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Review Article

Review on Process Validation of Famciclovir 500 mg Tablets

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ABSTRACT

Validation is best viewed as an impartment and integral part of cGMP. Validation is therefore one element of quality assurance programs associated with a particular process. Then word validation simply means "assessment of validity" or action of proving effectiveness. This process involves addition of granulating agent to the dry mixed material and converting into granules. The goal of quality system is to consistently produce products that are suitable for their intended use. Process validation is a key element in assuring that these principles and goals are met. In this study concurrent process validation was carried out for Famciclovir 500 mg. In tablet dosage form, critical parameters like dry mixing, granulation, drying, sifting and milling, lubrication compression and Coating were taken up for validation studies. In-process quality monitoring of all critical processing steps was done for three production batches. LOD of the dried, milled and lubricated granules were checked and found within the limit. Assay after lubrication was within the specified limit, indicating blend uniformity. Physical parameters, dissolution and assay were checked and results found within the acceptance criteria. During packing operation, bulk pack were checked and found satisfactory. Thus process validation of Famciclovir 500 mg was successfully completed and found within the specifications.

Keywords: Process validation, Famciclovir, Lactose anhydrous, Sodium starch glycollate.

INTRODUCTION[1-12]

USFDA Defines validation as

"Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

WHO guidelines Defines validation as

"Validation is documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results." Validation act of proving, in accordance of GMPs that any process actually leads to expected results. Documented evidence that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

WHY VALIDATION?

- If would not be feasible to use equipment not knowing if it will produce the product we want, not to employ the people with no assurance that they can do or fail to implement process checks or examination to assure that product meet specifications.
- The pharmaceutical industry uses expensive material sophisticated facilities and equipments and highly qualified personals.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failure, rejects, reworks, recalls, complaints are the sufficient part of total production cost.
- Detailed study and controlled of the manufacturing process batch validation is necessary if failure cost is to be reduced and productivity is improved. There are three reasons by pharmaceutical industry are concerned that their processes perform consistently expected that is, that are validated.
- Assurance of quality, cost reduction.

Government regulations

Validation is considered to be integral part of

GMPs essentially world wide, compliances with validation requirements is necessary for obtaining approval to manufacture and to introduce new products. The FDA's cGMP refer to the concepts of the validation in both sections. They state that such control procedure shall be established to monitor out put and to validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in process materials and drug materials. The Accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented. A generally stated requirement for process validation is contained in the medicinal device GMP regulations. Where deviations from device specification could occur as result of manufacturing process itself. There shall be written procedures describing any process controls necessary to assure conformance to specifications.

How validation is done?

The principle is characterized by harmony between the results obtained and requirements. This supposes specific requirements and objectives

- Available means
- Choices, which are justified in relation to objectives
- Each stage should begin when the previous stage is over.

Certain depositions should be defined:

How norms should be dealt with

- How modifications should be dealt with controlling evaluation will involve
- Set data for decision making
- Evaluation before decision making
- Justifying the decision
- Follow-up

TYPES OF VALIDATION

- **Prospective validation**

Prospective validation is defined as the Establishment of documented evidence that a system does what it purports to do based on a pre planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally under taken when ever new formula, process or facility must be validated before routine pharmaceutical formulation commences. In fact validation of process by this approach often leads to transfer of the manufacturing process from the development function to product. The objective of prospective validation is to prove or demonstrate that the process will work in accordance with a validation master plan or protocol prepared for pilot product trails.

- **Retrospective validation**

Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past.

- **Concurrent validation**

It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

- **Revalidation**

It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes.

PROCESS VALIDATION

"Process Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

Objectives of process validation

1) The manufacturing process, in addition to the individual equipment, must be validated.
2) The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.
3) A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.
4) Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.
5) In the end, process validation will ensure a robust product that is highly reproducible over time.

Advantages of process validation

1) Expanded real time monitoring and adjustment of process.
2) Enhanced ability to statistically evaluate process performance and product variables. e.g., individuals; mean; range; control limits
3) Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
4) Improved ability to set target parameters and control limits for routine production, correlating with validation results.
5) Enhanced reporting capability.

PROCESS VALIDATION PROTOCOL

"A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment and design points on what constitutes acceptable test results."

The validation protocol should be numbered, signed and dated, and should contain Protocol Approval sheet, Validation Team, Batches under validation, Introduction, Product profile, Objective, Scope, Validation criteria, Reference documents, General check points, Responsibilities, Manufacturing formula, Details of the equipment/facilities to be used (including measuring/ monitoring/ recording) with its calibration status, Process flow chart, Manufacturing procedure, Rationale for selection of critical steps and its parameters for validation, Process steps, control variables and response to be measured, Sampling plan (The samples to be taken- where, when, how, how many and the allowable range of variability), Sampling procedure, Specifications, Raw materials – Rationale, Wet granulation – Rationale, Compression – Rationale and Procedure, Calibration, Acceptance criteria, Validation report preparation, Deviation, Approach for handling out of specification results, Revalidation criteria, Summary and Conclusion.

MATERIALS AND METHODS

All the materials are listed in Table 1.

EVALUATION OF TABLET[3-8]

The critical parameters considered during the process validation of Famciclovir 500 mg tablets were Dry Mixing, Granulation, Drying, Milling, Blending/Lubrication, Compression, Coating and bulk Packing.

Dry mixing

The dry-mixing step involves mixing of active ingredients with other additives using Rapid Mixer Granulator (RMG). Mixing speed and mixing time are the critical variables. Mixing speed is kept constant, mixing time shall be studied to validate dry mixing step also analyse the tapped, untapped density for record purpose only. In dry mixing stage 3 batches like I, II and III are considered for validation. Dry mixing results of all the batches are well within the acceptance criteria. Result of dry mixing are shown 03 no. table.

