9.2 Potency calculation for Ibuprofen:

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

Actual quantity to be added is calculated as:

$$\text{Actual quantity of Ibuprofen} = \frac{400 \times 100 \times 100}{\text{\% Assay of Ibuprofen on dried basis} \times (100 - \%\text{LOD})} \text{ mg/tablet}$$

** Quantity Maize starch varies based on assay content of Paracetamol and Ibuprofen for keeping the core tablet weight constant.

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

## 10.0 PACKING MATERIAL COMPONENTS:

| Material code | Components | Vendor |
|---|---|---|
| PMG00067 | 172x0.04mm printed Aluminum blister foil | Daga Poly Laminators PVT Ltd. |
| PMPV0036 | 176mm PVC clear back foil | ICM plastic PVT Ltd. |

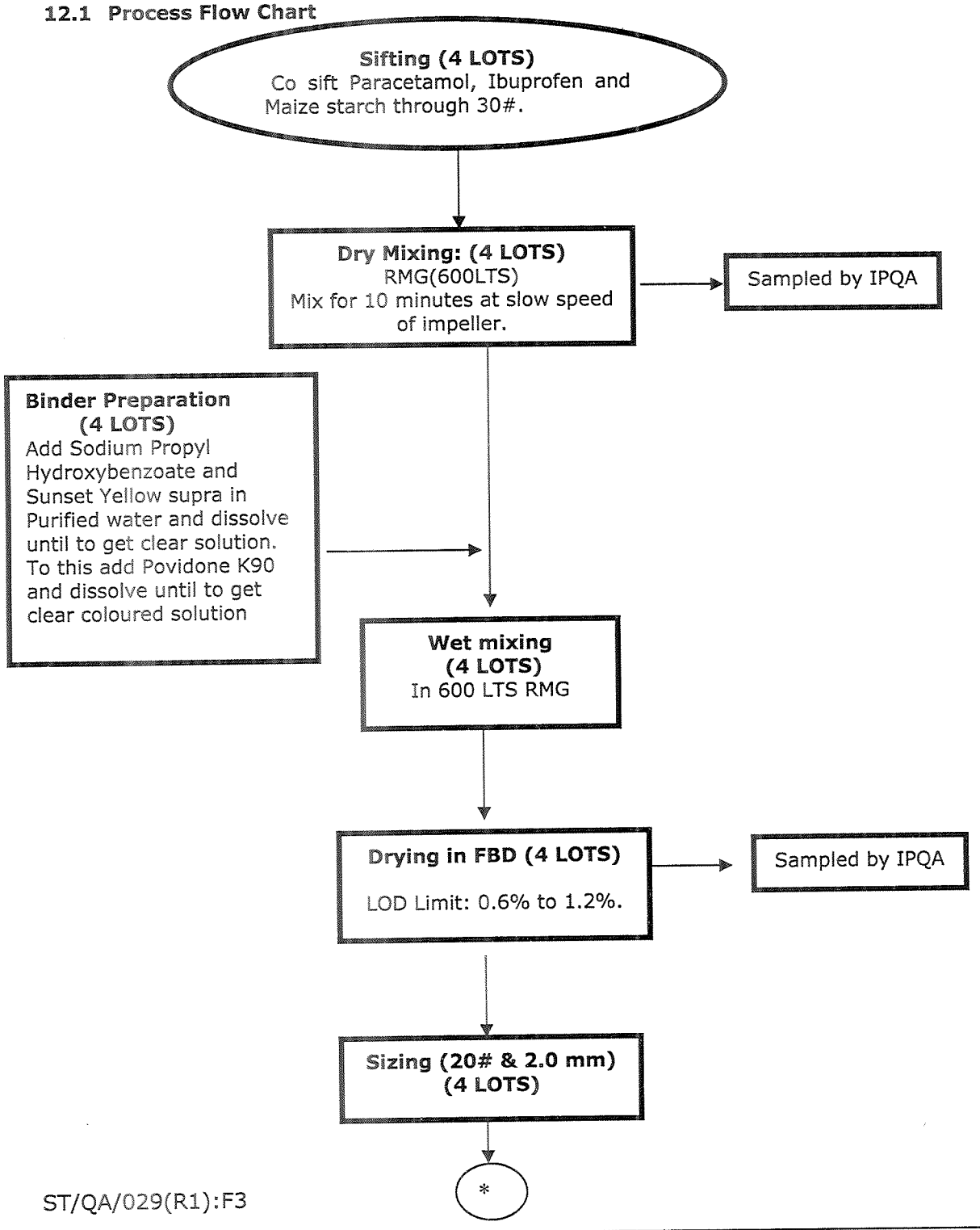
## 11.0 EQUIPMENT DETAILS:

