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To Perform Process Validation (Concurrent) of Metformin Hydrochloride Sustained Release Tablet to Ensure Optimised Reproducibility of Product.

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ABSTRACT
Validation is the process of establishment of documented evidence that the process, methods and procedure that are carried out will leads ti the expected results.
Sustained release are the type of solid dosages form that is designed to release the drugs over an extended period of time to achieve the therapeutic levels.
The aim of the present study is to perform concurrent process validation metformin Sustained release tablet to ensure optimization and reproducibility.to conduct the validation three consecutive batches were selected. All instruments required to carry out con-current validation were calibrated as per SOPs. All raw materials used in the manufacturing of the product were verified for the release status. Tablet was manufactured by wet granulation method. Granulation was excellent at 10 minutes .Drying was excellent at temperature of 50 ± 5^0C because %LOD was in limit . Blending was excellent at 8 minutes . For compression parameters like Average weight, Weight of 20 tablets, Hardness, Thickness, Diameter, Friability and Assay were according to specification.. All parameters at various stages of tablet manufacturing were as per specifications, so the process was validated properly along with the hold time studies.All parameters at various stages of tablet manufacturing were as per specifications, so the process was validated properly.
KEYWORDS: Con-current validation, Metformin Hydrochloride, Sustained Released , critical parameters, process validation

I. INTRODUCTION

The word validation means the assessment of validity. validation was first proposed by two FDA officials,Ted byers and bud loftus in 1979 in USA, to enhance the quality of pharmaceuticals and by the time it became an integral part of good Manufacturing practice.

As validation is an essential part of Quality Assurance, it covers the process ,system , facilities and aims at determining whether they perform their intended functions adequately and consistently as specified.Validation in itself does not improve the process but conforms that the process have been properly developed and are under control.

Pharmaceutical process validation is one of the important elements of GMP. Process Validation is establishment and performance of activities required to obtain documented assurance that a manufacturing process are accurate so that the requirement that are specified on product properties and process variables are compiled with. Process validation is one of the essential steps in maintaining and achieving the quality,safety,efficacy and purity of the finished product.

The basic aim of Quality system is to produce the product that id fit for the use and in order to meet this the proper knowledge and understanding of the process and performance is necessary. As we know the scenario the complexity of the medical products,sometime end product testing is alone not enough to assure the quality of the product for various reasons and some end product tests have restricted sensitivity.

Process validation is documenting and assuring the process within the predetermined specification and the end product will meet its expected criteria and quality attributes with reproducible and constant results.

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DEFINITIONS [13,14]

- According to USFDA, the goal of validation is the establishment of the documented evidence that will leads to high assurance that the process which is carried out will gives us the results that will meet the predetermined specification and various Quality attributes.
- According to European commession validation is the Action of providing the principles of GMP that any procedure, process, equipment, material,activity or system actually lead to the expected results.

OBJECTIVES OF PROCESS VALIDATION [30]

- Ensure the product with zero defect.
- Reduction of the regulatory non compliance.
- It helps in the elimination of the defective cost.
- Identification of the sources of variations that results from men ,materials, methods and equipments.
- The reproducibility of the product is ensured.
- Initiation of proper record keeping system that includes all the testing and manufacturing process.
- The quality and safety of the product must be assured.

SCOPE OF VALIDATION[30]

- The requirement of the validation is an adequate infrastructure comprises of documentation, manpower,organization and finances.
- The proper considerable preparation and planning of validation (including sampling and responsibilities of task during validation is performed).
- The personnel should be properly qualified and experienced.
- The proper participation of the Quality personnel and management personnel.

TYPES OF PROCESS VALIDATION [2-6,7,8]

- Prospective Validation
- Concurrent validation
- Retrospective Validation
- Re-validation

- **Prospective Validation**

Prospective validation is mainly an experimental plan that is known as validation protocol and it is executed before the process is put into commercial use.When the product is in development phase the process of production is broken into various stages and every single step is evaluated on the basis of theoretical data and trial consideration in order to determine the critical parameters that might have consequences on quality of final products.This kind of validation is likely to be carried out in case of introduction of the new drug products and the manufacturing process of those products.

