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Process Validation for Famciclovir

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Abstract

The project entitled "Process validation of Famciclovir 500 mg Tablets" was carried out at Macleods Pharmaceuticals as the validation batch met the specification of tablets. Process validation study on three consecutive batches, Batch No. A, B,and C 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, coating and container packing. It shall also establish the suitability of equipments and area used for the production. The process of manufacturing was carried as per the approved batch manufacturing card. The all process validation batches had been manufactured and validated in full compliance with cGMP requirement.

Key-words: Process validation, Famciclovir, GMPs.

Introduction

-"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." [1]

Conducting process validation is not only a regulatory requirement, but also makes a great deal of sense from engineering as well as a business point of view. It is evident that pharmaceutical companies that are well versed in conducting process validation have a competitive advantage over those who are not. Process validation is required, in both general and specific terms, by the Current Good Manufacturing Practices regulations for finished pharmaceuticals, 21 CFR parts 210 and 211. A requirement for process validation is set forth in general terms in sections 211.100 written procedures; deviations-which states, in parts; "there shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality and purity; they purport or are represented to posses". Several sections of cGMP regulations states, validation requirement in more specific terms. Excerpts from some of the sections are: Section 211.100 sampling and testing of in process materials and drug products.

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a) "Control procedures shall be established to monitor the output and validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in process material and drug products." Section 211.113 control of microbiological contamination

b) "Appropriate written procedures, design to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process."

The requirement of process validation is implicit in the language of schedule M, Good manufacturing practices regulation which states "To achieve the objective, each licensee shall evolve methodology and procedure which should be documented and kept for reference and inspection".

Process validation is required by the medical device GMP regulation, 21 CFR parts 820. Section 820.5 requires every finished device manufacturer to states: "Prepared and implement a quality assurance program that is appropriate to the specific device manufactured". Section 820.3 states: "All activities necessary to verify confidence in the quality of the process used to manufacture a finished device".

A generally stated requirement for process validation is contained in section 820.100, states: "Written manufacturing specification and processing procedure shall be established, implemented, and controlled to assure that device conforms to its original design or any approved changes in that design". Validation is an essential element in the

establishment and implementation of a process procedure, as well as in determining what process controls are required in order to assure conformance to specification.

Section 820.100(a) (1), states: "Control measures shall be established to assure that the designed basis for device, components and packaging is correctly translated in to approved specification".

To validate the process of manufacturing of Famciclovir tablets using the Wet Granulation Technology. The objective of this exercise is to develop a PROCESS VALIDATION PROTOCOL to validate the process and have documented evidence to ensure that critical process variables are checked during validation. Also to demonstrate the process capability of the product meets its predetermined specifications and quality attributes.

Material and Methods

Famciclovir, Lactose Anhydrous, Sodium Starch Glycolate (Type A), Hydroxy Propyl Cellulose, Magnesium Stearate, Opadry White, Purified Water is provided by Macleods Pharmaceuticals Limited, Daman Unit-2.

Table 1: List of Instruments

Equipment	Capacity	Model No.
Weighing balance (In Calibration) (LC GC)	210 g, 600 g, 100 kg	NA
Vibro sifter (20 #, 40 #, 60	550 mm	GMP SS316
Multimill (Sams)	0.5 mm, 2.5 mm	GMP
Rapid mixer granulator (Kevin)(High shear granulator)	50 L 150 L	HSMG- 150
Fluid bed drier (Alliance)	30 kg	GM 305
Octagonal blender	380 L	GMP
20 station compression machine (Cadmach)	21500 – 93600 tablets/hour	CPMD- 320
Coating machine	150 L	SC-36
Metal Detector(M R Equipment)	NA	Digital Tablet Metal Detector
Deduster (Chamunda Tablet	NA	CPMDB- 80
Mechanical Stirrer (Pharmachem Equipment Pvt. Ltd.)	NA	NA
Tablet Inspection Belt(V Ranganathan Engineering Works)	NA	GMP
Paste Preparation Vessel	25 L	GMP

Manufacturing procedure:

Sifting

Famciclovir was sifted through #40 ASTM (American Society of Testing and Materials) sieve (#425 u) using a Vibro sifter .Lactose was sifted Anhydrous through #40 ASTM sieve (#425 u) using a Vibro sifter. Sodium starch Glycolate was sifted through #40 ASTM sieve (#425 u) using a Vibro sifter.

