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PROCESS VALIDATION OF EXTENDED-RELEASE BI-LAYERED TABLET CONTAINING DAPAGLIFLOZIN, SITAGLIPTIN & METFORMIN HYDROCHLORIDE

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Keywords:

Dapagliflozin, Sitagliptin, Metformin hydrochloride, and Process validation

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ABSTRACT: The Purpose of research was to study process validation for Dapagliflozin 10 mg, Sitagliptin 100 mg and Metformin Hydrochloride 500 mg (Extended Release) Bilayered Tablets. The critical process parameters were identified with the help of process capability and evaluated by challenging its lower & upper release specifications. Three initial process validation batches (I, II, III) of the same size, method, equipment & validation criteria were taken. The critical parameters involved in sifting, dry mixing, preparation, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication, compression stage, coating & finished stage were identified and evaluated as per validation master plan. The process indicated that this process validation provides high degree of assurance that manufacturing process produces a product meeting its predetermined specification and quality attributes. Process validation is the validation of each and every step of the processes which involves series of activities carried out in order to have the assurance of the products manufactured. Each and every step should be scientifically planned, conducted and documented appropriately and for this one should have sound knowledge and understanding regarding the process as well as the product.

INTRODUCTION:

Process validation as per USFDA: Process validation, as outlined by the United States Food and Drug Administration (FDA), is a systematic approach to ensuring the consistency and reliability of manufacturing processes in industries such as pharmaceuticals, medical devices, and biotechnology. It is an integral part of current Good Manufacturing Practices (cGMP) regulations, aimed at safeguarding public health by ensuring that products meet their intended quality standards.

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The FDA's process validation guidance emphasizes the need for manufacturers to demonstrate control over critical aspects of production that can affect product quality, safety, and efficacy. This involves establishing documented evidence that the manufacturing process consistently produces products meeting predetermined specifications and quality attributes. Process validation typically consists of three stages: process design, process qualification, and continued process verification.

During process design, manufacturers define the critical parameters and variables of the production process based on scientific principles and risk assessment. Process qualification involves conducting experiments and studies to confirm that the process is capable of consistently producing acceptable product quality. Continued process verification entails ongoing monitoring and

assessment to ensure that the validated process remains in a state of control throughout its lifecycle. By adhering to FDA guidelines on process validation, manufacturers can mitigate risks associated with product variability, contamination, and manufacturing errors, thereby enhancing product quality, safety and compliance with regulatory requirements [1].

WHO Guideline Define Process Validation: The World Health Organization (WHO) provides guidelines for process validation in pharmaceutical manufacturing to ensure that products consistently meet quality standards. According to WHO guidelines, process validation is defined as:

"Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes [2].

This definition highlights several key aspects of process validation:

Documented Evidence: Process validation requires comprehensive documentation to demonstrate that the manufacturing process has been thoroughly evaluated and validated.

Operated within Established Parameters: The process must be conducted within predetermined parameters, including critical process parameters (CPPs) and operating ranges, which have been determined through scientific evaluation and risk assessment.

Effective and Reproducible Performance: The validated process should consistently produce medicinal products that meet predefined specifications and quality attributes. This ensures that the process is capable of reliably manufacturing products of the desired quality.

Meeting Predetermined Specifications: Process validation aims to confirm that the manufactured products meet their predetermined quality standards, including specifications for identity, strength, purity and other quality attributes. Overall, process validation according to WHO guidelines is a systematic approach to ensuring the reliability and consistency of pharmaceutical manufacturing processes, ultimately contributing to the production of safe, effective, and high-quality medicinal products [3].

Types of Process Validation:

Prospective Validation: This type of validation occurs before commercial production begins. It involves systematically collecting and evaluating data to demonstrate that a manufacturing process is capable of consistently producing products meeting predetermined quality specifications. Prospective validation typically includes process design, qualification, and verification activities.

Concurrent Validation: Concurrent validation occurs during the early stages of commercial production. It involves monitoring and evaluating process performance and product quality in real-time while production is ongoing. This approach allows for immediate identification and correction of any issues that may arise during production.

Retrospective Validation: Retrospective validation involves validating a process based on historical data and manufacturing records. This approach may be used when there is a long history of production data available, and there is confidence that the process has consistently met quality standards in the past. However, it may not be suitable for new processes or those with significant changes.

Revalidation: Revalidation is the process of repeating validation activities periodically or whenever significant changes are made to the manufacturing process, equipment, or critical parameters. Revalidation ensures that the process remains in a state of control and continues to produce products of the desired quality after changes have been implemented.

Validation of Cleaning Procedures: Cleaning validation is a critical aspect of pharmaceutical manufacturing, especially for equipment used in multi-product facilities. It involves demonstrating that cleaning procedures effectively remove residues of previous products, cleaning agents, and microbial contaminants to prevent cross-contamination and ensure product quality and safety.

Each type of process validation plays a crucial role in confirming the reliability, consistency, and compliance of manufacturing processes with regulatory requirements and quality standards. The selection of the appropriate validation approach depends on factors such as the stage of production, the complexity of the process, and the specific regulatory requirements applicable to the industry [4, 5].

Process Validation Approch:

General Consideration: Process validation is a critical aspect of ensuring the quality and reliability of manufacturing processes, regardless of whether a therapeutic item is produced using an enhanced or standard method. Before a product is introduced to the market, its manufacturing process must undergo approval. In certain exceptional cases, concurrent approval may be granted. The validation process should confirm the suitability of the control strategy for both the process design and the quality of the final product. This includes covering every strength produced and every manufacturing facility used for producing the marketed product. In situations where variations exist in strengths, batch sizes, or pack sizes, a bracketing strategy may be suitable. However, it is crucial that validation includes all recommended locations. For each product, process validation data demonstrating the suitability of the manufacturing process at each manufacturing location should be generated. These data should be retained at the manufacturing site and be readily accessible for examination if not specified in the dossier. Validation should be conducted in compliance with Good Manufacturing Practice (GMP) guidelines. Process validation can be executed in a conventional manner, regardless of the chosen development strategy. However, if an improved development method has been utilized or if substantial product and process knowledge have been gained from historical data and manufacturing experience, continuous process verification may also be implemented. It may be necessary to combine continuous process verification with traditional process validation. Continuous process verification, commonly facilitated by in-line, on-line, or at-line monitoring techniques, provides additional information and knowledge about the process. This information can be invaluable in making process changes and improvements.