Parameters

Time of mixing : 7 minutes

Agitator speed : Slow

Granulation

The granulation is to be performed using RMG. The granulation step involves converting the powder into wet dough mass. Mixing time influences the granule strength, bulk density of blend, dissolution, hardness of tablets etc. Binder solution is being used for granulation. The granulation end point is critical process and the end point of granulation shall be checked against the amperage readings of impeller of the RMG, which gives the co-relation to the granulation end point. Result of granulation shown in table no. 03. Parameters are as below:

Binder addition time : 1 minutes

Total amount of binder : 8.81 kg

Agitator reading : 8±1

Chopper reading : 4±1

Drying

The drying step involves drying of wet mass. The level of moisture in the granules is important factor. If level of moisture is more in granules then blend will have poor flow & distribution characteristics. If level of moisture in blend is less it will produce tablet with capping, high friability and chipping problems. During drying the desired LOD will be maintained in the granules which will influence the quality parameters like tablet hardness, flow properties, physical properties during compression. Drying of granules in FBD controls the level of moisture. Inlet temperature of FBD is most critical variable for the same. LOD is checked at regular interval to establish the correlation with outlet temperature. Drying results of the batches are well with in the acceptance criteria. Results of Loss on drying are shown in Table 3.

Analysis : Loss on drying (by IR moisture balance analyzer)

Acceptance criteria : NMT 0.9-1.5 % w/w

Milling

Sizing of granules is to be obtained by sifting of granules from specified sieve and retention of granules on sieves is to be milled by using multimill, Speed of the multimill and Forward direction of knives is to be monitored and sample to be withdrawn at the end of the sizing operation

for the monitoring of particle size distribution, bulk density and LOD as a part of validation. Results of milled granules are shown in Table 3.

Analysis : Particle size distribution, Untapped bulk density, tapped bulk density and LOD.
Acceptance criteria : LOD : NMT 0.9-1.5 % w/w at 105°C

Blending/Lubrication

This step involves mixing of magnesium stearate with drug granules & other blending material. Sifted lubricants shall transfer to octagonal blender containing dried granules of famciclovir and mix for 10 minutes at slow speed. Sifted magnesium stearate shall transfer to octagonal blender and Mix for 3 minutes at slow speed. The purpose of blending is to get a uniform distribution of API. This is followed by mixing of the un lubricated blend with lubricant to get good flow and anti-adhesion property of the blend. Mixing speed and time are critical variables in this process. Mixing speed is kept constant. Mixing time is critical since under mixing will result in non-uniform distribution of drug and poor flow where as over mixing will result in de- mixing leads to non-uniform distribution of drug. Checking content uniformity of API at fixed time shall validate blending time. In blending stage three batches i.e. Batch I, II and III shall be considered for validation. Blending results of all the batches are well with in the acceptance criteria. Results of content uniformity during blending were shown in Table 9. Results of particle size distribution, bulk density, LOD and assay of composite sample at the end of lubrication are shown in Table 3.

Analysis : Blend uniformity, particle size distribution, Bulk density, LOD and Assay
Acceptance criteria : LOD: NMT 2.0 % w/w
Assay: 95.0 -105.0 %

Compression

This step involves consistent flow of an adequately lubricated, uniform blend, into dies where the granules are being compressed into tablets. Compression is to be carried out as per batch manufacturing record. Collect the samples at various stages i.e. at Minimum Hardness, Maximum Hardness, Minimum Speed, Maximum Speed and At Optimum speed Initial stage, Middle stage and End stage of compression and carry out the testing of physical parameters such as Appearance, Group wt., Diameter, Hardness, Thickness, Friability, Disintegration time and Average wt., Dissolution at max hardness only and Assay. In compression stage three batches i.e. Batch No A, B and C shall be considered for validation. Compression results of all the batches are well with in the acceptance criteria. Various physical parameters, approximate sample size, acceptance criteria during compression and results of various physical parameters are shown in Table 4 and 5.

Thickness, Length and Width

30 tablets were randomly selected from each batch and their thickness, length and width were measured by using digital Vernier caliper.

Hardness

The crushing strength of prepared tablets was determined for 6 tablets of each batch by using Erweka tablet hardness tester. The mean of hardness was determined.

Friability

9 tablets (Approximate 6.5 g) were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were deducted and weighed again. The percentage friability was measured using the formula,

$\% F = \{1-(W_t/W)\} \times 100$

Where,

% F = friability in percentage
W = Initial weight of tablet
W_t = weight of tablets after revolution

Disintegration time

6 tablets were placed in the tablet disintegration test apparatus and on it. Disintegration time of the tablets was noted.

Weight variation

30 tablets were randomly selected from each batch and individually weighed. The average weight of 30 tablets was calculated. The batch passes the test for weight variation test if the tablet weight is within the acceptance criteria shown in Table 5.

Capability Index

The capability indices to be calculated for weight sample using following formula:

Cp = (USL – LSL)/6s
CpU = (USL - X)/3s
CpL = (X – LSL)/3s
CpK = min (CpU, CpL)
(smallest of the values for CpU and CpL i.e. Capability Index)

Where,

USL = upper specification limit for weight
LSL = lower specification limit for weight
X = mean for weight
S = standard deviation

Capability result are shown in table no. 21.

Dissolution

Medium: water; 900 mL
Apparatus 2: 50 rpm
Time: 30 minutes
Procedure
Pour 900 mL of dissolution medium in each vessel. Allow sufficient time for the dissolution medium to equilibrate at 37°C±0.5°C. Adjust stirring element speed to 50 rpm. Immerse the paddle in the dissolution medium so that there is a distance of 2.5 cm ± 0.2 cm between the bottom of the paddle and inside bottom of the vessel. Put tablet in each of the vessels taking care to exclude air bubbles from the surface of the dosage form unit. Start the apparatus.
At the end of the specified time, withdraw 10 mL aliquot from a zone midway between the surface of the dissolution medium and the top of the rotating paddle and filter through 0.45 µm nylon filter (25 mm). Discard first 2 mL of the filtrate. Dilute 5 mL of the filtrate to 100 mL with diluent, mix. and analyse on HPLC
Tolerance
Not less than 80 (Q) % of the labeled amount of $C_{14}H_{19}N_5O_4$ is dissolved in 30 minutes.
Uniformity of dosage units meet the requirements.
The results are shown in Table 5.