This type of validation is usually carried in formulation and development phase to figure out each and every steps so that the minimization of variation and errors can be achieved when the respective batches are scaled for commercial purpose.

Various major steps are performed in this type of validation that are the formulation design,various steps of manufacturing,sampling collection planning with that of batch record design also raw material testing and specifications and compatibility testing, compilation of pilot runs,technology transfer from scale up to commercial batches along with listing the important processes and environmental controls.

- **Concurrent validation**

Concurrent validation is performed in commercial batches and the it is carried iut during the production of batches. In this type of validation both the production and quality control are involved.

In this type of validation the critical steps are monitored very closely and the variations are also monitored so that the final product that is produced will give us the results as per the documented evidence.

Generally three consecutive batches are taken and the manufacturing steps like mixing, granulation ,drying,blending, compression ,coating and packaging along with sampling and Quality control testing are also an important part.

- **Retrospective Validation**

Retrospective validation is performed when the drug is already in the market and performed after the prospective and concurrent process validation of the drug products This type of validation is based on the several lots and over period of time.

Retrospective validation is used for the processes, facilities and process controls in operations that have not undergone a formally documented validation processes.

In this type of validation to keep the process remained in control the historical manufacturing data is reviewed.

- **Re-validation**

Re-validation is performed when there is change in any methods, equipments ,process parameter, packing material, Raw material,vendor

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etc.

When there is failure to meet the product and process specification in batches then also requirement of validation

In any pharmaceutical plant re-validation is performed if any sort of changes is made in the batch size, formulation or when the consecutive batches of the manufacturing unit doesn't meet specification as stated in its product, when changes are made in the site location, equipment size and capacity or new advance equipment are introduced for the further processing or when new manufacturing methods and control are to be followed or changes are made in them.

There are two type of re-validation:

- Re-validation after change in process, equipment,production area and system.
- Periodic re-validation.

1.5. DOCUMENTATION IN VALIDATION [30]:

The various documentation are prepared during the validation process they are as follows;

- Standard operating process(SOPs)
- Validation protocol (VP)
- Validation master plan (VMP)
- Validation reports (VR)
- Validation master plan (VMP)

The Process validation activities can be described in three stages.[9,10,11]

- **Stage 1** – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Pre-validation phase or the qualification phase: It covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification installation qualification, master production documents, operational qualification, process capability.

- **Stage 2** – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing. Designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.
- **Stage 3** – Continued Process Verification/Validation Maintenance Phase: Ongoing assurance is gained during routine production that the process remains in a state of control. Validation requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures. At this stage the validation team also assures that there have been no changes/ deviations that should have resulted in re-qualification and re-validation.

Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.[11]

According to the FDA, assurance of product quality is derived from careful and systemic attention to a number of important factors, including: selection of quality components and materials, adequate product and process design, and (statistical) control of the process through in-process and end-product testing. Thus, it is through careful design (qualification) and validation of both the process and its control systems that a high degree of confidence can be established that all individual manufactured units of a given batch or succession of batches that meet specifications will be acceptable.

Elements of Validation[12,14-17]

Definition of the Qualification:

Qualification is defined as it is documented evidence that specific equipment or a system is feet or ready for intended use. Qualification is divided in to following

- Design Qualification,
- Installation Qualification
- Operational Qualification,
- Performance Qualification,
- Change Control

Process validation for solid dosage forms

Materials:

Metformin Hydrochloride (Active), Polyvinyl Pyrrolidone (PVP) K30 (Diluent &Binder), Isopropyl alcohol(Binder),HPMC K100 M (Lubricant), Strearic.acid (Lubricant) All the materials used for manufacturing of the tablets were of IP grade and chemicals used in the analysis were of analytical grade. Table No 1

Reagents: Absolute ethanol, Distilled Water.