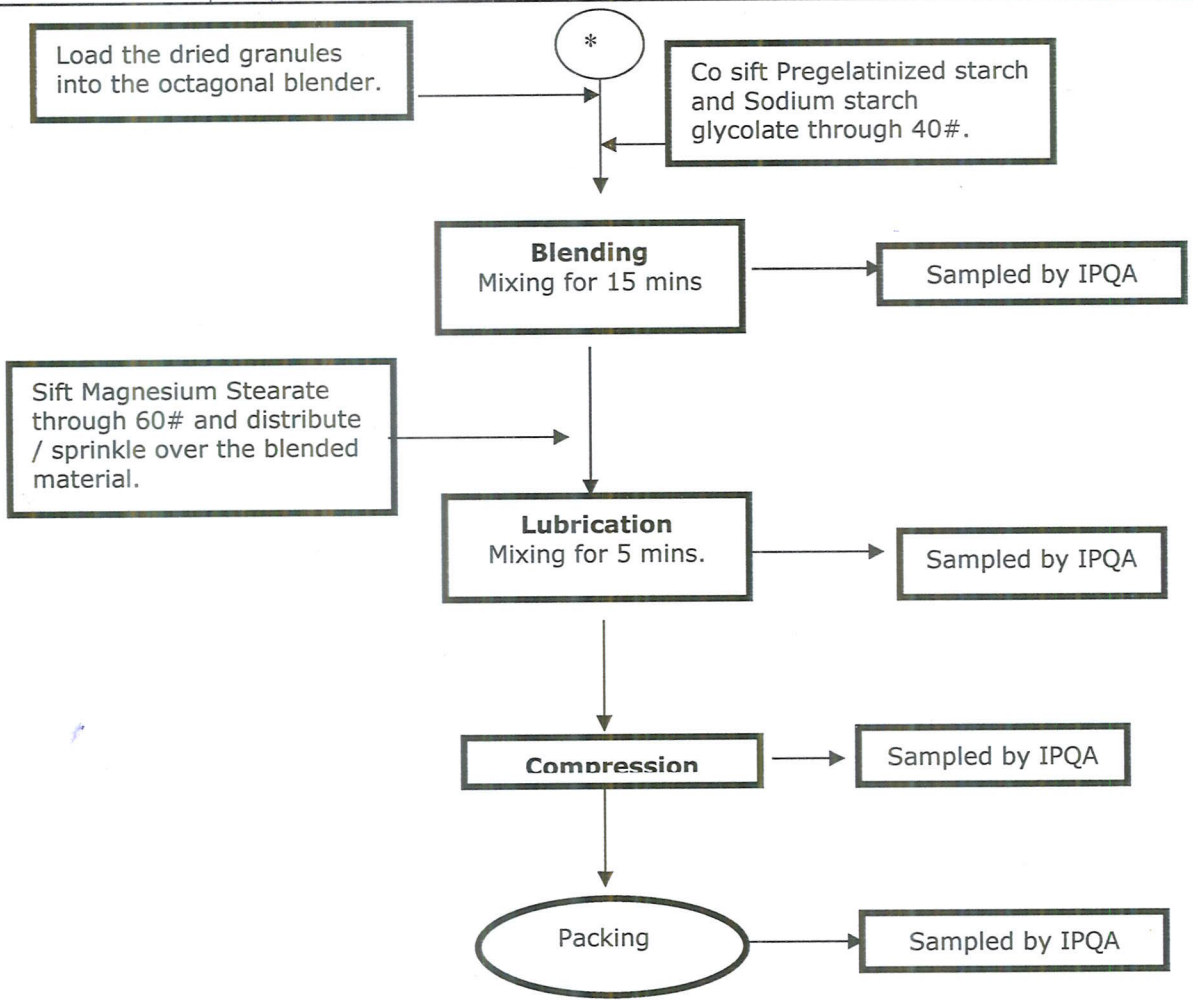
Table 1: List of major process equipment to be used in the manufacturing:

| 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/001<br>ST/PRWB/002 |
| 2.0 | Vibratory Sifter | GEM Pharma | ST/PRVS/001 or<br>ST/PRVS/002 or<br>ST/PRVS/003 or<br>ST/PRVS/004 |
| 3.0 | Fluid bed drier(250kg) | GEM Pharma | ST/PRFD/003 |
| 4.0 | Rapid mixer granulator(600L) | GEM Pharma | ST/PRRG/005 |
| 5.0 | Multimill | GEM Pharma | ST/PRG/009 |
| 6.0 | Octagonal Blender (2200L) | SRI KARPAGA VINAYAGAR | ST/PROB/001 |
| 7.0 | Compression Machine 27 stn. | CADMECH | ST/PRCM/001 or<br>ST/PRCM/003 or<br>ST/PRC/004 or<br>ST/PRCM/004 |
| 8.0 | Blister packing machine | Rapid pack<br>Rapid pack-240 | ST/PPB/001<br>ST/PPB2/001 |

## 12.0 PROCESS DESCRIPTION:

### 12.1 Process Flow Chart




Load the dried granules into the octagonal blender.
*
Co sift Pregelatinized starch and Sodium starch glycolate through 40#.
Blending
Mixing for 15 mins
Sampled by IPQA
Sift Magnesium Stearate through 60# and distribute / sprinkle over the blended material.
Lubrication
Mixing for 5 mins.
Sampled by IPQA
Compression
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 and Ibuprofen tablets comprises of following stages:

| Stage | Manufacturing Procedure |
|---|---|
| 1 Dispensing | Dispense the raw material as per the standard operating procedure. |
| 2. Sifting | Co sift equal amount Paracetamol, Ibuprofen and Maize starch through 30#. |
| 3.Dry Mixing | Load sifted materials into RMG and mix for 10 minutes at slow speed of impeller and chopper off. |
| 4. Binder Preparation | Add Sodium Propyl Hydroxybenzoate and Sunset Yellow supra in Purified water and dissolve until to get clear solution. To this add Povidone K90 and dissolve until to get clear coloured 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 fast/slow speed impeller/chopper ON at fast/slow speed.<br>If required add additional Purified water and mix for 2-3minutes to form a required granules. |
| 6. Drying and Sizing | Load the wet granules into FBD and air drying for 10-15 minutes with intermittent racking.<br>Continue the drying at the temperature of 50°C±5°C until LOD reaches the limit 0.6% to 1.2%. Sift the dried granules through 16#. Mill the retained granules through 2.0mm screen and pass through 20#.<br>**NOTE: Dispensing, Sifting, Dry Mixing, Binder Preparation, Granulation, Drying and Sizing 4 Lots.** |
| 7. Blending and Lubrication | Load the dried granules into the octagonal blender.<br>Co sift Pregelatinized starch and Sodium starch glycolate through 40#. Mix for 15minutes.<br>Sift the Magnesium Stearate through 60# and distribute / sprinkle over the blended material Mix for 5 minutes.<br>Unload the final lubricated granules into the suitable container lined with double poly bag with proper status label. |