Assay

Weigh 20 tablets and determine the average weight. Weigh accurately and transfer intact tablets equivalent to about 2000 mg of Famciclovir to a 1000 mL volumetric flask. Add about 200 mL of diluent and sonicate for 5 min to disperse the tablets. Add about 500 L of diluent and sonicate for 10 min with intermittent shaking. Dilute to volume with diluent, mix. Filter the solution through 0.45 µm nylon filter (25 mm), discarding first 2 mL of the filtrate. Dilute 5 mL of the subsequent filtrate to 200 mL with diluent, mix and analyse on HPLC. The results are shown in Table 5.

Coating

This step involves consistent flow of an adequately compressed tablet , into coating pan where the compressed tablet are coated . Coating is to be carried out as per batch manufacturing record. Collect the samples at various stages i.e. at different lot and carry out the testing of physical parameters such as Appearance, Thickness, length, width, Disintegration time, group and average wt., uniformity of weight , % weight gain, Dissolution. In coating stage three batches i.e. Batch No A, B and C shall be considered for validation. Coating results of all the batches are well with in the acceptance criteria. Various physical parameters, approximate sample size, acceptance criteria during coating and results of various physical parameters are shown in Table 6–8.

Thickness, Length and Width

30 tablets were randomly selected from each lot/ batch and their thickness, length and width were measured by using digital Vernier caliper.

Disintegration time

6 tablets were placed in the tablet disintegration test apparatus and on it. Disintegration time of the tablets was noted. The result noted in table no. 8.

Uniformity of weight/ Average weight/Group weight

20 tablets were randomly selected from each lot/ batch and individually weighed. The average weight of 20 tablets was calculated. The batch passes the test for weight variation test if the tablet weight are within the acceptance criteria shown in Table 8.

Packing

Bulk packing is to be done as per batch packing record and involves packing of tablets in HDPE container pack . In packing stage three batches i.e. Batch I, II and III shall be considered for validation. Packing results of all the batches are well with in the acceptance criteria. Results of bulk packing were shown in Table 9.
Validated parameters:

Bulk counting machine speed	: 15 to 25 container/ minute (Challenge on minimum to maximum speed)
Tablet counting	: 30 tablet/container.

Finished product analysis report is shown in Table 10.

RESULTS AND DISCUSSION

All the results are tabulated in Table 4 - 10
The quality system regulation defines process validation by establishing objective evidence that a process consistently produces a result or product meeting its predetermined specifications. The goal of quality system is to consistently produce products that are suitable for their intended use. Process validation is a key element in assuring that these principles and goals are met.
In this study concurrent process validation was carried out for one product. In tablet dosage form, critical parameters were taken up for validation studies.
In tablet dosage form, the critical parameters are:

- Dry Mixing
- Granulation
- Drying
- Milling
- Blending/Lubrication
- Compression
- Coating

- Bulk Packing

Dry mixing
The dry-mixing step involves mixing of Famciclovir with other additives using Rapid mixer granulator. The mixing of the active ingredient depends on the mixing time.

Granulation
The granulation is to be performed using RMG. The granulation step involves converting the powder into wet dough mass. Mixing time influences the granule strength, bulk density of blend, dissolution, hardness of tablets etc. Binder solution is being used for granulation. The granulation end point is critical process and the end point of granulation shall be checked against the amperage readings of impeller of the RMG, which gives the co-relation to the granulation end point. If binding not given to the dry mixed product then granules formation is not properly.

Drying
The drying step involves drying of wet mass. Moisture in granules is important factor. If moisture is more in granules it will lead to poor flow and sticking problem. If moisture is less it will lead to capping, high friability and chipping. During drying the LOD of granules should be taken in to consideration. The inlet temperature of the FBD is controlled during the drying process and the outlet temperature is monitored and correlated with the corresponding LOD of the granules under drying.

Milling
Dried granules were than sifted and milled on multimill. At the end of milling, composite sample was withdrawn and tested for particle size distribution, bulk density and LOD. Results obtained were found well within the limit and recorded.

Blending/Lubrication
The blending of three batches was performed and the samples at the designated locations were drawn after 3 minutes of blending after transferring magnesium stearate to octagonal blender for determining the blend uniformity and RSD values of famciclovir . The RSD values meet the acceptance criteria. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous. Hence the blending time of 3 minutes after addition of magnesium stearate as mentioned in the BMR stands was validated.

Compression
The compression for all the three batches has been validated for minimum and maximum hardness, minimum and maximum speed and at optimum speed; initial stage, middle stage and end stage of compression. The results of physical parameters like appearance, thickness, length, width, hardness, friability, disintegration time, group weight, average weight, uniformity of weight and capability index, dissolution and assay of the tablets were well within the acceptable limits. The results are comparable among all the three batches.

Coating
The coating for all the three batches has been validated and different parameter were verified such as appearance, group weight,length, width, Thickness, Disintegration time, uniformity of weight, % weight gain, Average weight, Dissolution were well within the acceptable limits. The results are comparable among all the three batches.

Bulk packing
This process involves packing of tablets in HDPE container. speed of machine , counting of tablet and leak test are critical variables. Induction sealing is required to get proper sealing, less temperature will lead to improper sealing which cause leakage and higher temperature will result in burning or spoilage of HDPE container . Leak test and counting verification are carried out to establish the above variables during bulk packing operation.