Dry mixing

The ingredients were mixed in RMG for 7 min at slow speed Agitator.

Granulation

Dissolve Hydroxypropyl cellulose in purified water under stirring and stir to form clear solution. Add binder solution to the blend in RMG and granulate at slow speed with impeller. After addition of binder solution, start impeller and chopper intermittently slow /fast speed till granules of required consistency is obtained. If required add additional quantity of purified water to get required consistency of granules. .(Total water not exceed more than 170 mg for 500 mg strength and calculate respectively for 125mg and 250 mg strengths) Mill the wet mass through 8 mm screen on multimill at medium speed knives forward direction.

Drying

The wet granules were dried in fluid bed dryer at an inlet temperature of 550C- 650C till the desired LOD is achieved (LOD limit: 0.9% w/w to 1.5 % w/w at 700C).

Size reduction

The dried granules were sifted though #20 ASTM sieve (#850 u).Mill the retained granules through 2.0mm screen fitted on multimill at fast speed knife forward direction and sift the milled granules though #20 ASTM sieve (#850 u). If required, mill the retained granules though 1.5 mm screen fitted on multimill at fast speed knives forward direction and sift the milled granules though #20 ASTM sieve (#850 u).The sized granules were transferred to low shear blender and mix for 02 minutes at slow speed. The sample sent to QC for particle size distribution test for milled granules (Limit-#20 ASTM sieve pass NLT 95%, #60 ASTM sieve retains NLT 25 % and NMT 60%, #100 ASTM sieve passed NMT 60%)

Pre lubrication

Lactose anhydrous was sifted though # 40 ASTM sieve (#425 u).Low substituted Hydroxypropyl cellulose was sifted though # 40 ASTM sieve (#425u).Sodium starch glycolate was sifted though # 40 ASTM sieve (#425 u).The sifted ingredients were transferred in low shear blender and mix for 10 minutes at slow speed.

Lubrication

Magnesium stearate was sifted through #60 ASTM sieve (#250u).Transfer the sifted magnesium stearate in low shear blender and mix for 3 minutes at slow speed.

Blend Analysis

Intimate the quality assurance Department for sampling and quality control Department for analysis of blend as per current in process specification.

Compression

The approved blend was compressed on rotary compression machine as per following

For 500 mg strength:

18 mm X 8.5 mm oval shaped, concave punches having "ML72" embossed on upper punch and plain on lower punch.

Coating

Preparation of coating dispersion:

Take purified water in stainless steel tank and stir to form vortex. Add Opadry white Y-1 7000 to the vortex, avoiding power floatation on the liquid surface and stir for 45 minutes. Preheat the bed of core tablets to a temperature of 45OC to 55 OC. Spray the coating solution on the rolling tablet. Continue spraying till the target weight build up of 13.2mg ± 2mg for 500mg is achieved on core tablet of 660mg.

Finished product analysis

Intimate to Quality Assurance department for sampling and Quality control department for analysis of product as per current finished product specifications.

Packaging

Pack the coated tablets as per current approved packing specifications

Table 2: Process Steps and Control variable

Processing stage	Control variables	Measured response
Blending	☐Load (Kg)☐ Speed☐ Time	☐ Load (Kg)☐ Speed☐ Time
Milling	☐ Screen size	☐ Screen size
Slugging	☐ Speed of compaction	☐ Appearance of compacted
Sizing (Sifting & Milling)	☐ Sieve size☐ Screen size ☐ Speed of mill	☐ Sieve analysis
Blending	☐Load (Kg)☐ Blending time☐ Speed of Blender	☐Description☐ Blend uniformity by % Assay of Amlodipine Besylate☐ Particle size distribution☐
Compression	☐ Speed of the machine / Stages of Operation	☐ Appearance☐ Average weigh☐ Uniformity of weight☐ Diameter☐ Thickness
Packaging	☐ Temperature (Forming & sealing) ☐	☐ Pocket Formation☐ Quality of