| Stage | Manufacturing Procedure |
|---|---|
| 8.0 Compression | Compress the blend as single layer tablet by using<br>Upper Punch: 19.3x9.0mm oval shape biconcave with break line.<br>Lower punch: 19.3x9.0mm oval shape biconcave plain.<br>Dies : 19.3x9.0mm.<br>Pass the compressed tablets through deduster to remove powder particles. |

| | |
|---|---|
| Description | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side. |
| Average Weight per tablet | 1040mg± 3.00%<br>(1008.800mg-1071.200mg) |
| Weight of 20 tablets | 20.800±3.00%<br>(20.176g to 21.424g) |
| Uniformity of weight | Average weight ± 5%<br>(988.000mg to 1092.000mg) |
| Thickness | 7.90± 0.3mm (7.60 to 8.20 mm)<br>*** |
| Hardness | 160 N to 230 N<br>*** |
| Friability | NMT 1.0%w/w |
| Disintegration Time | NMT 15 mins at 37°C±2°C |

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

| | |
|---|---|
| 9.0 Inspection | Inspect the tablets visually for removing defected tablets. |
| 10.0 Metal detector | Tablets pass through the metal detector. |
| 11.0 Packing | Perform packing on blister 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** |
|---|---|---|
| Co sift equal amount Paracetamol, Ibuprofen and Maize starch through 30#. Load sifted materials into RMG and mix for 10 minutes at slow speed of impeller and chopper off. | **MIXING TIME** | Samples shall be withdrawn from 10 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 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** | **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 Pregelatinized starch and Sodium starch glycolate through 40#. Mix for 15 minutes. | **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 18.2) separately into the tarred using sampling thief after **15 minutes** mixing. 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 5 minutes. | **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) separately into the tarred vials using sampling thief after **5 minutes** mixing. Use these samples for blend uniformity test as per 13.2.2.2<br>**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 and Ibuprofen) | Individual sample values between 85% to 115% & RSD: NMT 5 % Average value between 90% to 110%. | Specification and test procedure no: IMSG00121-00 IMTG00121-00 |
| **13.2.2** | **BLENDING & LUBRICATION PROCESS:** | | |
| **13.2.2.1** | **BLENDING – PRE LUBRICATION:** | | |
| **1** | **Blend uniformity:** (Paracetamol and Ibuprofen) | Individual sample values between 85% to 115% & RSD: NMT 5 % Average value between 90% to 110%. | Specification and test procedure no: IMSG00121-00 IMTG00121-00 |
| **13.2.2.2** | **LUBRICATION:** | | |
| **1** | **Appearance** (pooled sample) | Light orange colour powder | Specification and test procedure no: IMSG00121-00 IMTG00121-00 |
| **2** | **Blend uniformity:** (Paracetamol and Ibuprofen) | 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 **8.20mm** 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.<br>**To fix standard compression force:**<br>Adjust the compression force to achieve the thickness at standard limit **7.90mm** 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.<br>**To fix maximum compression force:**<br>Adjust the compression force to achieve the thickness at lower limit **7.60mm** 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.<br>**This challenge study is applicable for first validation batch only.**<br>**Fixed compression forces shall be verified in next two consecutive validation batches.** | **i)Appearance**<br><br>**ii) Average weight** (20 tablets)<br><br>**iii) Weight Variation** (20 tablets)<br><br>**iv)Thickness** (Average 10 tablets)<br><br>**v) Friability**<br><br>**vi)Hardness** (Average of 10 tablets)<br><br>**vii)Disintegration time** | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side.<br><br>1040mg± 3.00% (1008.800mg-1071.200mg)<br><br>Not more than 2 of the individual masses deviate from the average mass by more than ±5%.<br><br>7.90mm± 0.3mm (7.60mm to 8.20 mm)<br><br>Not more than 1.0% w/w<br><br>160 N to 230 N<br><br>Not more than 15 minutes | Specification and test procedure no:<br><br>IMSG00122-00<br>IMTG00122-00 |