CONCLUSION
Process validation study on three consecutive batches, Batch I, II and III of Famciclovir 500 mg tablets having batch size of 112500 tablets was successfully completed and the manufacturing critical process parameters were validated of this transferred product to show that the process was under control. The study includes the validation of critical steps of manufacturing such as blending, compression and blister packing. It shall also establish the suitability of equipments and area used for the production. The all process validation batches had been manufactured and validated in full compliance with cGMP requirement.
Based on the results of the validation data, it shall be concluded that the manufacturing process consistently produces the product of pre-determined quality parameters. The Process validation showed that there was no significant batch-to-batch variation and all the process variables were studied and it showed consistent and reproducible results. Therefore it can be concluded that the process stands validated and the data can be used in regulatory submission.

Table 1: List of Raw materials and their Functions

S. No.	Ingredients	Function
1	Famciclovir	API (Antiviral)
2	Lactose anhydrous	Diluent /Filler
3	Sodium starch glycolate	Disintigrating agent
4	Hydroxy propyl cellulose	Binder
5	Purified water	Vehicle
6	Lactose Anhydrous	Diluent
7	Low-Substituted Hydroxy propyl cellulose	Diluent
8	Sodium starch glycolate	Lubricant, Glidant
9	Magnesium stearate	Lubricant
10	Opadry white Y-1-7000	Coating material

Table 2: List of Equipments and their Uses

S. No.	Equipment name	Used for
1.	Vibro sifter (20 #, 40 #, 60 #, 80 #,100 # sieves)	Sifting of raw materials
2.	Multimill	Milling
3.	Rapid mixer granulator (High shear granulator)	Dry mixing and granulation
4.	Paste kettle	Preparation of paste
5.	Mechanical stirrer	Stirring
6.	Fluid bed dryer	Drying
7.	Octagonal blender	Blending
8.	Unit dose Sampler	Sampling of granules
9.	20 station compression machine (Cadmach)	Compression
10.	Deduster	Dedusting of tablet
11.	Metal detector	Detecting metal, if any
12.	Tablet inspection belt	Inspection of tablets
13.	Coating pan	Coating
14.	Bulk pack machine	Packing of tablets
15.	Analytical balance	Weighing
16.	IR (Electronic) moisture balance analyzer	LOD
17.	Roche friabilator	Friability
18.	Tablet disintegration test apparatus	Disintegration Time
19.	Hardness Tester (Erweka)	Hardness
20.	Vernier calipers	Thickness, length and width
21.	Leak test apparatus	leak test
22.	Infra-red	Identification
23.	UV-visible spectrometer	Identification, Dissolution, Assay
24.	High performance liquid chromatography	Related substances

Table 3: Result of granulation stage

Result of Bulk Density (Dry Mix)							
Batch No.	**Lot**	**Tapped Bulk Density (gm / ml)**		**Untapped Bulk Density (gm / ml)**		**LOD at 70°C IR Balance**	
A	I	0.65		0.46		1.01	
	II	0.64		0.48		0.74	
B	I	0.63		0.48		1.33	
	II	0.63		0.48		1.96	
C	I	0.64		0.47		1.02	
	II	0.63		0.46		1.04	
Acceptance Criteria		For Record					
Observation during Wet Granulation							
Operation		**RESULTS**					
Mixing		**Batch No.: A**		**Batch No.: B**		**Batch No.: C**	
		Lot-I	**Lot-II**	**Lot-I**	**Lot-II**	**Lot-I**	**Lot-II**
Total amount of binder		8.81 kg	8.81 kg	8.81 kg	8.81 kg	8.80 kg	8.79 kg
Binder addition time		01 min	01 min	01 min	01 min	01 min	01 min
Additional amount purified water added (if any)		0.80 kg	0.90 kg	0.80 kg	0.90 kg	0.90 kg	0.90 kg
Ampere reading at end point	Agitator (8±1)	8.5 A	8.5 A	8.5 A	8.5 A	8.3 A	8.2 A
	Chopper (4±1)	4.2 A	4.3 A	4.2 A	4.2 A	4.1 A	4.2 A
Total Granulation Time		04 min 30 sec	04 min 30 sec	04 min 30 sec	04 min 30 sec	04 min 30 sec	04 min 30 sec
Result of Loss on Drying							

Sample location	Wt Requi-red (g)	Batch A				Batch B				Batch C			
		Lot I		Lot II		Lot I		Lot II		Lot I		Lot II	
		Wt Taken (g)	LOD % w/w	Wt Taken (g)	LOD % w/w	Wt Taken (g)	LOD % w/w	Wt Taken (g)	LOD % w/w	Wt Taken (g)	LOD % w/w	Wt Taken (g)	LOD % w/w
T1	2 – 5	2.1	1.4	2.0	0.9	2.0	1.2	2.2	1.1	2.2	1.3	2.1	1.2
T2	2 – 5	2.0	1.4	2.0	1.3	2.1	1.1	2.1	1.0	2.1	1.4	2.1	1.3
M1	2 – 5	2.0	1.0	2.1	1.0	2.2	1.1	2.3	1.2	2.2	1.1	2.1	1.0
M2	2 – 5	2.1	1.3	2.2	1.1	2.3	1.2	2.3	1.2	2.1	1.1	2.1	1.3
M3	2 – 5	2.1	1.4	2.0	1.3	2.1	1.1	2.3	1.0	2.1	1.3	2.0	1.2
B1	2 – 5	2.1	1.2	2.1	1.1	2.1	1.3	2.1	1.0	2.1	1.1	2.0	1.0
B2	2 – 5	2.1	1.3	2.0	1.0	2.1	1.4	2.1	1.1	2.1	1.4	2.4	1.2

Result of Milling - Particle size distribution

Sieve Size	Acceptance Criteria	% w/w Retention					
		Batch A		Batch B		Batch C	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
20 # Passed through	NLT 95%	99.34	99.43	98.24	98.58	98.95	99.07
60 # (Retention)	NLT 25 % TO NMT 60 %	42.55	42.67	47.38	46.93	36.55	39.51
100 # Passed through	NMT 60 %	34.30	33.50	35.28	33.94	46.60	44.04