Process Validation Approach for Product: Process validation is a systematic approach aimed at gathering and analyzing data to scientifically demonstrate the capability of a manufacturing process to consistently produce high-quality products. This comprehensive evaluation spans from the initial process design phase through to commercial production. The process validation activities encompass three key stages, as outlined below:

Stage 1 – Process Design: During this initial stage, the commercial manufacturing process is meticulously defined. This process design is informed by knowledge acquired through developmental and scale-up activities. The aim is to establish a robust manufacturing process that ensures product quality and consistency.

Stage 2 – Process Qualification: In this stage, the process design undergoes rigorous evaluation to ascertain its capability for reproducible commercial manufacturing. Various parameters and variables are assessed to ensure that the process consistently meets predetermined quality standards and specifications. The goal is to confirm that the manufacturing process is capable of consistently producing products of the desired quality.

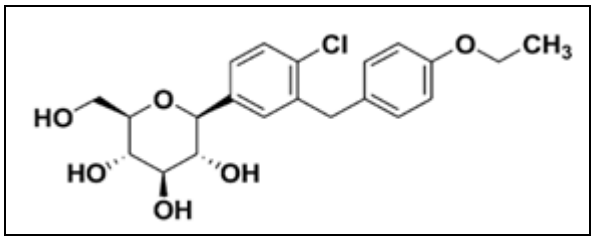
Stage 3 – Continued Process Verification: This stage involves ongoing monitoring and assessment during routine production to ensure that the validated process remains in a state of control. Through continuous monitoring and analysis, assurance is gained that the process continues to produce products meeting the required quality standards. Any deviations or discrepancies are promptly addressed to maintain process integrity and product quality [6, 7, 8, 9, 10].

Drug Profile:

Dapagliflozin: Dapagliflozin is an s-odium-glucose cotransporter 2 (SGLT2) inhibitor, and it was the first SLGT2 inhibitor to be approved. Suggested for the treatment of type 2 diabetes. Dapagliflozin improves glycemic management in adults when paired with diet and exercise because it causes glycosuria, which is the inhibition of glucose reabsorption in the proximal tubule of the nephron. Studies have looked into dapagliflozin as

a stand-alone medication or in combination with other oral hypoglycemic medications like insulin [11].

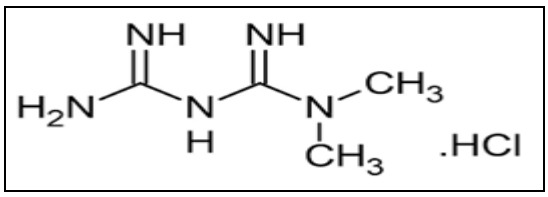
Structure:



CHEMICAL FORMULA: $C_{21}H_{25}CLO_6$

Metformin Hydrochloride: Metformin is a biguanide antihyperglycemic medication that is prescribed as first-line treatment for type II diabetes. Since, metformin reduces blood glucose levels in people with type II diabetes without producing hypoglycemia, it is regarded as an antihyperglycemic medication. It is frequently referred to as a "insulin sensitizer" since it lowers insulin resistance and lowers plasma fasting insulin levels in a way that is clinically meaningful. This medication also has the well-known benefit of mild weight loss, which makes it a good option for obese people with type II diabetes [12].

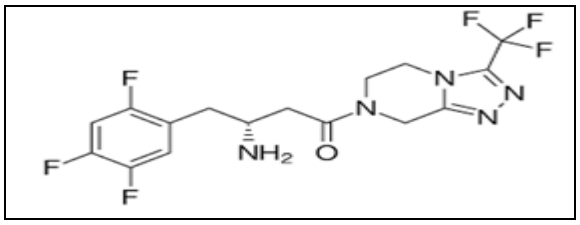
Structure:



CHEMICAL FORMULA- $C_4H_{12}CLN_5$

Sitagliptin: Sitagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor intended to help individuals with type 2 diabetes mellitus improve their glycemic control. It is taken in conjunction with diet and exercise. This drug improves blood sugar regulation by increasing insulin in response to glucose and decreasing glucagon [13].

Structure:



CHEMICAL FORMULA- $C_{16}H_{15}F_6N_5O$

MATERIAL AND METHODS:

Material:

- DapagliflozinPropanediol monohydrate eq. to Dapagliflozin
- Sitagliptin Phosphate Monohydrate eq. to Sitagliptin
- Microcrystalline Cellulose
- Colour Yellow Oxide Of Iron
- Dibasic calcium Phosphate Anhydrous
- PVPK 30
- Isopropyl Alcohol
- Colloidal Silicon Dioxide
- Croscarmellose sodium
- Magnesium Stearate
- Metformin hydrochloride
- Methocel k100 M
- Polyvinyl Pyrrolidone k-90
- Methocel K4 M
- H.P.M.C. (E 5)
- Methylene Dichloride

Product Description:

TABLE 1: PRODCYT DETAILS

Product Name	Dapagliflozin 10 mg, Sitagliptin 100 mg and Metformin Hydrochloride 500 mg (Extended Release) Tablets
Generic Name	Dapagliflozin and Metformin Tablets
Label claim	Each film coated Bilayered contains: DapagliflozinPropanediol Monohydrate Equivalent to Dapagliflozin ----------10 mg Sitagliptin Phosphate Monohydrate IP Equivalent to Sitagliptin----------100 mg Metformin Hydrochloride IP----------500 mg

	(As Extended Release) Colour: Yellow oxide of Iron.
Average weight	1000 mg
Shelf Life	24 Month
Dosage form	Oral solid dosage form
Therapeutic category	Dapagliflozin: Sodium-glucose co-transporter 2 (SGLT2) inhibitors Sitagliptin: Diabetes Mellitus, Type 2 Metformin: Anti diabetes
Storage condition	Store below 30°C. Protect from light and moisture.

