PROCESS VALIDATION PROTOCOL

GLICLAZIDE AND METFORMIN HYDROCHLORIDE SUSTAINED RELEASE TABLETS 60/850mg

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	Safetab Life Science, Puducherry.		
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Protocol Number	PVP/20/004	MFC No.	ST/MFC/130/R0
Effective Date	04/06/2020	Market	EXPORT

1.0 APPROVAL

Prepared By	Name	Designation	Signature	Date
QUALITY ASSURANCE	R. Silambarasan	Jr. Executive Q.A		01/06/2020

Reviewed By	Name	Designation	Signature	Date
PRODUCTION	G. Vijayalakshmi	Sr. Production manager		02/06/2020
QUALITY CONTROL	M/S. V. JAYAKUMAR	AGM - QC		02/06/20

Approved By	Name	Designation	Signature	Date
QUALITY ASSURANCE	K. Chandrasekar	AGM - QA		03/06/2020

2.0 SCOPE:

This protocol is applicable for the manufacturing and sampling of validation batches of Gliclazide and Metformin Hydrochloride sustained release tablets 60/850mg with a batch size of 5.0 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 Gliclazide and Metformin Hydrochloride sustained release tablets 60/850mg, to be manufactured at Safetab Life Science, Plot No: A-67 & 68, 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:

Gliclazide and Metformin Hydrochloride sustained release tablets 60/850mg is a solid dosage which contains Gliclazide and Metformin Hydrochloride as active ingredient. This is being manufactured at Safetab Life Science, Puducherry, with the batch size of 5.0 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. 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	Gliclazide and Metformin Hydrochloride Sustained Release Tablets 60/850mg
Label Claim	Each Uncoated bilayered sustained release tablet contains: Gliclazide BP 60 mg Metformin Hydrochloride BP 850 mg (in sustained release form) Colour: Approved colours are used.
Overages (% w/w)	NA
Shelf life	36 Months
Storage Condition	Store in a cool and dry place at temperature not exceeding 30C. Protect from light and moisture.
Batch Size	500000 Tablets
Therapeutic Use	Used for the treatment of type II diabetes mellitus.
Product Pack	Printed Foil: 186mm Blister foil Base Foil: 190mm PVC clear
Pack Style	Sales : 3x10'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:

Gliclazide part

Material Code	Ingredient	Grade	FUNCTION	Mg/Tablet	Quantity Kg/Batch 5.0 L	VENDOR
Dry Mixing and Granulation:						
RMAG0014	Gliclazide *	BP	Hypoglycemic agent	60.000	30.000	Kimia
RMED0014	Dicalcium Phosphate #	BP	Diluent	50.500	25.250	India phosphate
RMEM0036	Methocel K100 Premium LVCR (Hydroxypropyl Methylcellulose)	BP	Polymer	40.000	20.000	Dow
RMEI0004	Iron Oxide Red	USP	Colourant	1.000	0.500	Neelikon
RMEP0049	Povidone K30	BP	Binder	9.000	4.500	Haungshan Bonsun Pharmaceuticals
RMEM0029	Methylene chloride @	BP	Vehicle	100.000	50.000	Chemplast
BLENDING						
RMEM0035	Methocel K 100 Premium (Hydroxypropyl Methylcellulose)	BP	Polymer	10.000	5.000	Dow
RMET0012	Purified Talc	BP	Glidant	5.000	2.500	Imerys
RMEC0017	Colloidal silicon dioxide	BP	Adsorbent	2.000	1.000	Wacker
LUBRICATION						
RMEM0033	Magnesium stearate	BP	Lubricant	2.500	1.250	Nitika
Total				180.000	90.000	--------

Metformin hydrochloride part

Material Code	Ingredient	Grade	FUNCTION	Mg/Tablet	Quantity Kg/Batch 5.0 L	VENDOR
Dry Mixing and Granulation:						
RMAM0030	Metformin Hydrochloride **	BP	Anti-diabetic	850.000	425.000	Aarti Drugs
RMEM0035	Hydroxy Propyl Methylcellulose K 100M Premium	BP	Polymer	120.000	60.000	DOW
RMEM0031	Microcrystalline cellulose powder ##	BP	Diluent	60.000	30.000	Sigachi
RMEP0045	Povidone K90	BP	Binder	45.000	22.500	Haungshan Bonsun Pharmaceuticals
RMEI0010	Isopropyl Alcohol @	BP	Vehicle	88.000	44.000	Deepak fertilizers
RMEP0033	Purified water @	BP	Vehicle	132.000	66.000	Inhouse
BLENDING						
RMEM0035	Hydroxy Propyl Methylcellulose K 100M Premium	BP	Polymer	100.000	50.000	DOW
LUBRICATION						
RMEM0033	Magnesium stearate	BP	Lubricant	5.000	2.500	Nitika
			Total	1180.00	590.000	--------

***, **, #, ## Refer potency Calculation**
@ Does not in final product evaporates during the process.

9.0 CALCULATIONS:

9.1. Potency calculation for Gliclazide:

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

Actual quantity to be added is calculated as:

$$\text{* Actual quantity. Of Gliclazide} = \frac{60\text{mg} \times 100 \times 100}{\text{\% Assay of Gliclazide dried basis} \times (100 - \text{LOD \%})} \text{ mg/tablet}$$

Quantity of Dicalcium Phosphate varies based on assay and LOD content of Gliclazide for keeping the core tablet weight constant

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

9.2 Potency calculation for Metformin Hydrochloride:

The given quantity is based on 100% Assay on dried basis and without LOD.
Actual quantity to be added is calculated as:

$$\text{** Actual qty. of Metformin Hydrochloride} = \frac{850 \times 100 \times 100}{\text{\% Assay of Metformin Hcl on dried basis} \times (100 - \text{\% of LOD})} = \text{mg/tablet}$$

Quantity of Microcrystalline Cellulose Powder varies based on Assay content of Metformin Hydrochloride for keeping the core tablet weight constant.