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Machineries:
Machineries and equipments used were given in Table no. 3. All equipment and machineries were qualified as per SOPs before use.

Sifting:
Metformin HCl and PVP K-30 passed through 30 meshes sieve in a Mechanical sifter. All the materials are mixed in geometric proportional.

Dry mixing: The dry-mixing step involves mixing of specified product with other additives using Rapid Mixer Granulator (RMG). Samples were taken from top, middle and bottom of the High Shear Mixer Granulator at 6 min, 8 min and 10 min in which each sample contains 3.8 gm approx. for each location. Each was assay for the content and Quantity for the Assay as per Specification is 90 – 110%. Table No. 6

Binder Preparation:
Dissolve PVP k-30 in IPA.

Granulation:
During Granulation the dry mixed powder is transformed into granules by wet granulation method to increase the flow ability or compressibility. The granulation process helps in converting the powder into free flowing near spherical granular mass. Amount of granulating solution added, mixing speed and time are critical variables.

Drying:
At the end of 3 min, 4 min and 5 min. 3.8 gm samples were taken from top, middle and bottom of the Fluidised Bed Dryer (FBD). The samples were analysed by calculating the moisture content through Ir moisture Balance. In which sample place in the pan, light from the IR source fall on the sample and digital analog shows the reading of moisture content of the sample placed on the pan; specification is NMT 3%.

Blending: After addition of lubricant at 4 min, 6 min and 8 min samples were taken from the blender. The samples were analysed for Bulk analysis parameters as per QC Assay 95-105% and other parameters as per QC spec. Table No. 7

Compression: At the stage of compression at 11 RPM, 13 RPM and 15 RPM tablets were taken. Tablets were analysed for different tests such as Weight variation, average Weight, Thickness, Diameter, Hardness, Friability and Assay and compare with the specifications.See Table No.-8.

Blister Packing:
The samples were taken at different speed of the blister machine at speed of 35Blisters/min,40 Blisters/min,55 Blisters/min,50 Blisters/min at forming temperature 126^0c,$130^0$and 145 ^{0}c and 150^0c sealing temperature 160^0c, 170^0c,175^0c,178^0c and 180^0c respectively.table No. 9,10,11.

Test to be performed:
Weight Variation
WEIGHT VARIATION:
Weigh 20 tablets separately. Check whether all the tablets are within the specified limit or not.

CALCULATION:
% Max variation = Max. weight - Avg. weight x 100
Avg. weight
% Min variation = Min. weight - Avg. weight x 100 Table No. 8

Thickness
Twenty tablets taken as samples were from each batch and there thickness and diameter was measured by using digital vernier caliper. Results are shown in Table no. 8

Hardness
Measure hardness of 5 tablets with the help of a calibrated Hardness tester. Calculate average hardness as
below.
Sum of Hardness of 5 tablets
Average Hardness = ----------
= kg/sq.cm Table No. 8

Friability
TFor tablets with an average weight of 0.65g or less take a sample of whole tablets corresponding to about 6.5g and for tablets with an average weight of more than 0.65g take sample of 10 whole tablets.
Take the corresponding weight of tablets(X) as per above put them in Friability test apparatus. Set the instrument for 100 revolutions. Run the instrument. After 100 revolutions, take out the intact tablets from the instrument. All the tablets must be intact. Once again take the weight of tablets (Y) and calculate the friability by the following formula-
X - Y
Friability = ---------- x 100
X
= % Table No. 8

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Dissolution:
Apparatus No.2,
Medium. 1000 ml of phosphate buffer pH 6.8 prepared by dissolving 27.22 g of monobasic potassium phosphate in 1000 ml of water. Take 250 ml of this solution, add 112 ml of 0.2 M sodium hydroxide solution, then dilute to 1000 ml with water,
Speed and time. 100 rpm and 1 hour, 3 hours and 10 hours.
Withdraw a suitable volume of the medium and filter. Measure the absorbance of the filtered solution, suitably diluted if necessary, at the maximum at about 233 µm. Calculate the content ofC 4 H 11 N 5 .HCl in the medium from the absorbance obtained from a solution of known concentration of Metformin hydrochloride Table No. 8
RS in the same medium.
D. Not less than 25 per cent and not more than 50 per cent in 1 hour, not less than 45 per cent and not more than 75 per cent in 3 hours and not less than 80 per cent in 10 hours of C 4 H 11 N 5 HCl in the medium.