Results and Discussion

Table 5.1 Batches under validation

Sr. No	Batch No.	Manufacturing Date	Expiry Date
1	A	09/2015	08/2017
2	B	10/2015	09/2017
3	C	11/2015	10/2017

Table 5.2 Master formula **Batch size:** 112500 Tablets

Sr No.	Components	Specification	Weight / Tablet in
	Dry mixing		
1.	Famciclovir	IHS	500.000
2.	Lactose anhydrous (Super tab 21AN/DMV-Fonterra)	USP NF / Ph Eur	10.200

3.	Sodium starch Glycolate (Type A, Glycolys/Roquette)	USP NF / Ph.Eur	13.800
Granulation			
4.	Hydroxy Propyl cellulose (Klucel LF Pharma/Hercules {Aqualon})	USP NF / Ph.Eur	6.600
5.	Purified Water#	IHS	150.000
Lubrication			
6.	Lactose Anhydrous (Supertab 21 AN/ DMV-Fonterra)	USP NF / Ph.Eur	93.700
7.	Low-Substituted Hydroxy Propyl cellulose (L-HPC-LH-11/Shin Etsu)	USP NF / IHS	16.500
8.	Sodium starch Glycolate (Type A, Glycolys/Roquette)	USP NF / Ph.Eur	12.600
9.	Magnesium stearate (Vegetable origin/Ferro)	USP NF / Ph. Eur	6.600
Core tablet weight			660.000

 # Does not appear in final product

Coating Material			
10.	Opadry White Y-1-7000 (Color on)	IHS	19.800
11.	#Purified water	IHS	145.200
Weight Build up			13.200
Weight of final film coated tablet			673.200

The environmental conditions during the manufacturing of famciclovir granules were monitored and recorded stage wise.The stage wise temperature and relative humidity readings are tabulated below.

Recommended conditions:

Temperature: 23 ± 2°C Relative humidity: 45 ± 5%

Table 5.3 Observation table for temperature

Sr. No.	Unit operation	Observation of Temperature (°C)		
		A	B	C
1	Dispensing	22	22	23
2	Sifting	22	23	22
3	Granulation	23	22	22
4	Drying	24	24	22
5	Sifting &milling	22	22	24
6	Blending	23	22	23
7	Compression	22	23	22
8	Coating	23	22	22

Table 5.4 Observation table for humidity

Sr. No.	Unit operation	Observation of Relative Humidity (%)		
		A	B	C
1	Dispensing	49	47	48
2	Sifting	47	48	46
3	Granulation	48	47	46
4	Drying	46	44	45
5	Sifting &milling	46	48	49
6	Blending	49	48	47
7	Compression	47	48	49
8	Coating	46	47	47

Table 5.5 Usage of raw material (active):

Active Material	B.No.	Assay	LOD
Famciclovir IHS	A	99.8	0.189
	B	99.8	0.189
	C	99.7	0.169
Limit		98.5 – 102.0%	NMT 0.5 % w/w

DRY MIXING:

Dry mixing profile:

Name of Equipment: Rapid Mixer granulator (150 Liters)
Equipment make : Kevin
Time of mixing : 7 minutes
Agitator speed : Slow

Table 5.6 Weight Required For Dry Mix

Sample	Weight required (g)	Weight taken (g)					
		B. No. A		B. No. B		B. No. C	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
Composite	50 +3 g	50 +3 g	50 +3 g	50 +3 g	50 +3 g	50 +3 g	50 +3 g

Table 5.7 Result of Bulk Density (Dry Mix)

Batch No.	Lot	Tapped Bulk Density	Untapped Bulk Density	LOD at 70^{o}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		

GRANULATION:
Granulation process profile:
Name of Equipment : Rapid Mixer granulator (150 Liters)
Equipment make : Kevin
Speed of the mixer : Slow speed till dough mass of suitable consistency is obtained.
Impeller If required runs the mixer at high speed for some time

Table 5.8 Wet granulation:

Operation		**RESULLIILTLTS**					
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	8.5 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

DRYING
Drying process profile:
Name of Equipment: Fluid bed dryer (30 kg)
Equipment make: Alliance
Measured Response: LOD
Limit: 0.9-1.5% w/w at 105°C
Where T1=Top Left, T2 Top M1=Middle Lt .M2=Middle Corner M3= Middle Rt.
B1=Bottom Lt., B2= Bottom