| 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 100 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.<br>**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 | **i)Appearance**<br><br>**ii) Average weight** (20 tablets)<br><br>**iii) Weight Variation** (20 tablets)<br><br>**iv)Thickness** (Average 10 tablets)<br><br>**v) Friability**<br><br>**vi)Hardness** (Average of 10 tablets)<br><br>**vii)Disintegration time** | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side.<br><br>1040mg± 3.00% (1008.800mg-1071.200mg)<br><br>Not more than 2 of the individual masses deviate from the average mass by more than ±5%.<br><br>7.90mm± 0.3mm (7.60mm to 8.20 mm)<br><br>Not more than 1.0% w/w<br><br>160 N to 230 N<br><br>Not more than 15 minutes | Specification and test procedure no: IMSG00122-00 IMTG00122-00 |

| | | | | |
|---|---|---|---|---|
| | 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.** | | | |
| **13.2.3.3** | **Hopper Level (Hopper level - Challenge)** | | | |
| | **<u>For first batch only:</u>** 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 | **i)Appearance**<br><br>**ii) Average weight** (20 tablets)<br><br>**iii) Weight Variation** (20 tablets)<br><br>**iv)Thickness** (Average 10 tablets)<br><br>**v) Friability**<br><br>**vi)Hardness** (Average of 10 tablets) | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side.<br><br>1040mg± 3.00% (1008.800mg-1071.200mg)<br><br>Not more than 2 of the individual masses deviate from the average mass by more than ±5%.<br><br>7.90mm± 0.3mm (7.60mm to 8.20 mm)<br><br>Not more than 1.0% w/w<br><br>160 N to 230 N | Specification and test procedure no: IMSG00122-00 IMTG00122-00 |

| | | | | |
|---|---|---|---|---|
| | 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. 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.**<br>**This challenge study is applicable for first validation batch. Near empty level shall be verified in next two consecutive validation batches** | **vii)Disintegration time**<br><br>**viii)Assay:**<br>i) Ibuprofen BP 400mg<br><br>ii) Paracetamol BP 500mg<br><br>**ix) Dissolution**<br>i) Ibuprofen BP<br><br>ii) Paracetamol BP | Not more than 15 minutes<br><br>90.0% - 110.0% of the labeled claim<br><br>90.0% - 110.0% of the labeled claim<br><br>Not less than 80% of stated amount ibuprofen dissolved in 60 minutes<br>Not less than 80% of stated amount paracetamol dissolved in 60 minutes | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| 13.2.3.4 | Composite Sample (100 NO'S) to be collected to represent entire batch. | **i)Appearance** | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side. | |
| | | **ii) Average weight** (20 tablets) | 1040mg± 3.00% (1008.800mg-1071.200mg) | |
| | | **iii) Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than ±5%. | |
| | | **iv)Thickness** (Average 10 tablets) | 7.90mm± 0.3mm (7.60mm to 8.20 mm) | |
| | | **v) Friability** | Not more than 1.0% w/w | |
| | | **vi)Hardness** (Average of 10 tablets) | 160 N to 230 N | |
| | | **vii)Disintegration time** | Not more than 15 minutes | |
| | | **viii)Assay:** i) Ibuprofen BP 400mg | 90.0% - 110.0% of the labeled claim | |
| | | ii) Paracetamol BP 500mg | 90.0% - 110.0% of the labeled claim | |