Process Flow Diagram for the Manufacturing Process:

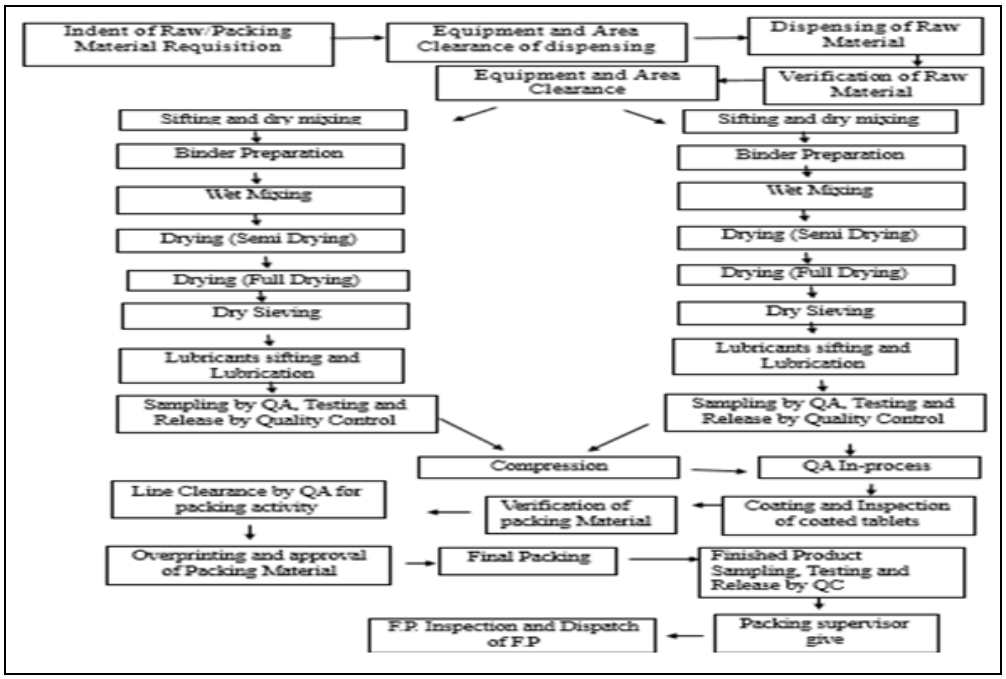


FIG. 1: MANUFACTURING FLOW DIAGRAM

Packing Flow Chart:

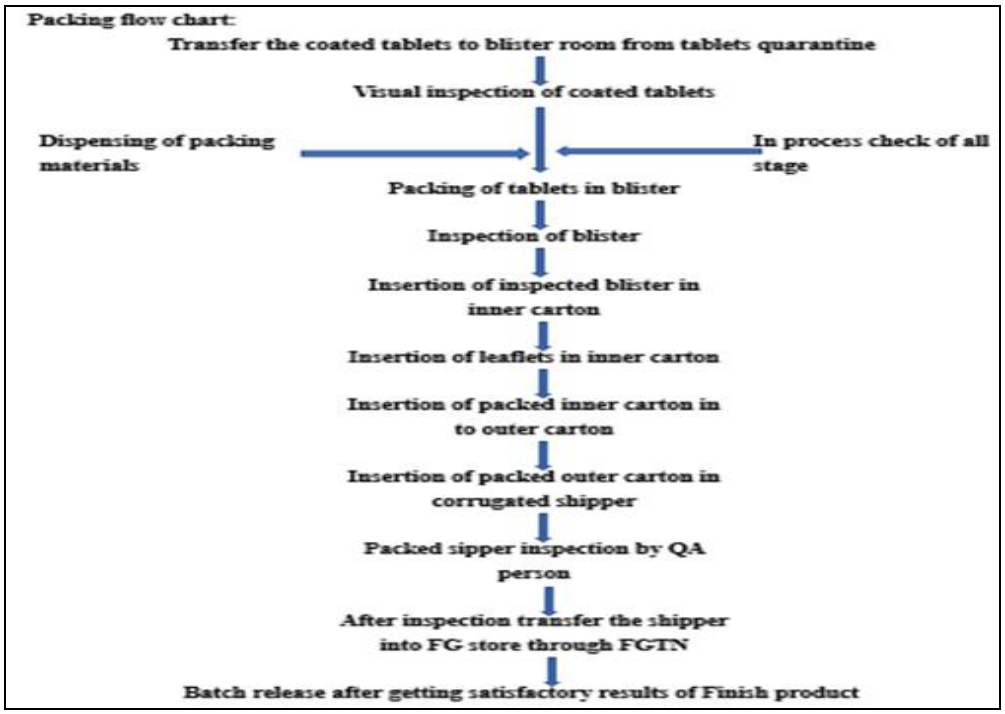


FIG. 2: PACKING FLOW DIAGRAM

Methodology:

Blending: Blending granules with other materials is crucial to ensure a uniform distribution of Dapagliflozin, Sitagliptin and Metformin Hydrochloride. This process is followed by mixing the blend to improve flow and prevent adhesion. The mixing speed and time are vital factors, with constant speed maintained to determine the appropriate mixing time.

Insufficient blending leads to non-uniform drug distribution and poor flow, while excessive blending can cause de-mixing and increased disintegration time. Proper blending is verified by assessing drug content uniformity at specified time intervals. Additionally, tests such as water content, bulk density, sieve analysis, compressibility index, content uniformity and RSD, angle of repose, and assay are conducted on final samples to gather comprehensive information.

Compression: In this step, the blended material is transformed into tablets according to set specifications. Key variables include the speed of the machine, tablet thickness, and hopper level. Regular checks are conducted to establish and maintain these variables. Parameters such as machine speed, tablet thickness, and hopper level are monitored at regular intervals to ensure adherence to specifications and consistent tablet quality.

- Description
- Weight variation (group and individual)
- Hardness
- Thickness
- Friability
- Disintegration time
- Dissolution time
- Content uniformity
- Microbial Limit Test
- Assay

Coating: The coating step involves applying a polymer film to the tablet surface, a critical process for tablet appearance and quality. Several variables such as pan RPM, Inlet and Exhaust temperatures, spray rate, gun distance, and air pressure significantly influence the coating process.

Pan RPM: Maintaining the specified RPM ensures even distribution of the coating solution on tablets. Deviations from this limit can lead to uneven coating distribution.

Inlet/Exhaust temperature: Proper temperature control is crucial for adequate drying of the coating. If temperatures stray from the specified range, issues like tablet twining, sticking, rough surfaces, or film cracking may occur.

Spray Rate: The spray rate directly affects coating uniformity. Improper spray rates can result in uneven coatings across the tablet surface.

Gun to Bed Distance: Maintaining an adequate distance between the spray gun and the tablet bed is essential. Incorrect distances can cause rough surfaces or over-wetting during coating.

Air Pressure: Both main and atomization compressed air pressures must be sufficient. Inadequate pressure levels can lead to issues such as peeling or rough surfaces on the tablets.

Finished: Finished product parameters play a crucial role in process validation, ensuring the quality and consistency of the final product.

These parameters are thoroughly evaluated to confirm that the manufacturing process consistently produces tablets that meet predetermined specifications and regulatory requirements. Key finished product parameters in process validation typically include:

- Appearance
- Weight Variation
- Hardness
- Thickness
- Friability
- Disintegration Time
- Dissolution Time
- Content Uniformity
- Impurities
- Assay
- Microbial limit test
- Residual solvent
- Related substance [14].