Assay:
Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 0.1 g of Metformin HCl, shake with 70 ml of water for 15 minutes, dilute to 100.0 ml with water and filter. Dilute 5.0 ml of the filtrate to 50.0 ml with water. Further dilute 5.0ml to 50.0 ml with water and measure the absorbance of the resulting solution at the maximum at about 232 nm. Calculate the content of C 4 H 11 N 5 HCL from the absorbance obtained by carrying out the assay simultaneously using Metformin hydrochloride RS. Table No. 8
Calculation:
Test abs X Std wt X Std conc. X purity X (100-LOD) X Avg. wt X 100
Std abs X Test wt X Test conc. X 100 X 100 X claim

=----------%

II. RESULT AND DISCUSSION

Table No. 1

S. No.	Item	RM Specification	Qty / Tab (mg)	Qty/Batch (kg)	Function
1	Metformin HCl	IP	1000	50.00	API
2.	PVPK-30	IP	15	0.750	Diluent
3.	PVPK-30	IP	15	0.750	Binder
4.	IPA	IP	0.18 ml.	9.0 lit.	Binder
5.	HPMC K-100M	IP	210	10.500	Lubricants
6.	Purified Talc	IP	12	0.600	Lubricants
7.	Stearic acid	IP	13	0.650	Lubricants
	Total		**1265 mg**		

Table No. 2

Parameters	Standards	Range
Appearance:	A White Colour, Oblong shape, Sustained Release uncoated tablet.	Not applicable
Average weight of 20 tablets:	25.3± 5% gram	24.03-26.56gm
Individual Weight Variation:	1265± 5% of average weight	1201.75-1328.25 mg
Thickness:	6.8 mm ± 0.5	6.3 mm – 7.3 mm
Hardness:	Not less than 5.00 Kg/cm^2	Not applicable
Friability:	Not more than 1.0%	Not applicable
Disintegration:	Not more than 15.00 min.	Not applicable

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Table No. 3

Sr. No.	Equipment Name	Make/model	Qualification Status
1.	Sifter	Saimach Pharmatech	Qualified
2.	Rapid mixer granulator	Saimach Pharmatech	Qualified
3.	Paste Making Vessel	Saimach Pharmatech	Qualified
4.	Fluid bed dryer	Saimach Pharmatech	Qualified
5.	Multimill	Saimach Pharmatech	Qualified
6.	Octagonal blender	Saimach Pharmatech	Qualified
7.	Rotary Compression	Saimach Pharmatech	Qualified
8.	Tablet De-Dusting Unit	Saimach Pharmatech	Qualified
9.	Blister packing	Saimach Pharmatech	Qualified
10.	Weighing Balance	pinnacale	calibrated
11.	Frability Tester	elctrolab	calibrated
12.	Hardness tester	elctrolab	calibrated
13.	Dissolution	Electrolab	calibrated
14.	UV Spectrophotometer	Agilent	calibrated

Table No. 4

Steps	**Control Variable**	**Critical Parameters to be checked**
Dry mixing	Impeller speed Time	Mixing time
Binder preparation and addition.	Time Temperature,	Mixing speed
Drying Inlet/outlet temperature & time	Inlet/outlet temperature & Drying time	Initial drying:…....°C Drying time:

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Lubrication	Time speed	Mixing time and speed
Compression	Pressure and turret speed	Machine speed
Packing	Packing machine speed	Speed and temperature