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

10.0 PACKING MATERIAL COMPONENTS:

Material code	Components	Vendor
PMG00077	Printed Foil: 186mm Blister foil	Sri velu foil printing
PVPV0021	Base Foil: 190mm PVC clear	Vipul Pharma

11.0 EQUIPMENT DETAILS:

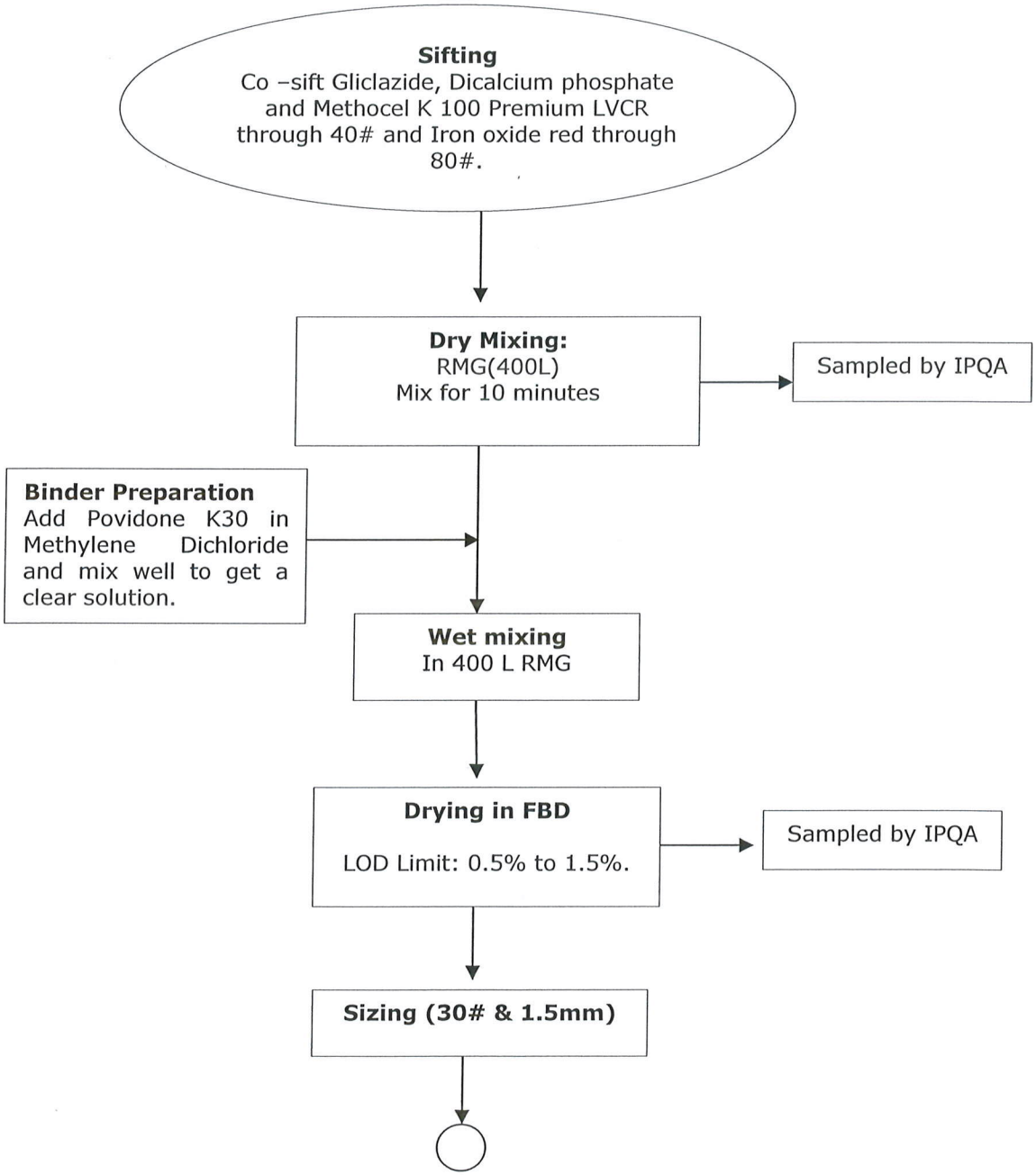
Table 1: List of major process equipment to be used in the manufacturing:

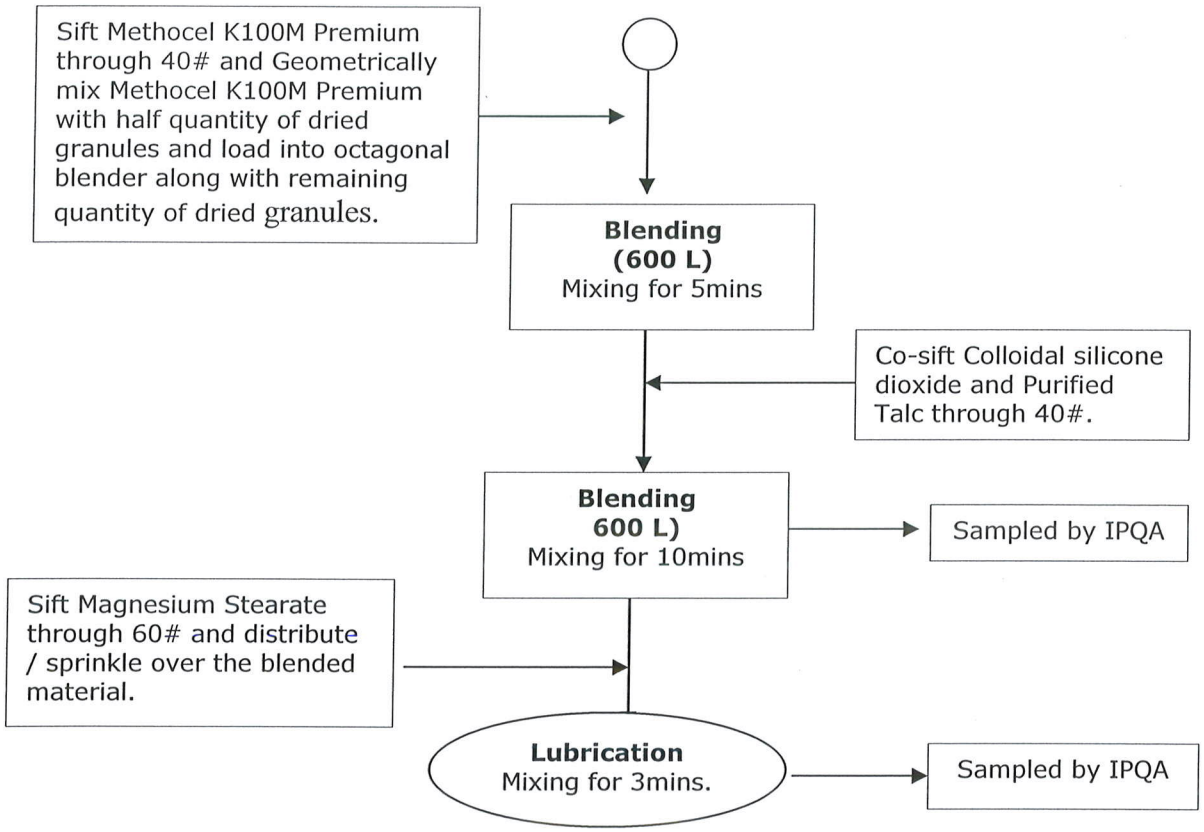
Sr. No.	Equipment	Make	Equipment No.
1.0	Weighing Balances	Essae Teraoka	ST/WB/189 ST/SRWB/001 ST/SRWB/002 ST/PRWB/002 ST/PRWB/001
2.0	Vibratory Sifter	GEM Pharma	ST/PRG/007 ST/PRG/006
3.0	Fluid bed drier(120kg)	GEM Pharma	ST/PRG/012
4.0	Rapid mixer granulator(400L)	GEM Pharma	ST/PRG/014
5.0	Multimill	GEM Pharma	ST/PRG/009 ST/PRG/010
6.0	Octagonal Blender (600L) Octagonal Blender (2200L)	GEM Pharma Sri Karpaga Vinayagar Fabrications	ST/PRG/015 ST/PROB/001
7.0	Compression Machine 27 stn.	CADMACH	ST/PRC/004 ST/PRCM/003 ST/PRCM/001
8.0	Blister Packing Machine	Rapid pack	ST/PPB/001 ST/PPB2/001