TABLE 2: SAMPLING PLAIN

Sr. no.	Processing step and sampling time	Sampling location	No. of sample	Tests
		Sampling plan for Dapagliflozin & Sitagliptin Layer:		
1.0	After drying at every interval	Upper Layer: U1 & U2 Middle Layer: M Lower Layer: L1 & L2 Rational: To challenge the in Process and LOD %	Sampling perform each interval	LOD
2.0	Pre-Lubrication (Part-I) (12 minutes)	Upper Layer: U1, U2 & U3 Middle Layer: M1, M2, M3 & M4 Lower Layer: L1, L2 & L3 Rational: To challenge the in Process and Blend uniformity.	3 X sampling (3 X 10 = 30 sample) X = average weight of tablets	Blend uniformity
3.0	Blending after Lubrication (3 minutes)	Upper Layer: U1, U2 & U3 Middle Layer: M1, M2, M3 & M4 Lower Layer: L1, L2 & L3 Rational: To challenge the in Process and Blend uniformity.	3 X sampling (3 X 10 = 30 sample) X = average weight of tablets	Blend uniformity
		Composite sample Rational: To challenge the in Process.	1 x 3 sample	Description, Assay, Partical size, Tap density, Bulk density & LOD
		Sampling plan for Metformin Hydrochloride:		
4.0	After drying at every interval	Upper Layer: U1 & U2 Middle Layer: M Lower Layer: L1 & L2 Rational: To challenge the in Process and LOD %	Sampling perform each interval	LOD
5.0	Pre-Lubrication (Part-I) (12 minutes)	Upper Layer: U1, U2 & U3 Middle Layer: M1, M2, M3 & M4 Lower Layer: L1, L2 & L3 Rational: To challenge the in Process and Blend uniformity.	3 X sampling (3 X 10 = 30 sample) X = average weight of tablets	Blend uniformity
6.0	Blending after Lubrication (5 minutes)	Upper Layer: U1, U2 & U3 Middle Layer: M1, M2, M3 & M4 Lower Layer: L1, L2 & L3 Rational: To challenge the in Process and Blend uniformity.	3 X sampling (3 X 10 = 30 sample) X = average weight of tablets	Blend uniformity
		Composite sample Rational: To challenge the in Process.	1 x 3 Sample	Description, Assay, Partical size, Tap density, Bulk density & LOD
7.0	Compression	Low speed	1 Sample	Description & Assay
		Medium speed	1 Sample	Description & Assay
		High speed	1 Sample	Description & Assay
		Low hardness / Compaction force	1 Sample	Description & Dissolution
		High hardness / Compaction force	1 Sample	Description & Dissolution
		Composite sample after completion of batch Rational: To ensure the physical and chemical parameters	1 Sample	Physical parameter, Assay & Dissolution
		Composite sample: Rational: To ensure the microbial parameters	1 Sample	MLT
8.0	Coating	Composite sample: Rational: To ensure the physical and chemical parameters.	1 Sample	Physical parameter, Assay, Related substance, Residual solvent & Dissolution
		Composite sample: Rational:	1 Sample	MLT

		To ensure the microbial parameters		
9.0	Finish	Composite sample: Rational: To ensure the physical and chemical parameters.	1 Sample	Physical parameter, Assay, Related substance, Residual solvent & Dissolution
		Composite sample: Rational: To ensure the microbial parameters	1 Sample	MLT
10.0	Blister challenge	High temperature and low speed Rational: To ensure the Physical and chemical parameters	1 Sample	Description, Assay & Related substance
		High temperature and medium speed Rational: To ensure the Physical and chemical parameters	1 Sample	Description, Assay & Related substance
		High temperature and High speed Rational: To ensure the Physical and chemical parameters	1 Sample	Description, Assay & Related substance

RESULT AND DISCUSSION:

LOD- First Batch: I

TABLE 3: DAPAGLIFLOZIN & SITAGLIPTIN LAYER

Time of drying	Observation				
	Target LOD Limit: 2.0 % - 3.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 04 minutes	3.55 %	3.23 %	3.46 %	3.41 %	3.40 %
After 02 minutes	2.46 %	2.33 %	2.50 %	2.52 %	2.39 %

TABLE 4: METFORMIN HYDROCHLORIDE LAYER

Time of drying	Observation				
	Target LOD Limit: 3.0 % - 4.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
			LOT-I		
After 05 minutes	4.21 %	4.36 %	4.18 %	4.49 %	4.55 %
After 04 minutes	3.26 %	3.42 %	3.24 %	3.28 %	3.36 %
			LOT-II		
After 05 minutes	4.98 %	4.83 %	4.95 %	4.92 %	4.97 %
After 04 minutes	4.10 %	4.26 %	4.27 %	4.39 %	4.22 %
After 02 minutes	3.19 %	3.24 %	3.11 %	3.34 %	3.16 %
			LOT-III		
After 06 minutes	4.37 %	4.28 %	4.16 %	4.10 %	4.22 %
After 04 minutes	3.13 %	3.21 %	3.34 %	3.19 %	3.20 %

Second Batch: II

TABLE 5: DAPAGLIFLOZIN & SITAGLIPTIN LAYER

Time of drying	Observation				
	Target LOD Limit: 2.0 % - 3.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 02 minutes	3.86 %	3.95 %	3.90 %	3.92 %	3.89 %
After 02 minutes	3.26 %	3.29 %	3.43 %	3.39 %	3.33 %
After 02 minutes	2.26 %	2.21 %	2.50 %	2.61 %	2.54 %

TABLE 6: METFORMIN HYDROCHLORIDE LAYER: (LOT-I)

Time of drying	Observation				
	Target LOD Limit: 3.0 % - 4.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 05 minutes	4.95 %	4.81 %	4.86 %	4.90 %	4.88 %

After 04 minutes	4.32 %	4.24 %	4.16 %	4.25 %	4.30 %
After 02 minutes	3.22 %	3.39 %	3.41 %	3.25 %	3.36 %

TABLE 7: METFORMIN HYDROCHLORIDE LAYER: (LOT-II)

Time of drying	Observation				
	Target LOD Limit: 3.0 % - 4.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 05 minutes	4.93 %	4.95 %	4.82 %	4.87 %	4.91 %
After 03 minutes	4.16 %	4.09 %	4.63 %	4.22 %	4.18 %
After 02 minutes	3.59 %	3.27 %	3.35 %	3.40 %	3.31 %

TABLE 8: METFORMIN HYDROCHLORIDE LAYER: (LOT-III)