Milling - Bulk density and LOD

Batch	LOT	Untapped bulk density (g/mL)	Tapped bulk density (g/mL)	LOD (% w/w)
A	I	0.61 gm/ml	0.43 gm/ml	1.38
	II	0.61 gm/ml	0.41 gm/ml	1.12
B	I	0.61 gm/ml	0.45 gm/ml	1.06
	II	0.61 gm/ml	0.45 gm/ml	1.26
C	I	0.61 gm/ml	0.43 gm/ml	1.22
	II	0.63 gm/ml	0.42 gm/ml	1.28
Acceptance Criteria		To Record	To Record	(0.9-1.5 % w/w)

Result of Lubrication - Content uniformity

Sample	Batch A		Batch B		Batch C	
	3 min		3 min		3 min	
	Weight taken (g)	% Assay	Weight taken (g)	% Assay	Weight taken (g)	% Assay
T1	1.548	98.4	1.600	99.3	1.642	99.5
T2	1.547	98.1	1.630	99.3	1.629	98.9
T3	1.519	98.2	1.632	98.1	1.653	99.0
T4	1.532	98.5	1.614	98.6	1.653	98.9
M1	1.536	97.7	1.646	98.5	1.651	99.3
M2	1.544	98.0	1.659	99.5	1.640	99.4
M3	1.548	98.3	1.652	98.2	1.672	98.8
B1	1.537	97.8	1.619	98.0	1.655	98.3
B2	1.545	97.0	1.626	97.8	1.686	98.6
B3	1.542	98.3	1.655	97.9	1.675	98.5
Mean		98.0		98.5		98.9
RSD		0.46		0.65		0.40

Lubrication - particle size distribution

Sieve Size	Acceptance Criteria	% w/w Retention		
		Batch A	Batch B	Batch C
60 # ↑	For record	29.41	32.79	32.46
100 # ↑		22.27	20.16	20.36

Lubrication - Bulk density, LOD and Assay

Batch	Sample	Untapped bulk density (g/ml)	Tapped bulk density (g/ml)	LOD (% w/w)	Assay (%)
A	Composite	0.50	0.68	0.50	98.6
B		0.50	0.68	0.67	98.1
C		0.48	0.68	0.45	98.1
Acceptance Criteria		To record	To record	(NMT 2.0 % w/w)	For information only

Table 4: Various Physical parameters, Approximate sample size and Acceptance criteria during compression

S. No.	Individual In-process Test Parameter	Approximate sample size	Acceptance criteria
1	Appearance	30 tablets	White to off white, oval shaped, biconvex uncoated tablets engraved with "ML 72 " on one side and plain on other side.
2	Thickness	30 tablets	5.50 mm + 0.20 mm (5.30 mm - 5.70 mm)
3	Length	30 tablets	18.00 mm ± 0.20 mm
	Width	30 tablets	8.50 mm ± 0.20 mm
4	Hardness	6 tablets	170 ± 50 N (120 – 220 N)
5	Friability	9 tablets (Approx. 6.5 g)	NMT 1.0% w/w
6	Disintegration time	6 tablets	NMT 15 minutes
7	Weight of 30 tablets (Group weight)	30 tablets	19.80 g + 2.0 % (19.40 g – 20.20 g)
8	Average weight	30 tablets	660.0 mg + 2.0 % (646.8 mg - 673.2 mg)
9	Uniformity of weight	30 tablets	660.0 mg ± 5.0 % (627.0 mg – 693.0 mg)
10	Capability index	30 tablets	Not less than 1.33

Table 5.0: Result of compression stage

Result of Thickness

Thickness (mm)						
Stage of Sampling		Batch I		Batch II		Batch III	
		Min	Max	Min	Max	Min	Max
Minimum Hardness		5.51	5.62	5.52	5.65	5.50	5.64
Maximum Hardness		5.49	5.56	5.42	5.55	5.47	5.52
Minimum Speed		5.50	5.65	5.49	5.60	5.51	5.58
Maximum Speed		5.54	5.62	5.53	5.60	5.51	5.60
Initial stage	At Optimum Speed	5.55	5.62	5.50	5.55	5.56	5.64
Middle stage		5.51	5.60	5.50	5.55	5.52	5.65
End stage		5.50	5.58	5.49	5.54	5.55	5.61

Result of Friability (% w/w)				
Stage of Sampling		Batch I	Batch II	Batch III
Minimum Hardness		0.14	0.09	0.31
Maximum Hardness		0.09	0.10	0.12
Minimum Speed		0.21	0.24	0.23
Maximum Speed		0.09	0.13	0.14
Initial stage	At Optimum Speed	0.20	0.21	0.27
Middle stage		0.21	0.17	0.20
End stage		0.26	0.17	0.15

Length and Width							
Stage of Sampling	Parameter	Batch I		Batch II		Batch III	
		Min	Max	Min	Max	Min	Max
Minimum Hardness	Length	18.01	18.05	18.00	18.05	18.02	18.04
	Width	8.51	8.55	8.50	8.54	8.51	8.54
Maximum Hardness	Length	18.00	18.03	18.01	18.04	18.01	18.05
	Width	8.50	8.54	8.51	8.55	8.50	8.53
Minimum Speed	Length	18.01	18.04	18.00	18.03	18.00	18.03
	Width	8.51	8.55	8.50	8.53	8.51	8.54
Maximum Speed	Length	18.00	18.04	18.00	18.05	18.00	18.03
	Width	8.50	8.54	8.51	8.53	8.51	8.55
Initial stage (At Optimum speed)	Length	18.01	18.03	18.00	18.04	18.00	18.05
	Width	8.51	8.53	8.50	8.55	8.50	8.54
Middle stage (At Optimum speed)	Length	18.00	18.04	18.01	18.05	18.01	18.04
	Width	8.51	8.55	8.51	8.54	8.50	8.53
End stage (At Optimum speed)	Length	18.01	18.05	18.00	18.04	18.00	18.05
	Width	8.50	8.53	8.51	8.55	8.50	8.54