12.0 PROCESS DESCRIPTION:

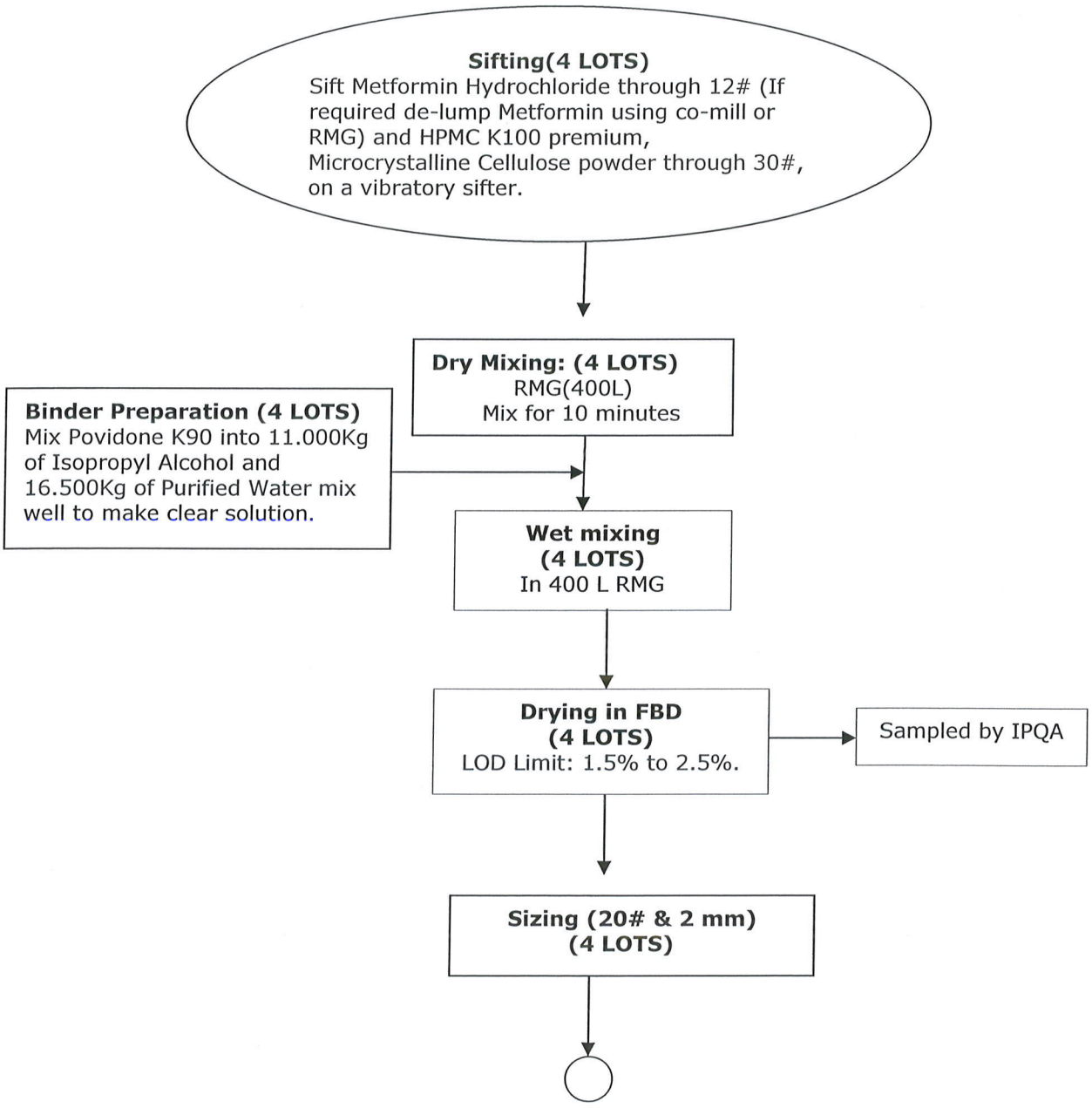
12.1 Process Flow Chart

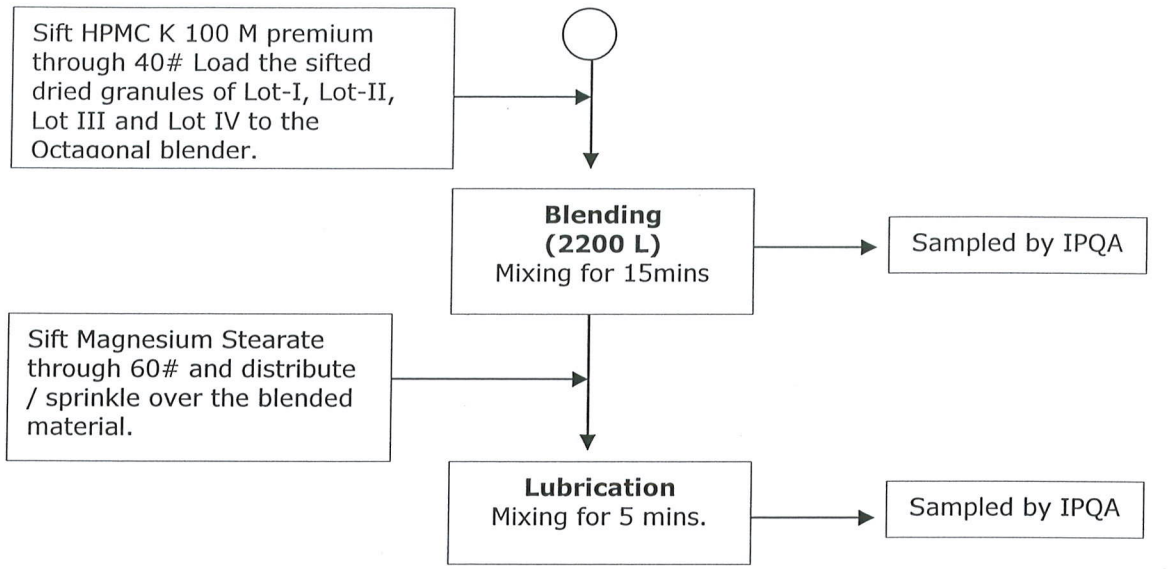
Gliclazide part



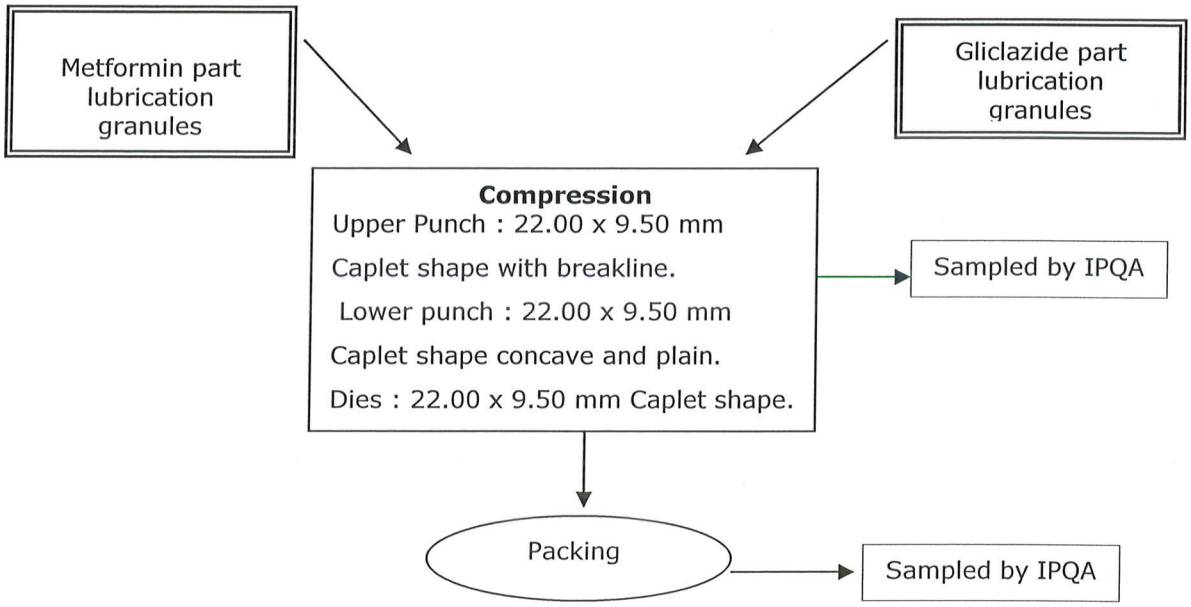

Sift Methocel K100M Premium through 40# and Geometrically mix Methocel K100M Premium with half quantity of dried granules and load into octagonal blender along with remaining quantity of dried granules.
Blending (600 L) Mixing for 5mins
Co-sift Colloidal silicone dioxide and Purified Talc through 40#.
Blending 600 L) Mixing for 10mins
Sampled by IPQA
Sift Magnesium Stearate through 60# and distribute / sprinkle over the blended material.
Lubrication Mixing for 3mins.
Sampled by IPQA