Time of drying	Observation				
	Target LOD Limit: 3.0 % - 4.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 05 minutes	4.87 %	4.85 %	4.90 %	4.76 %	4.80 %
After 03 minutes	4.21 %	4.41 %	4.09 %	4.31 %	4.35 %
After 02 minutes	3.25 %	3.27 %	3.35 %	3.40 %	3.31 %

Third Batch: III

TABLE 9: DAPAGLIFLOZIN & SITAGLIPTIN LAYER

Time of drying	Observation				
	Target LOD Limit: 2.0 % - 3.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 05 minutes	2.68 %	2.74 %	2.55 %	2.61 %	2.66 %

TABLE 10: METFORMIN HYDROCHLORIDE LAYER: (LOT-I)

Time of drying	Observation				
	Target LOD Limit: 3.0 % - 4.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 05 minutes	4.23 %	4.37 %	4.33 %	4.43 %	4.37 %
After 10 minutes	3.70 %	3.64 %	3.67 %	3.62 %	3.55 %

TABLE 11: METFORMIN HYDROCHLORIDE LAYER: (LOT-II)

Time of drying	Observation				
	Target LOD Limit: 3.0 % - 4.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 05 minutes	4.64 %	4.57 %	4.60 %	4.63 %	4.55 %
After 05 minutes	3.59 %	3.27 %	3.35 %	3.40 %	3.31 %

TABLE 12: METFORMIN HYDROCHLORIDE LAYER: (LOT-III)

Time of drying	Observation				
	Target LOD Limit: 3.0 % - 4.0 %				
Location:	**U1**	**U2**	**M**	**L1**	**L2**
After 05 minutes	4.95 %	4.87 %	4.94 %	4.71 %	4.85 %
After 05 minutes	3.25 %	3.27 %	3.35 %	3.40 %	3.31 %

Critical Quality Attributes of Lubricated Blend (CQA):

Test Results for Blend Uniformity: After 12 Minutes at 12 RPM

TABLE 13: DAPAGLIFLOZIN & SITAGLIPTIN LAYER

Sr. no.	Sampling location	Observation (Pre-lubricated blend)					
Batch No.		I		II		III	
		Dapagliflozin	**Sitagliptin**	**Dapagliflozin**	**Sitagliptin**	**Dapagliflozin**	**Sitagliptin**
1.	U1	101.02 %	98.47 %	97.88 %	97.17 %	97.99 %	97.77 %
2.	U2	101.87 %	98.15 %	102.46 %	99.46 %	97.49 %	97.54 %
3.	U3	100.43 %	97.69 %	102.44 %	98.96 %	98.44 %	98.00 %

4.	M1	101.24 %	98.00 %	100.67 %	98.23 %	99.69 %	97.67 %
5.	M2	101.32 %	97.77 %	99.55 %	97.97 %	97.15 %	97.45 %
6.	M3	101.91 %	98.20 %	101.64 %	98.54 %	96.91 %	97.51 %
7.	N	100.58 %	97.89 %	95.01 %	96.30 %	96.99 %	97.28 %
8.	L1	99.18 %	96.82 %	104.24 %	99.06 %	96.76 %	96.66 %
9.	L2	100.27 %	97.46 %	98.68 %	97.28 %	96.02 %	97.02 %
10.	L3	99.92 %	96.94 %	101.40 %	98.71 %	97.50 %	97.46 %
Average content (90 – 110 %)		100.77%	97.74%	100.40%	98.17%	97.49%	97.44%
RSD %		0.86 %	0.55 %	2.67 %	1.01 %	1.05 %	0.39 %

TABLE 14: PRE-LUBRICATED BLEND OF METFORMIN HYDROCHLORIDE LAYER: AFTER 15 MINUTES AT 12 RPM

Sr. no.	Sampling location	Observation (Pre-lubricated blend)		
Batch No.		I	II	III
1	U1	98.78 %	98.93 %	102.00 %
2	U2	96.67 %	94.41 %	102.84 %
3	U3	99.93 %	94.18 %	99.61 %
4	M1	99.59 %	95.56 %	99.14 %
5	M2	96.39 %	94.72 %	99.54 %
6	M3	98.86 %	97.69 %	102.09 %
7	N	97.98 %	95.27 %	102.63 %
8	L1	97.34 %	95.62 %	102.70 %
9	L2	96.75 %	95.32 %	100.32 %
10	L3	97.55 %	95.35 %	100.54 %
Average content (90 – 110 %)		97.98%	95.71%	101.14%
RSD %		1.28 %	1.55 %	1.44 %

Lubricated blend Test results for blend uniformity: After 3 Minutes at 12 RPM

TABLE 15: FOR DAPAGLIFLOZIN & SITAGLIPTIN LAYER

Sr. no.	Sampling location	Observation (Lubricated blend)					
Batch No.		I		II		III	
		Dapagliflozin	Sitagliptin	Dapagliflozin	Sitagliptin	Dapagliflozin	Sitagliptin
1	U1	100.26 %	97.78 %	102.25 %	99.35 %	97.12 %	97.91 %
2	U2	100.76 %	98.34 %	103.63 %	100.09 %	98.67 %	98.19 %
3	U3	101.85 %	98.52 %	101.73 %	99.41 %	99.17 %	98.81 %
4	M1	100.19 %	97.59 %	104.45 %	100.09 %	97.32 %	97.07 %
5	M2	100.84 %	97.97 %	104.57 %	100.15 %	97.71 %	97.70 %
6	M3	101.87 %	98.28 %	100.07 %	97.57 %	97.69 %	97.68 %
7	N	99.63 %	97.41 %	104.84 %	100.90 %	98.16 %	98.10 %
8	L1	99.33 %	97.24 %	101.81 %	98.78 %	97.26 %	97.58 %
9	L2	98.62 %	96.92 %	101.85 %	99.35 %	97.85 %	97.68 %
10	L3	99.75 %	97.27 %	101.06 %	99.42 %	97.50 %	97.42 %
Average content (90 – 110 %)		100.31%	97.73 %	102.63 %	99.51 %	97.85 %	97.81 %
RSD %		1.05 %	0.55 %	1.60 %	0.91 %	0.67 %	0.49 %

TABLE 16: PRE LUBRICATED BLEND OF METFORMIN HYDROCHLORIDE LAYER: AFTER 5 MINUTES AT 12 RPM

Sr. no.	Sampling location	Observation (Lubricated blend)		
Batch No.		I	II	III
1	U1	94.68 %	96.33 %	100.72 %
2	U2	94.96 %	95.41 %	106.34 %
3	U3	97.74 %	100.33 %	100.95 %
4	M1	95.93 %	99.63 %	100.66 %
5	M2	98.23 %	97.68 %	98.68 %
6	M3	96.52 %	99.04 %	101.65 %
7	N	97.41 %	98.27 %	102.62 %