Hardness							
Stage of Sampling	Hardness (Kg/cm^2)						Mean
Batch I							
Minimum Hardness	133	130	139	131	140	132	134
Maximum Hardness	200	186	190	185	179	180	187
Minimum Speed	155	160	159	152	151	150	155
Maximum Speed	166	162	160	157	155	153	159

Initial stage	At Optimum speed	157	160	162	163	159	158	160
Middle stage		160	158	155	153	166	167	160
End stage		153	156	157	169	160	158	159
Batch II								
Minimum Hardness		129	131	130	140	135	130	133
Maximum Hardness		189	190	196	188	185	192	190
Minimum Speed		165	159	162	168	166	158	163
Maximum Speed		158	162	160	159	161	160	160
Initial stage	At Optimum speed	163	169	170	168	167	166	167
Middle stage		160	163	164	159	162	163	162
End stage		168	159	162	160	163	158	162
Batch III								
Minimum Hardness		127	138	140	132	129	133	133
Maximum Hardness		187	183	181	190	179	177	183
Minimum Speed		155	160	159	162	163	160	160
Maximum Speed		166	169	159	170	161	168	166
Initial stage	At Optimum speed	168	163	158	154	165	170	163
Middle stage		172	158	165	161	169	161	164
End stage		160	163	172	169	170	165	167

Result of Disintegration time (minutes, determined at 37˚C ± 2˚C)

Stage of Sampling		Batch I	Batch II	Batch III
Minimum Hardness		09 min 43 sec	09 min 40 sec	09 min 50 sec
Maximum Hardness		10 min 30 sec	10 min 26 sec	10 min 24 sec
Minimum Speed		09 min 55 sec	10 min 00 sec	10 min 10 sec
Maximum Speed		10 min 15 sec	10 min 23 sec	10 min 28 sec
Initial stage	At Optimum speed	10 min 09 sec	09 min 50 sec	10 min 26 sec
Middle stage		09 min 50 sec	10 min 00 sec	10 min 19 sec
End stage		09 min 40 sec	10 min 11 sec	09 min 54 sec

Group weight (g)

Stage of Sampling		Batch I	Batch II	Batch III
Minimum Hardness		19.924	19.777	19.809
Maximum Hardness		19.868	19.820	19.858
Minimum Speed		19.818	19.814	19.855
Maximum Speed		19.847	19.812	19.854
Initial stage	At Optimum speed	19.856	19.858	19.826
Middle stage		19.888	19.880	19.827
End stage		19.917	19.803	19.805

Average weight (mg)

Stage of Sampling		Batch I	Batch II	Batch III
Minimum Hardness		664.1	659.2	660.3
Maximum Hardness		662.3	660.7	661.9
Minimum Speed		660.6	660.5	661.8
Maximum Speed		661.6	660.4	661.8
Initial stage	At Optimum speed	661.9	661.9	660.9
Middle stage		662.9	662.7	660.9
End stage		663.9	660.1	660.2

Uniformity of weight

Stage of Sampling		Individual weight of 30 tablets (mg)									
Batch no. A											
Minimum Hardness		662	664	665	662	671	671	664	662	671	659
		668	662	671	666	668	664	657	660	668	658
		659	662	659	666	663	664	661	660	666	671
Maximum Hardness		660	663	658	659	660	664	662	662	661	663
		659	657	656	659	668	660	663	664	666	660
		656	664	667	670	664	668	661	670	658	666
Minimum Speed		661	660	659	661	661	664	662	661	660	657
		668	657	660	662	661	657	658	661	660	659
		661	657	668	660	660	662	659	662	661	659
Maximum Speed		666	664	661	661	660	658	660	664	664	661
		660	660	656	660	660	661	658	662	667	664
		657	659	660	665	662	661	663	662	660	671
Initial	At Optimum Speed	662	664	662	661	664	659	660	658	661	664
		664	661	659	663	659	665	663	661	659	661
		665	665	659	663	662	663	662	661	662	665
Middle		658	656	670	667	663	667	668	660	664	666
		659	665	663	659	663	664	661	668	660	664
		663	659	662	662	660	664	664	660	668	661
End		671	661	659	662	665	658	666	671	659	662
		664	668	666	663	667	661	667	664	660	666
		671	660	661	663	670	662	664	664	665	657
Batch no. B											

Minimum Hardness		656	654	657	661	658	657	660	659	652	665
		660	652	665	652	666	652	666	658	665	658
		657	659	663	660	666	661	663	657	661	657
Maximum Hardness		662	660	662	657	661	662	667	664	658	665
		660	662	659	656	657	661	664	657	659	661
		659	662	663	663	657	661	660	662	657	662
Minimum Speed		656	667	658	653	662	661	669	658	656	660
		661	653	667	664	656	666	663	662	661	658
		660	663	663	658	664	659	653	661	660	662
Maximum Speed		665	661	659	656	664	667	663	664	656	663
		663	661	657	655	660	655	666	660	655	657
		656	664	656	657	663	667	661	661	661	659
Initial	At Optimum Speed	660	668	657	665	661	662	660	657	661	659
		656	661	660	662	660	662	664	659	663	668
		661	658	667	666	665	664	667	664	661	661
Middle		660	660	656	660	660	667	662	660	661	671
		659	658	660	666	661	666	665	664	662	666
		667	664	664	664	663	666	660	660	664	664
End		665	658	666	652	665	660	659	660	657	659
		658	657	665	663	668	656	654	657	658	658
		661	657	661	657	668	659	663	664	661	658
Batch no. C											
Minimum Hardness		665	660	657	668	661	660	666	666	664	658
		659	665	657	659	658	652	665	658	666	652
		657	654	656	657	665	663	659	660	663	659
Maximum Hardness		660	660	660	663	660	660	666	666	664	663
		666	661	660	662	663	665	666	665	661	660
		657	659	666	658	659	660	661	662	664	661
Minimum Speed		661	661	660	665	668	665	661	664	656	654
		667	659	662	660	666	661	665	662	657	668
		664	661	668	660	662	660	660	658	661	659
Maximum Speed		658	671	664	670	665	657	658	660	661	660
		659	657	660	662	663	655	666	671	664	659
		662	664	661	667	666	658	657	659	660	660
Initial	At Optimum Speed	662	663	663	657	661	667	659	662	660	662
		656	657	660	663	657	662	667	661	662	659
		664	657	654	663	662	658	657	661	665	665
Middle		661	660	656	665	667	658	663	660	658	664
		659	665	664	664	658	669	663	661	653	663
		656	654	658	660	662	658	663	661	660	665
End		656	656	663	664	667	663	657	659	656	664
		663	653	659	667	660	655	661	665	661	661
		659	661	668	660	657	655	660	660	655	660