Metformin part





Manufacturing process



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 Gliclazide and Metformin Hydrochloride Sustained Release Tablets 60/850mg comprises of following stages:

Stage	Manufacturing Procedure
1.0 Gliclazide part	
1.1 Dispensing	Dispense the raw material as per the standard operating procedure.
1.2 Sifting	Co –sift Gliclazide, Dicalcium phosphate and Methocel K 100 Premium LVCR through 40# and Iron oxide red through 80#.
1.3 Dry Mixing	Mix for 10 minutes at fast speed impeller and chopper ON at slow/fast speed.
1.4 Binder preparation	Add Povidone K30 in Methylene Dichloride and mix well to get a clear solution.
1.5 Granulation	**Granulation:(Wet mixing)** Binder addition: 1-2 minutes mixing at fast impeller speed and chopper at slow/fast speed. Racking. (If required add additional quantity of Methylene dichloride and mix for 1minutes to get the uniform granules.) Kneading: Mixing: 1-2 minutes mixing at fast speed impeller and chopper at slow/fast speed. Discharge the wet granules in FBD bowl for drying.
1.6 Drying and Sizing	Load the Wet granules into FBD bowl and air drying for 10 mins & steam drying at 60° C±5°C with intermittent racking at 10-15 minutes to achieve LOD limit 0.5%-1.5%. Mill the retained granules through 1.5mm screen and pass through 30#.

Stage	Manufacturing Procedure
1.0 Gliclazide part	
1.7 Blending	Sift Methocel K100M Premium through 40# and Geometrically mix Methocel K100M Premium with half quantity of dried granules and load into octagonal blender along with remaining quantity of dried granules. Mix for 5 minutes. Co-sift Colloidal silicone dioxide and Purified Talc through 40#. Load the above sifted materials into octagonal blender and mix for 10minutes.
1.8 Lubrication	Sift Magnesium Stearate through 60# and distribute / sprinkle over the blended material. Mix for 3 minutes. Unload the final blend into suitable containers lined with double polythene bag container with proper label.
2.0 Metformin part	
2.1 Dispensing	Dispense the raw material as per the standard operating procedure.
2.2 Sifting	Sift Metformin Hydrochloride through 12# (If required de-lump Metformin using co-mill or RMG) and HPMC K100 premium, Microcrystalline Cellulose powder through 30#, on a vibratory sifter.
2.3 Dry Mixing	Load the above sifted material into RMG. Mix for 10 minutes at slow speed of impeller.
2.4 Binder preparation	Mix Povidone K90 into Isopropyl Alcohol and Purified Water mix well to make clear solution.
2.5 Granulation	**Granulation:(Wet mixing)** Binder addition: 2 minutes mixing –impellers slow/chopper off. Racking Mixing time: 1 minutes at slow impeller/chopper at fast speed. Racking
2.6 Drying and Sizing	Air dries the wet granules for 10 minutes with intermittent racking. Steam Drying at 60° C±5°C with intermittent racking at every 15mins until LOD reaches the limit 1.5%to 2.5%. Mill the retained dried granules in 2.0 mm screen and pass through 20#. **NOTE: Dispensing, Sifting, Dry Mixing, Binder Preparation, Granulation, Drying and Sizing 4 Lots.**

2.7 Blending	Sift HPMC K 100 M premium through 40# Load the sifted dried granules of Lot-I, Lot-II, Lot III and Lot IV to the Octagonal blender. Mix for 15 minutes.
2.8 Lubrication	Sift Magnesium Stearate through 60# and Distribute / sprinkle over the blended material. Mix for 5 minutes. Unload the final blend into suitable containers lined with double polythene bag with proper status label.
3.0 Compression	Compress the blend as bilayer tablet by using 27- station Double Rotary Compression Machine with Upper Punch : 22.00 x 9.50 mm Caplet shape with breakline. Lower punch : 22.00 x 9.50 mm Caplet shape concave and plain. Dies : 22.00 x 9.50 mm Caplet shape .Pass the compressed tablets through deduster to remove powder Particles and through the metal detector.
4.0 Inspection	Inspect the tablets visually for removing defected tablets.
5.0 Packing	Perform packing on Blister packing machine.

Description	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides
Average Weight of tablet	1360 mg ± 5% (1292.00mg – 1428.000mg)
Weight of 20 tablets	27.200g ± 3 % (26.384g to 28.016g)
Uniformity of weight	±5% of actual average weight
Thickness	7.10 ± 0.30mm (6.80mm -7.40mm)***
Hardness	(250N-350N) ***
Friability	NMT 1.0%w/w

Note: * shall be monitored for first 5 batches.**

13.0 SAMPLING PLAN AND ACCEPTANCE CRITERIA:

13.1 CRITICAL PROCESS STAGES TO BE VALIDATED: (GLICLAZIDE PART)

13.1.1 DRY MIXING –GRANULATION STAGE:

DRY MIXING PROCEDURE (Refer MFR/BMR more details)	**CRITICAL PARAMETER TO BE VALIDATED**	**SAMPLING PROCEDURE**
Entire sifted quantity of Co –sift Gliclazide, Dicalcium phosphate and Methocel K 100 Premium LVCR through 40# and Iron oxide red through 80#. Mix for 10 minutes at fast speed impeller and chopper ON at slow/fast speed.	**MIXING TIME**	Sample of the dry mixed granules shall be withdrawn from 5 sampling points after completion of dry mixing for 10minutes, collect approximately 2.0gm of blend sample. Locations from top, middle and bottom level of the RMG (as per 18.1) separately. By using sampling thief. Use these samples for blend uniformity test as per 13.3.1.1