| | | | | |
|---|---|---|---|---|
| | | **ix) Dissolution**<br>i) Ibuprofen BP<br><br>ii) Paracetamol BP<br><br>**x)Related Substances**<br>i) Single maximum unknown purity.<br><br>ii) Total impurities. | Not less than 80% of stated amount ibuprofen dissolved in 60 minutes<br>Not less than 80% of stated amount paracetamol dissolved in 60 minutes<br><br>Not more than 0.20%.<br><br>Not more than 0.50% | |
| **13.2.4** | **Packing** | | | |
| **13.2.4.1** | Forming Temperature | a) 145°C to 175°C.<br><br>b) Leak test. | i) No Foil Damage.<br>ii) No pin holes observed in foil.<br>iii) No white patches / colour change in PVDC.<br>iv) Over printed details are legible.<br><br>No Blister should fail in leak test. | SOP.NO ST/QA/056 |

| | | | | |
|---|---|---|---|---|
| **13.2.4.2** | Blister Packing Machine Speed | a) Different speed 20,25, 30, & 40 Stroke and verify the Blister quality.<br><br>b) Leak test. | No Foil Damage, No broken Tablets, No Tablets Sticking to Foil, No ink lifting shall be observed, Blister should have proper cutting and knurling, Free flowing of tablets from hopper to guide track, Over printed details Are legible.<br>No Blister should fail in leak test. | SOP.NO ST/QA/056 |
| **13.2.4.3** | Verification of optimum sealing temperature and optimum speed range. | a) Blister 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 Blister should fail in leak test. | |
| **13.2.4.4** | Verification of optimum forming temperature and optimum speed range. | a) Blister 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>No Blister should fail in leak test. | |

| | | | | |
|---|---|---|---|---|
| **13.2.4.5** | Efficiency of Tablet Feeder | a) Chipping, breaking, & overlapping of tablets<br><br>b) Flow of tablets from hopper through chute to forming roller.<br><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>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 |
| **13.2.4.6** | **Impact assessment**<br>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. (Each run collect for 10 Blisters) | i) De blistered tablets.<br><br>Leak test. | Assay and Dissolution test to be performed when Related Substances meet with the specification.<br>Perform 3rd Re-Blistering analysis first. If the 3rd Re-Blistering analysis is meet the acceptance criteria, no need to perform the 1st and 2nd Re-Blistering analysis.<br>No Blister should fail in leak test | |
| **13.2.4.7** | 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 Blister should fail in leak test. | |

| | | | | |
|---|---|---|---|---|
| **13.2.4.8** | Blister Inspection system | a) Black pots detector<br><br>b) Shaped tablet detector<br>c) Foreign tablet detector<br><br>d) Half tablet detector<br><br>e) non filled detector | Blister with black spots tablet should be detected and rejected.<br>Blister with different shape tablet should be detected and rejected.<br>Blister with foreign tablet should be detected and rejected.<br>Blister with half tablet should be detected and rejected.<br>Blister with non filled pack should be detected and rejected. | |

| 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 3 Blisters | **Appearance** | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side. | Specification and test procedure no: FGSTSG031-00 FGTTSG031-00 |
| | | **Average weight** (20 tablets) | 1040mg± 3.00% (1008.800mg-1071.200mg. | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than 10%. | |
| **13.2.5.2** | **MIDDLE stage of operation** collect for 3 Blisters | **Appearance** | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side. | |
| | | **Average weight** (20 tablets) | 1040mg± 3.00% (1008.800mg-1071.200mg. | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than 10%. | |

| S.NO | SAMPLING LOCATION | MEASURED PARAMETER | ACCEPTANCE CRITERIA | TEST PROCEDURE |
|---|---|---|---|---|
| **13.2.5.3** | **FINAL stage of operation** collect for 3 Blisters. | **Appearance** | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side. | Specification and test procedure no: FGSTSG031-00 FGTTSG031-00 |
| | | **Average weight** (20 tablets) | 1040mg± 3.00% (1008.800mg-1071.200mg. | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than 10%. | |
| **13.2.5.4** | Composite sample to be collected to represent entire batch (6 Blisters). | **Appearance** | Light orange coloured oval shape biconvex uncoated tablets with half break line on one side and plain on another side. | |
| | | **Average weight** (20 tablets) | 1040mg± 3.00% (1008.800mg-1071.200mg. | |
| | | **Weight Variation** (20 tablets) | Not more than 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than 10%. | |
| | | **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) Esherichia coli.<br>v) staphylococcus aureus. | |