Table No. 5

Stage of manufacturing	**Sampling interval**	**Sampling locations**	**Sample qty per location**	**Analytical parameters**	**Acceptance criteria**
Dry mixing	6 min. 8 min. 10 min.	T1, T2, T3, M1, M2, M3, B1, B2, B3, C1 for each time point	3X 1265= 3.8 gm approx. for each location	Assay of Metformin HCL	Assay: 95-105% & % RSD NMT 5.
Lubrication	4 min. 6 min.	T1, T2, T3,T4 B1, B2, B3,B4, C1, C2 for each time point	3X 1265 = 3.8 gm approx. for each location	Assay of Metformin HCL	Assay: 95-105% & % RSD NMT 5.
	8 min	Composite one samples	50 gm	Bulk analysis parameters as per QC	Assay 95-105% and other parameters as per QC spec.
Compression	Optimum speed	Initial Middle End	80 tablets at each stage	Assay, CU and physical parameters	As per QC spec for semifinish product
	Min speed & Max. speed	initial	80 tablets at each speed	Assay, CU & physical parameters	As per QC spec for semifinish product

Table No. 6

STAGE	**DRY MIXING**

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	Sampling location and Assay in % (Limit: 90-110 %)											
MMATERIAL	**Metformin Hcl**											
TTIME INTERVAL	**6.0 min.**											
BATCH NO.	**T1**	**T2**	**T3**	**M1**	**M2**	**M3**	**B1**	**B2**	**B3**	**C1**	**Mean**	**% RSD (NMT 5%)**
METT-22015	123.69	126.55	124.63	124.49	125.13	122.92	125.33	125.47	123.79	122.88	124.48	0.05
METT-22016	120.26	120.22	120.71	122.53	122.45	122.45	119.51	119.56	119.69	119.74	120.71	0.11
METT-22017	121.66	121.66	121.65	121.49	121.56	121.49	119.51	119.56	119.69	119.6	120.78	0.08
TTIME INTERVAL	**8.0 min.**											
METT-22015	122.93	127.36	124.69	132.32	123.21	114.94	114.46	114.48	114	112.2	120.06	0.03
METT-22016	123.63	125	124.96	124.13	124.26	124.11	124.89	124.84	124.89	123.43	124.41	0.12
METT-22017	121.65	121.65	119.74	121.66	121.56	121.49	121.94	121.94	122.33	122.48	121.644	0.09
TTIME INTERVAL	**10.0 min.**											
METT-22015	103.55	105.7	104.76	102.49	104.67	103.88	101.37	103.37	105	106.05	104.08	0.04
METT-22016	104.46	104.74	106.35	102.91	103.38	105.3	104.65	104.51	101.61	106.1	104.40	0.032
METT-22017	101.46	102.48	103.1	102.07	102.25	101.42	102.54	101.83	101.82	102.45	102.142	0.06

Table No. 7

STAGE	**LUBRICATION**
	Sampling location and Assay in % (Limit: 90-110 %)
MMATERIAL	**Metformin Hcl**
TTIME INTERVA	**4.0 min.**

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L												
BATCH NO.	**T1**	**T2**	**T3**	**M1**	**M2**	**M3**	**B1**	**B2**	**B3**	**C1**	**Mean**	**% RSD (NMT 6%)**
METT-22015	96.39	96.19	97.16	98.4	98.2	97.06	98.44	97.36	100.38	97.73	0.03	96.39
METT-22016	98.31	98.31	97.81	99.98	103.86	103.9	103.56	100.24	97.99	100.44	0.12	98.31
METT-22017	99.37	98.88	98.9	99.04	96.14	96.41	95.83	95.87	93.52	97.11	0.12	99.37
TTIME INTERVAL	**6.0 min.**											
METT-22015	98.25	96.91	98.24	97.46	97.07	97.21	98.76	97.6	98.36	97.76	0.04	98.25
METT-22016	97.95	102.02	101.83	97.99	101.44	102.95	102.83	102.77	100.06	101.09	0.07	97.95
METT-22017	98.49	98.39	98.22	98.35	100.58	100.33	100.26	100.26	97.14	99.11	0.14	98.49
TTIME INTERVAL	**8.0 min.**											
METT-22015	90.35%	97.03	90.19	95.78	95.16	98.62	95.21	99.15	95.19	95.185	0.09	90.35
METT-22016	98.22%	98.7	97.95	97.77	98.59	98.49	98.31	102.69	98.86	98.84	0.07	98.22
METT-22017	98.13%	98.05	98.29	98.26	94.56	94.92	94.05	94.37	97.14	96.41	0.16	98.13