T1 T2
M1 M2 M3
B1 B2

Figure 5.1: Sampling points in fluid bed dryer bowl

Table 5.9: Observation of drying process

Operation	RESULTS					
	Batch No.: A		Batch No.: B		Batch No.: C	
	Lot-I	Lot-II	Lot-I	Lot-II	Lot-I	Lot-II
Total Drying Time (Min)	180 min	180 min	180 min	180 min	195 min	193 min
Inlet Temperature (ºC)	60 to 65°C	60 to 65°C	60 to 65°C	60 to 64°C	57 to 64°C	59 to 64°C
Final Outlet Temp. (ºC)	51°C	51°C	51°C	51°C	51°C	51°C

Table 5.10 Results For During Drying Granules

Sample	Weight required (g)	Weight taken(g)					
		Batch No. A		Batch No. B		Batch No. C	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
1	Approx 2 g	2.039	2.485	2.051	2.049	2.289	2.093
2	Approx 2 g	2.026	2.070	2.030	2.024	2.200	2.035
3	Approx 2 g	2.034	2.065	2.126	2.415	2.037	2.061

Sample	Acceptance Criteria	Results of LOD in % w/w					
		Batch No. A		Batch No. B		Batch No. C	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
1	Limit :Till desired LOD achieved 0.9-1.5% w/w	8.75	10.26	11.61	10.32	9.98	6.60
2		4.15	5.91	8.34	8.56	6.61	4.18
3		3.20	2.86	4.38	5.30	3.69	2.38

Table 5.11 Results For After Drying Granules

Sample	Weight required (g)	Weight taken (g)					
		Batch No. A		Batch No. B		Batch No. C	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
T1	2 – 5 g	2.132	2.036	2.033	2.155	2.183	2.059
T2	2 – 5 g	2.036	2.039	2.060	2.133	2.090	2.088
M1	2 – 5 g	2.026	2.136	2.240	2.259	2.192	2.060
M2	2 – 5 g	2.048	2.164	2.261	2.297	2.098	2.046
M3	2 – 5 g	2.127	2.016	2.076	2.261	2.108	2.026
B1	2 – 5 g	2.073	2.076	2.079	2.087	2.056	2.013
B2	2 – 5 g	2. 049	2.032	2.099	2.102	2.103	2.433

Result of Lod Of Bulk Samples (Dried Granules)

Sample	Acceptance Criteria	Results of LOD in % w/w					
		Batch No. A		Batch No. B		Batch No. C	
		Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
T1		1.43	0.93	1.18	1.07	1.28	1.21
T2		1.35	1.33	1.07	1.04	1.35	1.30
M1		1.00	1.04	1.12	1.24	1.14	1.02
M2	Limit : 0.9-1.5 W/V % w/w	1.28	1.11	1.19	1.18	1.14	1.27
M3		1.37	1.29	1.06	0.97	1.29	1.23
B1		1.21	1.06	1.30	0.96	1.07	1.04
B2		1.27	1.03	1.43	1.14	1.43	1.19
Average		1.27	1.11	1.19	1.09	1.24	1.18

Table 5.13 Result Of Sieve Analysis (Milled Granules)

Sieve Size	Micrometer	Acceptance Criteria	% w/w					
			Batch No.: A		Batch no.: B		Batch no.: C	
			Lot I	Lot II	Lot I	Lot II	Lot I	Lot II
20#	850 µm	Pass through #20- NLT 95%Retention on #60 – NLT 25 to NMT60% Pass through #100- NMT 60%	99.34	99.43	98.24	98.58	98.95	99.07
60#	250 µm		42.55	42.67	47.38	46.93	36.55	39.51
100#	150 µm		34.30	33.50	35.28	33.94	46.60	44.04

Table 5.14 Result Of Bulk Density And Lod (Milled Granules)

Batch No.	Lot	Tapped Bulk Density	Untapped Bulk Density	LOD (70°C/IR Balance)
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		For record		(0.9-1.5 % w/w)