Capability Index

Stage of Sampling		Batch I	Batch II	Batch III
Minimum Hardness		2.26	2.46	2.53
Maximum Hardness		2.61	4.00	3.91
Minimum Speed		4.10	2.62	2.92
Maximum Speed		3.36	2.89	2.44
Initial stage	At Optimum speed	4.96	3.16	3.29
Middle stage		2.92	3.09	2.85
End stage		2.49	2.75	2.80

Dissolution

Batch	At Maximum Hardness - Dissolution %						Mean (%)
A	91	96	93	92	94	95	**94**
B	89	98	99	100	89	96	**95**
C	96	98	97	98	94	96	**97**

% Assay

Stage of Sampling		Batch A	Batch B	Batch C
Minimum Speed		98.1	97.0	97.6
Maximum Speed		98.9	98.8	98.0
Initial stage	At Optimum speed	99.1	97.2	97.9
Middle stage		98.8	98.0	98.6
End stage		98.8	99.2	98.3

Table 6: Coating Parameters

COATING PARAMETERS		OBSERVATION					
Parameters	Specified	Batch No: A		Batch No: B		Batch No: C	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
Pan load (36")	Approx. 37.125 kg per lot	35.72	35.72	35.92	35.93	36.03	36.02
Inlet Temperature	65 ± 5°C	68	68	68	68	68	68
Exhaust Temperature	50 ± 5°C	50	50	50	50	50	50
Pan speed	1 - 10 RPM	03	03	03	03	03	03
Peristaltic pump speed	3 – 20 RPM	08	08	08	08	08	08
Spray rate	12± 5g/gun/min	14	14	14	14	14	14
Bed temperature	45 ± 5°C	48	48	48	48	48	48
No of spray guns	3	3	3	3	3	3	3
Distance Between gun and Tablet Bed	22 ± 3 cm	20	20	20	20	20	20
Diameter of the nozzle of spray gun	1.2 mm	1.2	1.2	1.2	1.2	1.2	1.2
Atomising Pressure	3 ± 1 kg/cm²	3	3	3	3	3	3

Table 7: INDIVIDUAL INPROCESS TEST DATA DURING COATING

S. No.	Parameter	Specification
1	Appearance	White to off-white, oval shaped, biconvex film coated tablets engraved with "ML 72" on one side and plain on other side.
2	Weight of 20 tablets	13.464 g ± 2.0% (13.19 g - 13.73 g)
3	Average weight	673.2 mg ± 2.0% (659.74 mg - 686.66 mg)
4	Thickness	5.60 mm ± 0.20 mm (5.40 mm - 5.80 mm)
5	Disintegration time (With Disc)	NMT 20 Minutes
6	Uniformity of Weight	673.2 mg ± 5% (639.54 mg - 706.86 mg)
7	Length**	18.10 mm ± 0.20 mm
8	Width**	8.60 mm ± 0.20 mm

Table 8: Result at coating stage

Observation of appearance								
Appearance								
Stage of Sampling			**Batch no. A**		**Batch no. B**		**Batch no. C**	
Coating (Lot I)			Complies		Complies		Complies	
Coating (Lot II)			Complies		Complies		Complies	
Results of Thickness								
Stages of Sampling	**Thickness (mm)**						**Min**	**Max**
Batch No. A								
Coating (Lot I)	5.52	5.61	5.63	5.65	5.66	5.64	**5.52**	**5.66**
Coating (Lot II)	5.60	5.63	5.59	5.65	5.62	5.51	**5.51**	**5.65**
Batch No. B								
Coating (Lot I)	5.52	5.61	5.63	5.64	5.58	5.59	**5.52**	**5.64**
Coating (Lot II)	5.60	5.61	5.65	5.58	5.54	5.56	**5.54**	**5.65**
Batch No. C								
Coating (Lot I)	5.60	5.64	5.58	5.62	5.56	5.59	**5.54**	**5.64**
Coating (Lot II)	5.57	5.62	5.63	5.62	5.65	5.60	**5.57**	**5.65**
Results of Length and Width								
Stage of Sampling	**Parameter**	**Batch no. A**		**Batch no. B**		**Batch no. C**		
		Min	**Max**	**Min**	**Max**	**Min**	**Max**	
Coating (Lot I)	Length	18.08	18.12	18.09	18.13	18.10	18.13	
	Width	8.58	8.62	8.58	8.62	8.57	8.64	
Coating (Lot II)	Length	18.09	18.13	18.09	18.13	18.08	18.13	
	Width	8.55	8.62	8.59	8.64	8.58	8.63	
Results of Disintegration Time (minutes, determined at 37°C ± 2°C)								
Stage of Sampling			**Batch no. A**		**Batch no. B**		**Batch no. C**	
Coating (Lot I)			12 min 56 sec		13 min 01 sec		13 min 09 sec	
Coating (Lot II)			13 min 03 sec		12 in 59 sec		13 min 02 sec	
Results of Group Weight(g)								
Stage of Sampling			**Batch no. A**		**Batch no. B**		**Batch no. C**	
Coating (Lot I)			13.537		13.491		13.466	