Table No. 8

Stage		**COMPRESSION**				
PRODUCT		**Metformin Hcl SR 1000 mg Tablet**				
Standards		**Speed.**	**Appearance**	**Wt. of 20 Tablets**	**Individual Weight Variation**	**Thickness**
	Standard	**15**	**To Comply**	**25.3 gm ± 5%**	**1265**± 5%	**6.8± 5%**
Batch No.	**Stages**					
METT-22015	Initial	12	Complies	25.374 g.	1268.7 mg.	6.88mm
METT-22016		12	Complies	25.35 g.	1267.5 mg.	7.046mm
METT-22017		12	Complies	25.314 g.	1265.7 mg.	6.892mm

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METT-22015	Middle	13	Complies	25.266 g.	1263.3 mg.	6.9mm
METT-22016		13	Complies	25.28 g.	1264 mg.	6.901mm
METT-22017		13	Complies	25.3 g.	1264.1 mg.	6.892mm
METT-22015	End	11	Complies	25.38 g.	1268.9 mg.	6.97mm
METT-22016		11	Complies	25.372 g.	1268.6 mg.	7.013mm
METT-22017		11	Complies	25.43 g.	1271.42 mg.	6.969mm
METT-22015	Min. Speed	11	Complies	25.272 g.	1263.6 mg.	6.609mm
METT-22016		11	Complies	25.074 g.	1253.7 mg.	6.966mm
METT-22017		11	Complies	25.45 g.	1272.8 mg.	6.948mm
METT-22015	Max. speed	15	Complies	25.18 g.	1259.0 mg.	6.627mm
METT-22016		15	Complies	25.514 g.	1275.7 mg.	7.001mm
METT-22017		15	Complies	25.44 g.	1272.1 mg.	6.948mm
METT-22015	Composite	13	Complies	25.22 g.	1261.1 mg.	6.93mm
METT-22016		13	Complies	25.338 g.	1266.9 mg.	6.99mm
METT-22017		13	Complies	25.4 g.	1269.6 mg.	6.947mm
Stage		**COMPRESSION**				
PRODUCT		**Metformin Hcl SR 1000 mg Tablet**				
Standards		**Speed.**	**Hardness**	**Frabikity**	**Dissolution**	**Assay**
	Standard	**15**	**NLT 5kg/cm2**	**NMT 1%**	**NLT 80%**	**NLT 90% & NMT 110%**
Batch No.	**Stages**					
METT-22015	Initial	12	16.19 kg/cm2	0.61%	Max.: 99.82% Min.: 96.04%	98.29%
METT-22016		12	18.875 kg/cm2	0.82%	Max.: 94.89% Min.:	98.72%

					92.54%	
METT-22017		12	17.808 kg/cm2	0.11%	Max.: 99.58% Min.: 97.51%	97.51%
METT-22015	Middle	13	15.357 kg/cm2	0.23%	Max.: 105.22% Min.: 100.28%	97.56%
METT-22016		13	18.84 kg/cm2	0.74%	Max.: 101.06% Min.: 97.82%	99.87%
METT-22017		13	19.057 kg/cm2	0.12%	Max.: 101.19% Min.: 98.51%	98.36%
METT-22015	End	11	16.36 kg/cm2	0.81%	Max.: 108.35% Min.: 99.76%	104.32%
METT-22016		11	20.096 kg/cm2	0.75%	Max.: 101.26% Min.: 96.20%	96.11%
METT-22017		11	17.572 kg/cm2	0.73%	Max.: 99.84% Min.: 98.51%	96.41%
METT-22015	Min. Speed	11	15.565 kg/cm2	0.60%	Max.: 100.12% Min.: 95.26%	96.55%
METT-22016		11	18.428 kg/cm2	0.79%	Max.: 93.74% Min.: 92.12%	97.10%
METT-22017		11	18.39 kg/cm2	0.15%	Max.: 99.58% Min.: 97.51%	97.18%
METT-22015	Max. speed	15	14.395 kg/cm2	0.57%	Max.: 98.08% Min.: 94.31%	99.51%
METT-22016		15	18.365 kg/cm2	0.85%	Max.: 102.51%	101.48%