8	L1	96.09 %	100.61 %	102.20 %
9	L2	98.04 %	94.35 %	102.85 %
10	L3	95.10 %	95.75 %	100.18 %
Average content (90 – 110 %)		96.47 %	97.74 %	101.69 %
RSD %		1.38 %	2.25 %	2.02

Test Results for Composite Sample of Lubricated Blend:

TABLE 17: DAPAGLIFLOZIN & SITAGLIPTIN LAYER

Test	Specification	Observation (Lubricated blend)		
Batch No.		**I**	**II**	**III**
Description	To be record	Yellowish granular Powder	Yellow granular powder	Light Yellow granular powder
Assay of Dapagliflozin 33.333 mg/g ± 10 %	90 % – 110 %	99.49%	98.43 %	32.19 mg 96.58 %
Assay of Sitagliptin 333.333 mg/g ± 10 %	90 % – 110 %	97.14%	98.24 %	323.25 mg 96.97 %
Particle size: 40, 60 & 100 mesh	To be record	16.74% 29.59% 40.24%	14.66 % 35.75 % 52.97 %	14.14 % 32.77 % 51.21 %
Tap density	To be record	0.714 g/ml	0.667 g/ml	0.769 g/ml
Bulk density	To be record	0.556 g/ml	0.556 g/ml	0.625 g/ml
LOD %	2.0 % - 3.0 %	2.15 %	2.09 %	3.26 %
Microbial Limit Test:				
Total aerobic microbial count	1000 cfu/g	20 cfu/g	20 cfu/g	20 cfu/g
Total combined yeast / molds count	100 cfu/g	Nil	Nil	Nil
Escherichia coli	Should be absent	Absent	Absent	Absent
Salmonella enterica	Should be absent	Absent	Absent	Absent
Pseudomonas aeruginosa	Should be absent	Absent	Absent	Absent
Staphylococcus aureus	Should be absent	Absent	Absent	Absent

TABLE 18: METFORMIN HYDROCHLORIDE LAYER

Test	Specification	Observation (Lubricated blend)		
Batch No.		**I**	**II**	**III**
Description	To be record	A White coloured powder	White granular powder	Off White granular powder
Assay of Metformin Hydrochloride	740.741 mg/g (90 % - 110 %)	96.97 %	99.11 %	104.61 %
Particle size: 40, 60 & 100 mesh	To be record	10.02 % 25.62 % 44.07 %	12.32 % 31.12 % 48.65 %	24.74 % 41.09 % 60.00 %
Tap density	To be record	0.667 g/ml	0.625 g/ml	0.714 g/ml
Bulk density	To be record	0.526 g/ml	0.526 g/ml	0.556 g/ml
LOD %	2.0 % - 3.0 %	3.20 %	2.22 %	3.68 %
Microbial Limit Test:				
Total aerobic microbial count	1000 cfu/g	10 cfu/g	20 cfu/g	20 cfu/g
Total combined yeast / molds count	100 cfu/g	Nil	Nil	Nil
Escherichia coli	Should be absent	Absent	Absent	Absent
Salmonella enterica	Should be absent	Absent	Absent	Absent
Pseudomonas aeruginosa	Should be absent	Absent	Absent	Absent
Staphylococcus aureus	Should be absent	Absent	Absent	Absent

Critical Process Parameter (CPP) and Critical Quality Attributes (CQA) at Compression Stage:

TABLE 19: CRITICAL QUALITY ATTRIBUTES OF LOW SPEED: 12 RPM

Test	Specification	Batch No.: I	Batch No: II	Batch No.: III
Description	One side light yellow to yellow colored and another side white to off white colored, elongated, biconvex, uncoated tablets plain on both sides.	Complies	Complies	Complies
Assay of Dapagliflozin per Tablet	10 mg ± 10 % 9.0 mg to 11.0 mg	10.11 mg 101.10 %	9.90 mg 99.02 %	10.15 mg 101.52 %
Assay of Sitagliptin per Tablet	100 mg ± 10 % 90.0 mg to 110.0 mg	100.44 mg 100.44 %	100.08 mg 100.08 %	99.75 mg 99.75 %
Assay of Metformin Hydrochloride	500 mg ± 10 % 450 mg to 550 mg	498.49 mg 99.70 %	509.05 mg 101.81 %	502.50 mg 100.50 %

TABLE 20: CRITICAL QUALITY ATTRIBUTES OF MEDIUM SPEED: 14 RPM

Test	Specification	Batch No.: I	Batch No: II	Batch No.: III
Description	One side light yellow to yellow colored and another side white to off white colored, elongated, biconvex, uncoated tablets plain on both sides.	Complies	Complies	Complies
Assay of Dapagliflozin per Tablet	10 mg ± 10 % 9.0 mg to 11.0 mg	10.10 mg 100.99 %	9.85 mg 98.54 %	10.15mg 101.55 %
Assay of Sitagliptin per Tablet	100 mg ± 10 % 90.0 mg to 110.0 mg	100.13 mg 100.13 %	99.87 mg 99.87 %	99.89 mg 99.89 %
Assay of Metformin Hydrochloride	500 mg ± 10 % 450 mg to 550 mg	494.87 mg 98.97 %	503.97 mg 100.79 %	497.10 mg 99.42 %

TABLE 21: CRITICAL QUALITY ATTRIBUTES OF HIGH SPEED: 16 RPM

Test	Specification	Batch No.: I	Batch No: II	Batch No.: III
Description	One side light yellow to yellow colored and another side white to off white colored, elongated, biconvex, uncoated tablets plain on both sides.	Complies	Complies	Complies
Assay of Dapagliflozin per Tablet	10 mg ± 10 % 9.0 mg to 11.0 mg	10.21 mg 102.07 %	9.87 mg 98.37 %	10.28 mg 102.82 %
Assay of Sitagliptin per Tablet	100 mg ± 10 % 90.0 mg to 110.0 mg	101.29 mg 101.29 %	99.61 mg 99.61 %	100.85 mg 100.85 %
Assay of Metformin Hydrochloride	500 mg ± 10 % 450 mg to 550 mg	497.92 mg 99.58 %	495.48 mg 99.09 %	498.30 mg 99.66 %