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.	**LOD**	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-Sift Methocel K100M Premium through 40# and Geometrically mix Methocel K100M Premium with half quantity of dried granules and load into octagonal blender along with remaining quantity of dried granules. Mix for 5 minutes. Co-sift Colloidal silicone dioxide and Purified Talc through 40#. Load the above sifted materials into octagonal blender and mix for 10minutes	**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 from top, middle and bottom level of the Octagonal blender (as per 18.3) separately into the tarred using sampling thief after **10 minutes** mixing**.** Use these samples for blend uniformity test as per 13.3.2.1
Step - 2 Sift Magnesium Stearate through 60# and distribute / sprinkle over the blended material. Mix for 3 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 from top, middle and bottom level of the Octagonal blender (as per 18.3) separately using sampling thief after **3 minutes** mixing. Use these samples for blend uniformity test as per 13.3.2.2 **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 13.3.2.2

13.2 CRITICAL PROCESS STAGES TO BE VALIDATED: (METFORMIN PART)

13.2.1 DRY MIXING –GRANULATION STAGE:

DRY MIXING PROCEDURE (Refer MFR/BMR more details)	**CRITICAL PARAMETER TO BE VALIDATED**	**SAMPLING PROCEDURE**
Sift Metformin Hydrochloride through 12# (If required de-lump Metformin using co-mill or RMG) and HPMC K100 premium, Microcrystalline Cellulose powder through 30#, on a vibratory sifter. Mix for 10 minutes at slow speed of impeller.	**MIXING TIME**	Sample of the dry mixed granules shall be withdrawn from 5 sampling points after completion of dry mixing for 10minutes, collect approximately 2.0gm of blend sample. Locations from top, middle and bottom level of the RMG (as per 18.1) separately. By using sampling thief. Use these samples for blend uniformity test as per 13.4.1.1

13.2.2 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.	**LOD**	Samples of the dried granules shall be withdrawn from FBD bowl from 5 random locations (as per 18.2).

13.2.3 BLENDING AND LUBRICATION STAGE

BLENDING AND LUBRICATION PROCEDURE (Refer MFR/BMR more details)	**CRITICAL PARAMETER TO BE VALIDATED**	**SAMPLING PROCEDURE**
Step- Sift HPMC K 100 M premium through 40# Load the sifted dried granules of Lot-I, Lot-II, Lot III and Lot IV to the Octagonal blender. 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 from top, middle and bottom level of the Octagonal blender (as per 18.3) separately into the tarred using sampling thief after **15 minutes** mixing. Use these samples for blend uniformity test as per 13.4.2.1
Step - 2 Sift 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 from top, middle and bottom level of the Octagonal blender (as per 18.3) separately using sampling thief after 5 **minutes** mixing. Use these samples for blend uniformity test as per 13.4.2.2 **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 13.4.2.2

13.3 TEST PROGRAM AND ACCEPTANCE CRITERIA FOR VALIDATION: (GLICLAZIDE)

S.No.	MEASURED PARAMETERS	ACCEPTANCE CRITERIA	TEST PROCEDURE
13.3.1	**GRANULATION PROCESS :**		
13.3.1.1	**Dry Mixing:**		
1	**Blend uniformity:** (Gliclazide content)	Individual sample values between 54 mg to 66 mg / 151.500mg & RSD: NMT 5 % Average value between 57 mg to 63 mg /151.5mg	Specification and test procedure no: IMSG00129-00 IMTG00129-00
13.3.2	**BLENDING & LUBRICATION PROCESS:**		
13.3.2.1	**BLENDING – PRE LUBRICATION:**		
1	**Blend uniformity:** (Gliclazide content)	Individual sample values between 54 mg to 66 mg /177.5 mg & RSD: NMT 5 % Average value between 57 mg to 63 mg /177.5 mg	Specification and test procedure no: IMSG00129-00 IMTG00129-00
13.3.2.2	**LUBRICATION:**		
1	**Appearance** (pooled sample)	Red granular powder	Specification and test procedure no: IMSG00129-00 IMTG00129-00
2	**Blend uniformity:** (Gliclazide content)	Individual sample values between 54 mg to 66 mg /180 mg & RSD: NMT 5 % Average value between 57 mg to 63 mg /180 mg	
3	**Loss on drying** at 105°C for hours (pooled sample)	For information only	
4	**Bulk density** (pooled sample)	For information only	
5	**Tap density** (pooled sample)	For information only	

13.4 TEST PROGRAM AND ACCEPTANCE CRITERIA FOR VALIDATION: (METFORMIN)

S.No.	MEASURED PARAMETERS	ACCEPTANCE CRITERIA	TEST PROCEDURE
13.4.1	**GRANULATION PROCESS :**		
13.4.1.1	**Dry Mixing:**		
1	**Blend uniformity:** (Metformin HCL content)	Individual sample values between 765 mg to 935 mg / 1030mg & RSD: NMT 5 % Average value between 807.5 mg to 892.5 mg /1030mg	Specification and test procedure no: IMSG00128-00 IMTG00128-00
13.4.2	**BLENDING & LUBRICATION PROCESS:**		
13.4.2.1	**BLENDING – PRE LUBRICATION:**		
1	**Blend uniformity:** (Metformin HCL content)	Individual sample values between 765 mg to 935 mg /1175 mg & RSD: NMT 5 % Average value between 765 mg to 935 mg /1175 mg	Specification and test procedure no: IMSG00128-00 IMTG00128-00
13.4.2.2	**LUBRICATION:**		
1	**Appearance** (pooled sample)	White granular powder	Specification and test procedure no: IMSG00128-00 IMTG00128-00
2	**Blend uniformity:** (Metformin HCL content)	Individual sample values between 765 mg to 935 mg /1180 mg & RSD: NMT 5 % Average value between 765 mg to 935 mg /1180 mg	
3	**Loss on drying** at 105°C for 1hours (pooled sample)	For information only	
4	**Bulk density** (pooled sample)	For information only	
5	**Tap density** (pooled sample)	For information only	