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					Min.: 97.64%	
METT-22017		15	18.39 kg/cm2	0.15%	Max.: 99.84% Min.: 98.52%	95.69%
METT-22015	Composite	13	15.297 kg/cm2	0.63%	Max.: 107.32% Min.: 98.45%	99.43%
METT-22016		13	19.354 kg/cm2	0.80%	Max.: 100.13% Min.: 97.64%	99.76%
METT-22017		13	17.572 kg/cm2	0.31%	Max.: 101.88% Min.: 98.45%	101.88%

Table No. 9

Stage		**PACKING**					
		Batch No.: METT-22015					
Tests	**Standards**	**Results**					
		Initial	**Middle**	**End**	**Minimum**	**Maximum**	**Composite**
Machine Speed	50 Blisters /min	35	45	35	30	55	50
Forming Temperature	140	130	145	150	126	150	145
Sealing Temperature	175	170	178	175	160	180	175
Blister Quality	To comply	Comply	Comply	Comply	Comply	Comply	Comply
Leak Test	To comply	Comply	Comply	Comply	Comply	Comply	Comply
Printing Details	To comply	Comply	Comply	Comply	Comply	Comply	Comply
Assay Metformin HCl	NLT 90% & NMT 110 %	101.44%	100.06%	98.7%	98.86%	102.68%	98.22%

Table No. 10

Stage		**PACKING**					
		Batch No.: METT-22016					
Tests	**Standards**	**Results**					
		Initial	**Middle**	**End**	**Minimum**	**Maximum**	**Composite**
Machine Speed	50 Blisters/min	35	45	35	30	55	50

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Forming Temperature		170	130	145	150	126	150	145
Sealing Temperature		140	170	178	175	160	180	175
Blister Quality		To comply	Comply	Comply	Comply	Comply	Comply	Comply
Leak Test		To comply	Comply	Comply	Comply	Comply	Comply	Comply
Printing Details		To comply	Comply	Comply	Comply	Comply	Comply	Comply
Assay	Metformin HCl	NLT 90% & NMT 110 %	98.53%	99.29 %	99.13 %	97.34%	101.48%	101.29%

Table No. 11

Stage		**PACKING**					
		Batch No.: METT-22017					
Tests	**Standards**	**Results**					
		Initial	**Middle**	**End**	**Minimum**	**Maximum**	**Composite**
Machine Speed	50 Blisters/min	35	45	35	30	55	50
Forming Temperature	170	130	145	150	126	150	145
Sealing Temperature	140	170	178	175	160	180	175
Blister Quality	To comply	Comply	Comply	Comply	Comply	Comply	Comply
Leak Test	To comply	Comply	Comply	Comply	Comply	Comply	Comply
Printing Details	To comply	Comply	Comply	Comply	Comply	Comply	Comply
Assay Metformin HCl	NLT 90% & NMT 110 %	99.43%	99.48%	99.85%	99.26%	99.34%	100.41%

Table No. 12

Stage		**COMPRESSION**			
PRODUCT		**Metformin Hcl SR 1000 mg Tablet**			
Standards		**Appearance**	**Wt. of 20 Tablets**	**Individual Weight Variation**	**Thickness**
	Standard	**To Comply**	**25.3 gm ± 5%**	**1265**± 5%	**6.8± 5%**
Batch No.	**Stages**				
METT-22015	Initial	Complies	25.22 g.	1261.1 mg.	6.93mm
METT-22016		Complies	25.338 g.	1266.9 mg.	6.99mm
METT-22017		Complies	25.4 g.	1269.6 mg.	6.947mm