TABLE 22: CRITICAL QUALITY ATTRIBUTES OF LOW HARDNESS

Test	Specification	Batch No.:I	Batch No: II	Batch No.: III
Description	One side light yellow to yellow colored and another side white to off white colored, elongated, biconvex, uncoated tablets plain on both sides.	Complies	Complies	Complies
Dissolution of Dapagliflozin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	97.36 %	102.76 %	100.72 %
Dissolution of Sitagliptin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	98.63 %	104.86 %	100.67 %
Dissolution of Metformin Hydrochloride:				
1st hour	20.0 % – 45.0 %	35.00 %	34.88 %	33.55 %
3rd hour	40.0 % – 80.0 %	62.66 %	66.46 %	60.05 %
10th hour	Not Less Than 75.0 %	99.37 %	99.06 %	98.22 %

TABLE 23: CRITICAL QUALITY ATTRIBUTES OF HIGH HARDNESS

Test	Specification	Batch No.: I	Batch No: II	Batch No.: III
Description	One side light yellow to yellow colored and another side white to off white colored, elongated, biconvex, uncoated tablets plain on both sides.	Complies	Complies	Complies
Dissolution of Dapagliflozin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	96.83 %	99.63 %	98.31 %
Dissolution of Sitagliptin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	97.87 %	103.10 %	99.94 %
Dissolution of Metformin Hydrochloride:				
1st hour	20.0 % – 45.0 %	35.05 %	32.92 %	33.40 %
3rd hour	40.0 % – 80.0 %	63.42 %	63.68 %	59.53 %
10th hour	Not Less Than 75.0 %	99.58 %	98.99 %	97.72 %

TABLE 24: CRITICAL QUALITY ATTRIBUTES RESULT FOR COMPOSITE SAMPLE OF AFTER COMPLETION OF BATCH

Critical process parameter steps	Specification	Observation		
		Batch No.: I	Batch No: II	Batch No.: III
Description	One side light yellow to yellow colored and another side white to off white colored, elongated, biconvex, uncoated tablets plain on both sides.	Complies	Complies	Complies
Weight of 20 Tablets	19.500 g ± 2.0 % (19.110 g –19.890 g)	974.845 mg	19445.0 mg	19489.1 mg
Uniformity of weight of 20 Tablets	975.00 mg ± 5.0 % (926.25 mg – 1023.75 mg)	978.1 mg	970.7 mg	968.1 mg
Thickness	6.30 mm ± 0.20 mm (6.10 mm – 6.50 mm)	6.36 mm	6.22 mm	6.26 mm
Hardness	NLT 10.0 kg/cm2	25.19 kp	28.78 kp	25.73 kp
Friability	NMT 1.0 %	0.06%	0.08 %	0.0308 %
Assay of Dapagliflozin per Tablet	10 mg ± 10 %	10.01 mg	9.95 mg	9.74 mg
	9.0 mg to 11.0 mg	100.07%	99.54 %	97.38 %
Assay of Sitagliptin per Tablet	100 mg ± 10 %	99.15 mg	99.93 mg	97.59 mg
	90.0 mg to 110.0 mg	99.15%	99.93 %	97.59 %
Assay of Metformin Hydrochloride	500 mg ± 10 %	500.16 mg	499.17 mg	500.88 mg
	450 mg to 550 mg	100.83%	99.83 %	100.18 %
Dissolution of Dapagliflozin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	100.98%	98.36 %	93.52 %
Dissolution of Sitagliptin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	102.52%	97.20 %	95.43 %
Dissolution of Metformin Hydrochloride:				
1st hour	20.0 % – 45.0 %	36.18%	37.08 %	33.40 %
3rd hour	40.0 % – 80.0 %	60.34%	61.80 %	58.99 %
10th hour	Not Less Than 75.0 %	97.47 %	100.59 %	96.38 %
Microbial Limit Test:				
Total aerobic microbial count	1000 cfu/g	10 cfu/g	20 cfu/g	20 cfu/g
Total combined yeast / molds count	100 cfu/g	Nil	Nil	Nil
Escherichia coli	Should be absent	Absent	Absent	Absent
Salmonella enterica	Should be absent	Absent	Absent	Absent
Pseudomonas aeruginosa	Should be absent	Absent	Absent	Absent
Staphylococcus aureus	Should be absent	Absent	Absent	Absent

TABLE 25: CRITICAL QUALITY ATTRIBUTES TEST RESULTS OF COATING STAGE

Critical process parameter steps	Specification	Observation		
		Batch No.: I	**Batch No: II**	**Batch No.: III**
Description	Light yellow colored on One side & other side white elongated, biconvex, film coated bi-layered tablets, plain on both sides.	Complies	Complies	Complies
Weight of 20 Tablets	20.000 g± 2 % (19.600 g – 20.400 g)	20.1285 g	20.0128 g	20.0139 g
Uniformity of weight of 20 Tablets	1000 mg ± 5 % (950 mg to 1050 mg)	1021.2 mg	977.5 mg	993.1 mg
Thickness	6.40 mm ± 0.20 mm (6.20 mm to 6.60 mm)	6.51 mm	6.31 mm	6.42 mm
Content uniformity of Dapagliflozin	85 % -115 %	1. 99.10 % 2. 99.60 % 3. 99.29 % 4. 99.35 % 5. 99.38 % 6. 99.14 % 7. 99.31 % 8. 99.41 % 9.99.62 % 10. 99.47 %	1. 100.65 % 2. 99.74 % 3. 98.29 % 4. 97.78 % 5. 101.08 % 6. 101.59 % 7. 100.60 % 8. 96.82 % 9. 100.65 % 10. 98.03 %	1. 94.88 % 2. 93.64 % 3. 94.87 % 4. 96.86 % 5. 97.00 % 6. 98.41 % 7. 94.53 % 8. 97.75 % 9. 96.23 % 10. 98.28 %
	RSD %	0.17 %	1.66 %	1.75 %
Assay of Dapagliflozin per Tablet	10 mg ± 10 % 9.0 mg to 11.0 mg	10.09 mg 100.92%	9.83 mg 98.31 %	9.73 mg 97.37 %
Assay of Sitagliptin per Tablet	100 mg ± 10 % 90.0 mg to 110.0 mg	98.44 mg 98.44%	98.19 mg 98.19 %	97.13 mg 97.13 %
Assay of Metformin Hydrochloride per Tablet	500 mg ± 10 % 450 mg to 550 mg	506.22 mg 101.24 %	501.16 mg 100.23 %	501.80 mg 100.36 %
Dissolution of Dapagliflozin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	97.50 %	98.96 %	97.91 %
Dissolution of Sitagliptin	NLT 70% (D) of the labeled claim to be dissolved in 45 minutes	101.75 %	99.64 %	98.44 %
Dissolution of Metformin Hydrochloride:				
1st hour	20.0 % – 45.0 %	33.25 %	34.73 %	33.84 %
3rd hour	40.0 % – 80.0 %	66.86 %	61.08 %	59.82 %
10th hour	Not Less Than 75.0 %	101.02 %	99.52 %	97.50 %
Related substance:				
Single maximum unknown impurity	NMT 0.5 %	Not detected	0.01 %	0.011 %
Total impurities	NMT 2.0 %	Not detected	0.01 %	0.017 %
Residual solvent:				
Isopropyl Alcohol	NMT 5000 ppm	NA	1467 PPM	792 ppm
Methylene Dichloride	NMT 600 ppm	NA	23 PPM	22 ppm