Coating (Lot II)	13.472				13.486			13.480		
Results of Average Weight (mg)										
Stage of Sampling	**Batch no. A**				**Batch no. B**			**Batch no. C**		
Coating (Lot I)	676.7				674.5			673.3		
Coating (Lot II)	673.6				674.3			674.0		
Results of Uniformity of Weight										
Stage Of Sampling	**Individual weight of 20 tablets (mg)**									
Batch no. A										
Coating (Lot I)	673	671	681	680	675	669	678	683	676	681
	677	678	677	673	680	681	681	673	675	672
Coating (Lot II)	673	676	674	673	673	672	672	678	677	677
	672	675	673	671	672	669	674	675	670	676
Batch no. B										
Coating (Lot I)	673	672	671	671	678	679	673	669	669	672
	677	676	674	676	674	679	681	674	677	677
Coating (Lot II)	671	670	668	673	675	673	674	684	674	668
	669	679	672	679	677	678	674	677	676	675
Batch no. C										
Coating (Lot I)	675	675	669	674	676	676	677	669	673	670
	674	669	677	670	676	674	671	674	674	673
Coating (Lot II)	676	674	672	676	669	672	675	674	667	677
	670	679	681	675	673	679	670	671	678	672

Result % Weight Gain

Sr. No.	**Batch A**		**Batch B**		**Batch C**	
	Lot I	**Lot II**	**Lot I**	**Lot II**	**Lot I**	**Lot II**
1	1.93	2.23	1.63	1.64	2.07	2.96
2	1.19	2.96	1.79	0.30	2.07	2.67
3	3.38	0.59	1.34	1.65	1.35	1.34
4	3.09	0.89	2.09	1.19	1.34	1.78
5	2.22	1.49	2.51	2.07	1.18	0.30
6	0.75	0.74	2.50	1.63	1.63	1.34

Results of Dissolution

Stages of Sampling	**Dissolution (%)**						**Mean**
Batch No. A							
Coating (Lot I)	97	97	100	98	100	99	**98**
Coating (Lot II)	95	96	99	99	98	96	**97**
Batch No. B							
Coating (Lot I)	100	100	100	100	97	99	**99**
Coating (Lot II)	99	99	96	99	99	98	**98**
Batch No. C							
Coating (Lot I)	97	102	104	101	103	100	**101**
Coating (Lot II)	100	103	98	101	104	102	**101**

Table 9: Bulk packing and Leak test

Batch	**Frequency**	**Counting machine speed**	**Tablet counting**	**Leak test**
I	Initial	15	30	Pass
	Middle	25	30	Pass
	End	20	30	Pass
II	Initial	15	30	Pass
	Middle	25	30	Pass
	End	20	30	Pass
III	Initial	15	30	Pass
	Middle	25	30	Pass
	End	20	30	Pass

Table 10: Finished product analysis report

S. No	Tests	Specification	Batch no.(Results)		
			A	B	C
1.0	**Description**	White to off-white, oval shaped, biconvex, film coated tablets engraved with "ML 72" on one side and plain on the other side.	Complies	Complies	Complies
2.0	**Identification** A. By HPLC B. By IR	 The retention time of the principal peak in the chromatogram of sample preparation should correspond to that of the principal peak in the chromatogram of standard preparation, as obtained in the "Assay". Infrared absorption spectrum of the residue should exhibit maxim at the same wavelengths as that of the Famciclovir reference/working standard.	Complies	Complies	Complies
3.0	**Average weight** (mg)	673.2 ± 2.0 %	676.0	674.6	673.1
4.0	**Disintegration Time** (minutes; determined at 37°C ±2°C)	Not more than 20	10 min 50 sec	11 min 10 sec	14 min 02 sec
5.0	**Water** (By KF, % w/w)	Not more than 2.5	1.48	0.75	0.73
6.0	**Dissolution** (in 0.1 N Hydrochloric acid; 900 mL; paddle, 50 rpm; 30 min by HPLC, % amount of labeled)	Not less than 80 (Q)	100 101 100 101 100 101	96 98 102 96 98 100	97 101 103 100 102 99
7.0	**Uniformity of Dosage Units** (By Weight variation, as Famciclovir [$C_{14}H_{19}N_5O_4$] Acceptance value	Less than or equal to 15.0	1.0	1.0	1.1
8.0	Related substances (By HPLC, %w/w) Monohydroxy impurity Any other individual impurity Total impurities	 Not more than 0.15 Not more than 0.10 Not more than 0.70	 0.063 Below Limit 0.063	 0.042 Below Limit 0.042	 0.038 Below Limit 0.038
9.0	Assay (By HPLC) Famciclovir [C14H19N5O4] - mg / tablet - % label claim	 475.0 to 525.0 95.0 to 105.0	 493.60 98.7	 496.45 99.3	 497.99 99.6
10.0	Residual Solvents	Should comply with option 2 of USP residual solvents <467>	Complies	Complies	Complies
11.0	Polymorphism (By XRD) A. Identification of polymorphic form I and form II B. Content of monohydrate form (%)	Diffractogram pattern should exhibit the characteristic peaks of Form-I at 2θ values of 15.5 and 15.9 ± 0.2° and the characteristics peaks of Form-II at 2θ values of 16.2 and 16.4 ± 0.2°. Not more than 5	Form I at 2θ value of 15.5 and 15.9 Form II at 2 θ value of 16.1 and 16.4 Below Limit	Form I at 2θ value of 15.5 and 15.9 Form II at 2 θ value of 16.1 and 16.3 Below Limit	Form I at 2θ value of 15.5 and 15.9 Form II at 2 θ value of 16.1 and 16.4 Below Limit

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