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METT-22015	**14th day**	Complies	25.412 g.	1270.6 mg.	6.959mm
METT-22016		Complies	25.43 g.	1271.7 mg.	6.926mm
METT-22017		Complies	25.38 g.	1268.9 mg	6.931mm
METT-22015	**30th day**	Complies	25.142 g.	1257.1 mg.	6.761mm
METT-22016		Complies	25.154 g.	1257.7 mg.	6.794mm
METT-22017		Complies	25.138 g.	1256.9 mg	6.817mm
METT-22015	**60 day**	Complies	25.136 g.	1256.8 mg.	7.005mm
METT-22016		Complies	25.276 g	1263.8 mg	7.027mm
METT-22017		Complies	25.332 g.	1266.6 mg.	7.026mm
METT-22015	**90 day**	Complies	25.212 g.	1260.6 mg.	6.856mm
METT-22016		Complies	25.421 g.	1271.08 mg.	6.9615mm
METT-22017		Complies	25.386 g.	1269.315 mg.	6.925 mm

Table No. 13

Stage		**COMPRESSION**			
PRODUCT		**Metformin Hcl SR 1000 mg Tablet**			
Standards		**Hardness**	**Frabikity**	**Dissolution**	**Assay**
	Standard	**NLT 5kg/cm2**	**NMT 1%**	**NLT 80%**	**NLT 90% & NMT 110%**
Batch No.	**Stages**				
METT-22015	Initial	15.297 kg/cm2	0.63%	Max.: 107.32% Min.: 98.45%	99.43%
METT-22016		19.354 kg/cm2	0.80%	Max.: 100.13% Min.: 97.64%	99.76%
METT-22017		17.572 kg/cm2	0.31%	Max.: 101.88% Min.: 98.45%	101.88%
METT-22015	**14th day**	19.154 kg/cm2	0.50%	Max.: 101.26% Min.: 96.20%	101.26%
METT-22016		19.108 kg/cm2	0.23%	Max.: 101.26% Min.: 96.20%	99.47%
METT-22017		19.743 kg/cm2	0.34%	Max.: 101.266% Min.: 96.2028%	99.40%

METT-22015	**30th day**	14.303 kg/cm2	0.16%	Max.: 98.79% Min.: 93.51%	99.44%
METT-22016		21.049 kg/cm2	0.13%	Max.: 96.71% Min.: 93.51%	100.33%
METT-22017		21.049 kg/cm2	0.15%	Max.: 98.79% Min.: 95.76%	100.18%
METT-22015	**60 day**	14.564 kg/cm2	0.32%	Max.: 103.08% Min.: 97.62%	98.48%
METT-22016		20.576 kg/cm2	0.15%	Max.: 101.58% Min.: 96.29%	96.21%
METT-22017		20.587 kg/cm2	0.35%	Max.: 101.58% Min.: 96.29%	98.79%
METT-22015	**90 day**	14.159 kg/cm2	0.09%	Max.: 98.85% Min.: 92.46%	99.05%
METT-22016		19.347 kg/cm2	0.50%	Max.: 98.75% Min.: 96.70%	97.76%
METT-22017		18.209 kg/cm2	0.50%	Max.: 108.24% Min.: 93.88%	95.85%

III. CONCLUSION

Based on the above summary the Manufacturing Quality Control tesing and Packing process of Metspire1000 Sustained Release tablets of batch size 0.5 lakh tablets (MET-22015,MET-22016,MET-22017) was performed successfully.

All the parameters tested was found in specified limits and the concurrent process validation was carried to provide highly consistent data.

The process stands validated and it provided a high degree of assurance meeting the different quality attributes consistently within the standard set parameters at various stages of the operations of validation.

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