## 14.0 PROCESS PARAMETERS:

| Manufacturing Process Stages | Critical Process Parameters | Set-Point |
|---|---|---|
| **Dry Mixing** | Mixing Time | 10 min |
| **Drying** | LOD | 0.6 to 1.2% |
| **Sizing** | Sifter Screen | 16# |
| | Miller Screen | 2.0mm |
| **Blending** | Mixing Time | 15 min |
| **Lubrication** | Mesh size | 60# |
| | Lubrication Time | 5 min |
| **Compression** | Compression Machine Speed | 10 – 35 rotation/min *** |
| | Hardness | 160 N to 230 N *** |
| **Packing** | Sealing temperature | 190°C to 205°C *** |
| | Speed of blister packing machine | 30-40 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 Ibuprofen and Paracetamol Tablets.

**18.0 SAMPLING LOCATION DIAGRAM:**

**18.1 Sampling Plan Diagram of RMG:**

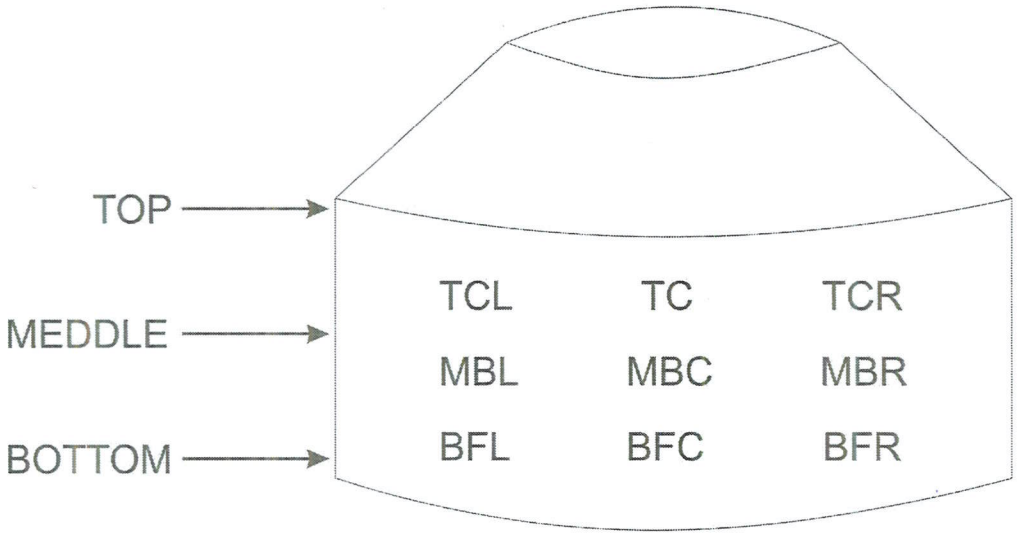



**Fig. No.1**

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**

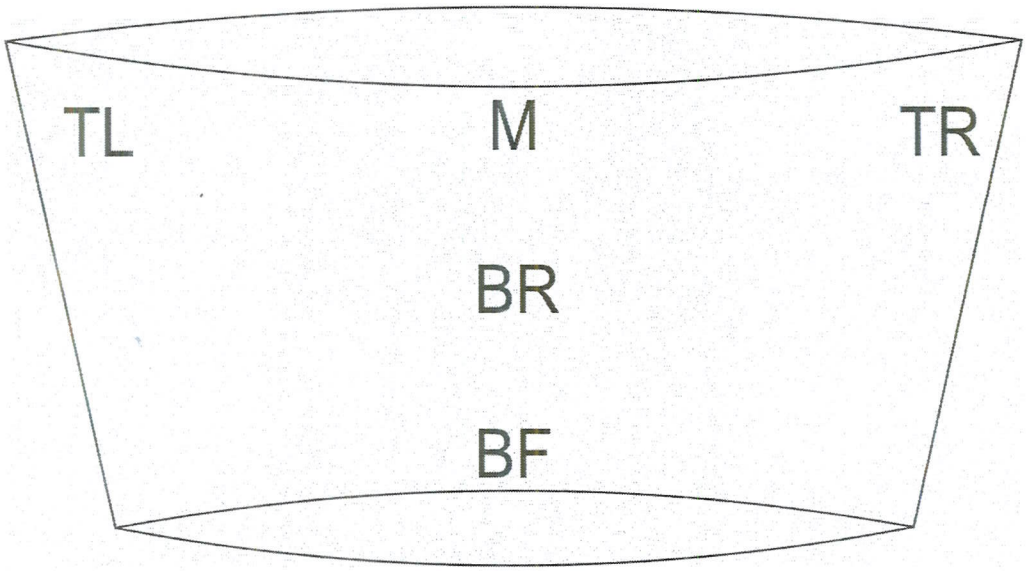



**Fig. No.2**

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

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

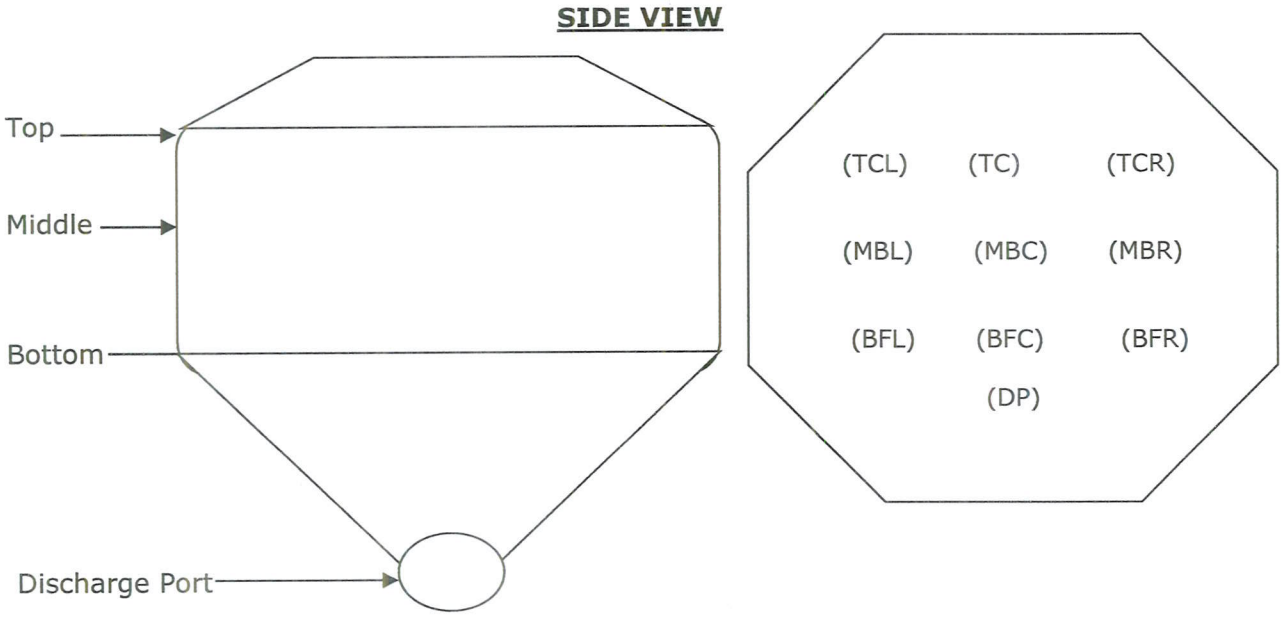



**Fig-3**

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