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S.NO	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.4.3	**COMPRESSION PROCESS:**			
13.4.3.1	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 **6.80** 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 **7.10** mm 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. **To fix maximum compression force:** Adjust the compression force to achieve the thickness at lower limit **7.40** 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. **This challenge study is applicable for first validation batch only.**	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	Specification and test procedure no: IMSG00130-00 IMTG00130-00
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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%.	
		Thickness (Average 10 tablets)	7.10 ± 0.30mm. (6.80mm - 7.40mm)	
		Friability	Not more than 1.0% w/w	
		Hardness (Average of 10 tablets)	(250N-350N)	
		Dissolution a) Gliclazide	2^{nd}hr. – NMT 25% 5^{th} hrs. – 30 to 60% 12^{th} hrs. – NLT 70%	
		b) Metformin Hydrochloride	1^{th} hr. – 20 to 40% 3^{th} hrs. – 45 to 65% 10^{th} hrs. – NLT 85%	

S.NO	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	Fixed compression forces shall be verified in next two consecutive validation batches.			
13.4.3.2	**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, 12rpm, 14rpm, 16rpm, 18rpm & 20 rpm,** 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 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. **To fix the Maximum**	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	IMSG00130-00 IMTG00130-00
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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%.	
		Thickness (Average 10 tablets)	7.10 ± 0.30mm. (6.80mm - 7.40mm)	
		Friability	Not more than 1.0% w/w	
		Hardness (Average of 10 tablets)	(250N-350N)	

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S.NO	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	Speed: Similarly check on the last sample collected at 20rpm. 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.**			
13.4.3.3	**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	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	IMSG00130-00 IMTG00130-00
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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 PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
	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. 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**	**Thickness** (Average 10 tablets)	7.10 ± 0.30mm. (6.80mm - 7.40mm)	
		Friability	Not more than 1.0% w/w	
		Hardness (Average of 10 tablets)	(250N-350N)	
		Dissolution a) Gliclazide	2^{nd}hr. – NMT 25% 5^{th} hrs. – 30 to 60% 12^{th} hrs. – NLT 70%	
		b) Metformin Hydrochloride	1^{th} hr. – 20 to 40% 3^{th} hrs. – 45 to 65% 10^{th} hrs. – NLT 85%	
		Assay (Gliclazide & Metformin Hydrochloride)	90% to 110%	

S.NO	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.4.3.4	Composite Sample (100 NO'S) to be collected to represent entire batch.	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	IMSG00130-00 IMTG00130-00
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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%.	
		Thickness (Average 10 tablets)	7.10 ± 0.30mm. (6.80mm - 7.40mm)	
		Friability	Not more than 1.0% w/w	
		Hardness (Average of 10 tablets)	(250N-350N)	
		Dissolution a) Gliclazide b)Metformin Hydrochloride	2^{nd}hr. – NMT 25% 5^{th} hrs. – 30 to 60% 12^{th} hrs. – NLT 70% 1^{th} hr. – 20 to 40% 3^{th} hrs. – 45 to 65% 10^{th} hrs. – NLT 85%	
		Assay (Gliclazide & Metformin Hydrochloride)	90% to 110%	

S.NO	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.4.4	**FINISHED PRODUCT:**			
13.2.4.1	**Initial stage of operation** collect for 3 strips	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	Specification and test procedure no: FGSTSG033-00 FGTTSG033-00
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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%.	
13.4.4.2	**MIDDLE stage of operation** collect for 3 strips	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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 PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
13.4.4.3	**FINAL stage of operation** collect for 3 strips.	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	FGSTSG033-00 FGTTSG033-00
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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%.	
13.4.4.4	Composite sample to be collected to represent entire batch (4 strips).	**Appearance**	Red / white colored, Caplet shaped biconvex uncoated bilayered tablets with break line on one side and plain on other sides	
		Average weight (20 tablets)	1360 mg ± 5% (1292.00mg – 1428.000mg)	
		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. a) Total aerobic microbial count. b) Total yeast and mould count. ii) Pseudomonas	

S.NO	SAMPLING LOCATION	MEASURED PARAETER	ACEEPTANCE CRITERIA	TEST PROCEDURE
			aeruginosa. iii) Salmonella species. iv) Esherichia coli. v) staphylococcus aureus.	

14.0 PROCESS PARAMETERS:

Manufacturing Process Stages	Critical Process Parameters	Set-Point
Dry Mixing	Mixing Time	Colour 10 min White 10 min
Drying	LOD	Colour 0.5 to 1.5% White 1.5 to 2.5%
Sizing	Sifter Screen	Colour 30# White 20#
	Miller Screen	Colour 1.5mm White 2.0 mm
Blending	Mixing Time	Colour 10 min White 15 mins
Lubrication	Mesh size	Colour 60# White 60#
	Lubrication Time	Colour 3 min White 5 mins
Compression	Compression Machine Speed	10 – 35 rpm/min ***
	Hardness	250N-350N ***
Packing	Sealing temperature	190°C to 205°C ***
	Speed of blister packing machine	30-40 strokes/min ***

Note: * shall be monitored for first 5 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 Gliclazide and Metformin Hydrochloride Sustained Release Tablets 60/850mg.