TABLE 26: CRITICAL QUALITY ATTRIBUTES OF FINISH PRODUCT (CQA)

Test	Specification	Observation		
		Batch No.: I	**Batch No: II**	**Batch No.: III**
Description	Light yellow colored on One side & other side white elongated, biconvex, film coated bi-layered tablets, plain on both sides.	Complies	Complies	Complies
Identification of Dapagliflozin by HPLC	The retention time of the principal peak in the Chromatogram of the	Complies	Complies	Complies

	sample preparation corresponds to that in the chromatogram of the standard preparation as obtained in the Assay of Dapagliflozin.			
Identification of Sitagliptin by HPLC	The retention time of the principal peak in the Chromatogram of the sample preparation corresponds to that in the chromatogram of the standard preparation as obtained in the Assay of Sitagliptin.	Complies	Complies	Complies
Identification of Metformin Hydrochloride (By UV-VIS Spectrophotometer)	The sample preparation shows maxima at about 233 nm as in Assay of Metformin Hydrochloride.	Complies	Complies	Complies
Average weight	1000.00 mg ± 5 % (950.00 mg to 1050.00 mg)	1006.13 mg	992.9 mg	1001.1 mg
Uniformity of weight	± 5 %	Min. = -1.30 % Max. = +1.45 %	Min. = -1.80 % Max. = +1.33 %	Min. = -2.42 % Max. = +2.42 %
Uniformity of content Dapagliflozin Sitagliptin	85.00 to 115.00 % of average content	Dapagliflozin- 99.37 % Sitagliptin- 100.48 %	Dapagliflozin- 99.52 % Sitagliptin- 101.57 %	Dapagliflozin- 96.25 % Sitagliptin- 96.63 %
Dissolution of Dapagliflozin	NLT 70 % (D) of the labeled claim to be dissolved in 45 minutes.	97.50 %	98.96 %	97.91 %
Dissolution of Sitagliptin	NLT 70 % (D) of the labeled claim to be dissolved in 45 minutes.	101.75 %	99.64 %	98.44 %
Dissolution of Metformin Hydrochloride:				
1st hour	20.0 % – 45.0 %	33.25 %	34.73 %	33.84 %
3rd hour	40.0 % – 80.0 %	66.86 %	61.08 %	59.82 %
10th hour	Not Less Than 75.0 %	101.02 %	100.20 %	97.50 %
Related substance:				
Single maximum unknown impurity	NMT 0.5 %	Not Detected	0.006 %	0.006 %
Total impurities	NMT 2.0 %	Not Detected	0.006 %	0.010 %
Residual Solvents:				
Isopropyl alcohol	NMT 5000 ppm	995 ppm	1467 ppm	792 ppm
Methylene chloride	NMT 600 ppm	25 ppm	23 ppm	22 ppm
Assay:				
Assay of Dapagliflozin per Tablet	10 mg ± 10 % 9.0 mg to 11.0 mg	10.10 mg 101.0 %	10.44 mg 104.4 %	10.14 mg 101.4 %
Assay of Sitagliptin per Tablet	100 mg ± 10 % 90.0 mg to 110.0 mg	100.14 mg 100.14 %	101.34 mg 101.34 %	100.34 mg 100.34 %
Assay of Metformin Hydrochloride per Tablet	500 mg ± 10 % 450 mg to 550 mg	506.22 mg 101.24 %	501.18 mg 100.24 %	499.04 mg 99.81 %
Microbial Limit Test:				
Total aerobic microbial count	1000 cfu/g	10 cfu/g	10 cfu/g	10 cfu/g
Total combined yeast / molds count	100 cfu/g	Nil	Nil	Nil
Escherichia coli	Should be absent / g	Absent	Absent	Absent
Salmonella enterica	Should be absent / g	Absent	Absent	Absent
Pseudomonas aeruginosa	Should be absent / g	Absent	Absent	Absent
Staphylococcus aureus	Should be absent / g	Absent	Absent	Absent

TABLE 27: STATISTICAL EVOLUTION

Stage		Observation					
		Assay at Blend stage			Assay at Finish stage		
		Dapa.	Sita.	Met.	Dapa.	Sita.	Met.
First batch	I	99.49 %	97.14 %	96.97 %	101.0 %	100.14 %	101.24 %
Second batch	II	98.43 %	98.24 %	99.11 %	104.4 %	101.34 %	100.24 %

Third Batch	III	96.58 %	96.97 %	104.61 %	101.4 %	100.34 %	99.81 %
Mean (M)		98.17 %	97.45 %	100.23 %	102.27 %	100.61 %	100.76%
Lower specification Limit (LSL)		90 %	90 %	90 %	90 %	90 %	90 %
Upper specification Limit (USL)		110 %	110 %	110 %	110 %	110 %	110 %
Standard Deviation (SD) σ		1.47	0.69	3.94	1.86	0.64	0.83
Relative standard deviation (RSD)		1.50 %	0.71 %	3.93 %	1.82 %	0.64 %	0.82 %
Cp = (USL-LSL) / 6 σ		2.27	4.83	0.85	1.79	5.21	4.02
CpL = (Mean – LSL) / 3 σ		1.85	3.60	0.87	2.20	5.53	4.32
CpU = (USL- Mean) / 3 σ		2.69	6.06	0.83	1.39	4.90	3.71
Cpk = minimum (CpL, CpU) Limit: NLT 1.33		1.85	3.60	0.83	1.39	4.90	3.71

Note: Cpk value only for observation.

CONCLUSION: Process validation activity of three initial process validation batches (I, II, III) of the same size, method, equipment & validation criteria were taken, and activity has been complete successfully. All critical process parameter and critical quality attributes test results observed were satisfactory. On the basis of analytical data, the product Dapagliflozin, Sitagliptin and Metformin Hydrochloride Tablets are validated successfully.

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