18.0 SAMPLING LOCATION DIAGRAM:

18.1Sampling Plan Diagram of RMG:

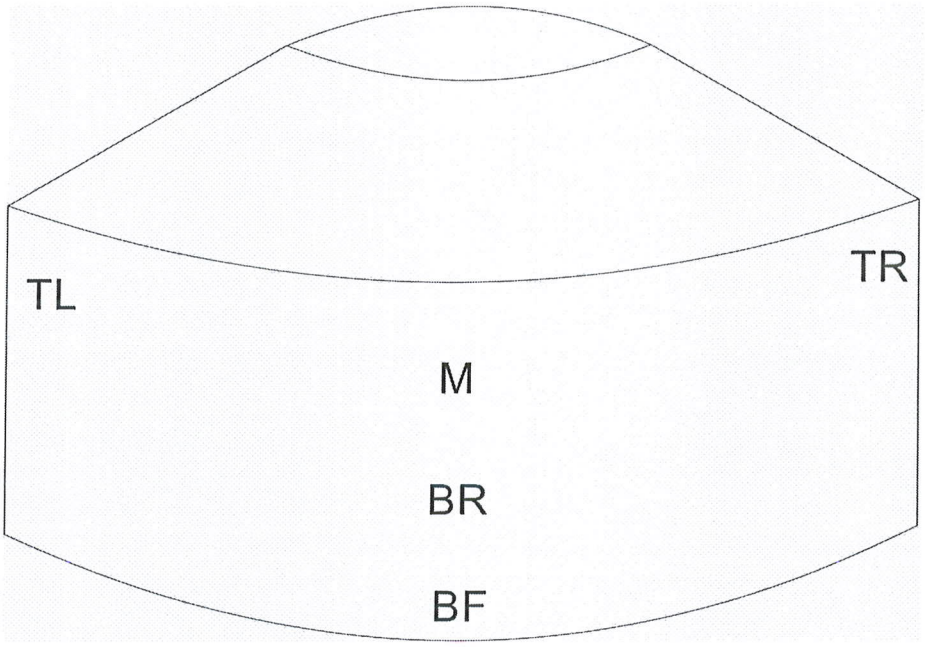

Fig. No.1

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

18.2 Sampling Plan Diagram of FBD:

SIDE VIEW

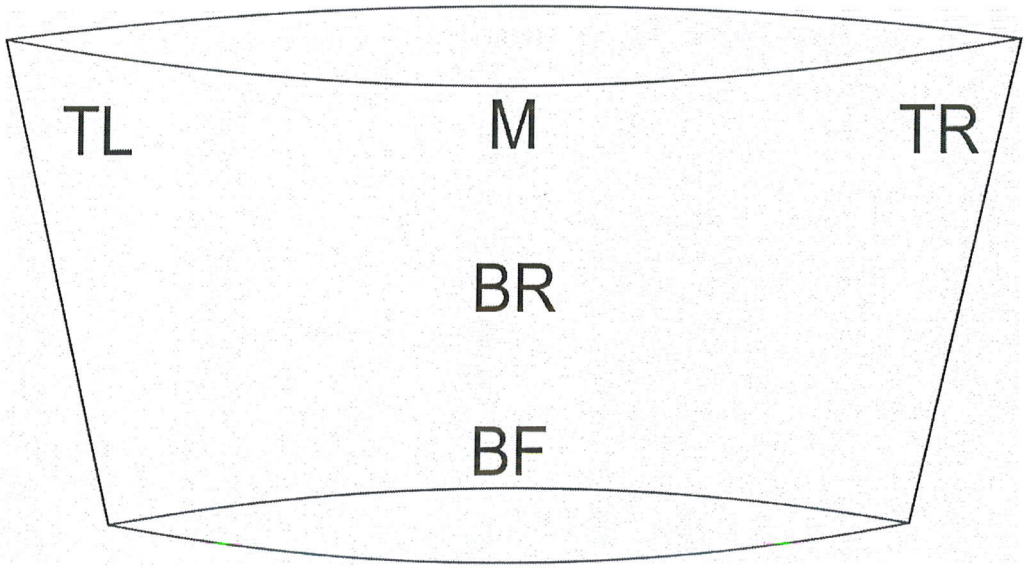

Fig. No.2

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

18.3 Sampling Plan Diagram of Octagonal Blender:

SIDE VIEW

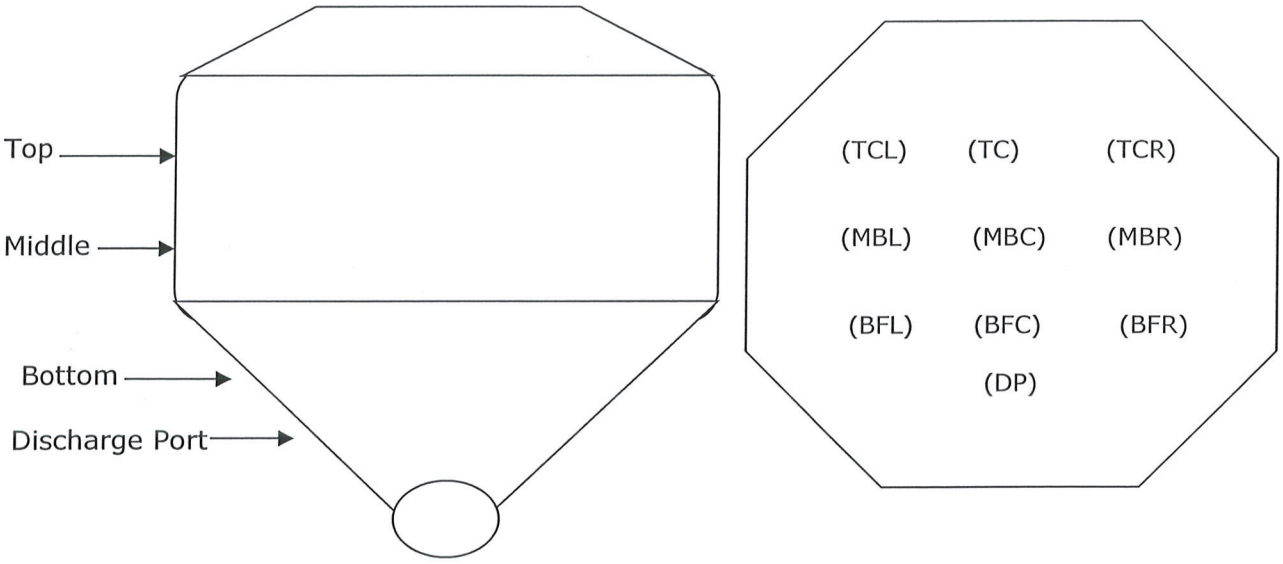

Fig-3

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