Table 5.15 Weight Required for Milled Granules- after 02 minutes mix in OGB

Sample	Weight required(g)	Weight taken (g)		
		B. No. A	B. No. B	B. No. C
Composite	50 g	50 g	50 g	50 g

Table 5.16 Result Of Sieve Analysis (Milled Granules)

Sieve(Size)	Micrometer	Acceptance Criteria	% w/w		
			Batch No.: A	Batch no.: B	Batch no.: C
20#	850 µm	Pass through #20 - NLT 95Retentionn#60 – NLT25 to NMT60% Pass through#100- NMT 60%	98.20	98.64	99.13
60#	250 µm		40.43	44.93	40.09
100#	150 µm		36.86	36.44	42.57

Table 5.17 Result of Bulk Density and Lod (Milled granules)

Batch No.	Tapped Bulk Density	Untapped Bulk Density
A	0.62 gm/ml	0.43 gm/ml
B	0.61 gm/ml	0.45 gm/ml
C	0.63 gm/ml	0.43 gm/ml
Acceptance Criteria	For record	

Table 5.19 Results for Lubricated Blend

Sample	Batch No. A		Batch No. B		Batch No. C	
	3 min		3 min		3 min	
	Weight taken	% Assay	Weight taken	% Assay	Weight taken	% 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
Min		97.0		97.8		98.3
Max		98.5		99.5		99.5
Mean		98.0		98.5		98.9
RSD		0.46		0.65		0.40

Table 5.20 Weight Required for Lubricated Granules

Sample.	Weight required(g)	Weight taken (g)		
		B. No. A	B. No. B	B. No. C
Composite	50 g	50 g	50 g	50 g

Table 5.21 Result Of Description, Bulk Density, Assay & Lod (Lubricated Granules)

Batch No.	Description	Tapped Bulk Density	Untapped Bulk Density	Assay (%)	LOD(At 80°Cfor 3 hr)
A	White powder	0.68 gm/ml	0.50 gm/ml	98.6	0.50
B	White powder	0.68 gm/ml	0.50 gm/ml	98.1	0.67
C	White powder	0.68 gm/ml	0.48 gm/ml	98.1	0.45
Acceptance Criteria	White to off white powder	For record	For record	For information only	(NMT 2.0 % w/w)

Table 5.22 Result Of Sieve Analysis (Lubricated Granules)

Sieve Analysis	Micrometer	Acceptance Criteria	% w/w Retention		
			B. No. A	B. No. B	B. No. C
60#	250 µm	For Record	29.41	32.79	32.46
100#	150 µm		22.27	20.16	20.36

Table 5.23 Percentage Batch yield at the end of lubrication:

Batch no.	% Yield	Limit*
A	**98.05**	***NLT 98.0%**
B	**97.86**	
C	**98.02**	

Yield Limit is tentative and will be finalized after 10 or more production batches

Table 5.24 Individual In-Process Test Data during Compression:

Sr.No.	Parameter	Approximate sample size	Specification
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	Weight of 30 tablets	30 tablets	19.80 g ± 2.0 %
3	Average Weight	30 tablets	660.0 mg ± 2.0 %(646.8 mg - 673.2 mg)
4	Uniformity of weight	30 tablets	660.0 mg ± 5.0 % (627.0mg – 693.0 mg)
5	Thickness	30 tablets	5.50 mm ± 0.20 mm
6	Hardness	6 tablets	170 ± 50 N (120 – 220 N)
7	Disintegration time (With Disc)	6 tablets	NMT 15 minutes
8	Friability	9 tablets	NMT 1.0% w/w
9	Length**	30 tablets	18.00 mm ± 0.20 mm
10	Width**	30 tablets	8.50 mm ± 0.20 mm
11	Capability Index	30 tablets	Not less than 1.33

Table 5.25 Observation of Appearance

	Appearance		
Stage Of Sampling	**Batch no. A**	**Batch no. B**	**Batch no. C**
Minimum Hardness	Complies	Complies	Complies
Maximum Hardness	Complies	Complies	Complies
Minimum Speed	Complies	Complies	Complies

Maximum Speed		Complies	Complies	Complies
Initial	At Optimum Speed	Complies	Complies	Complies
Middle		Complies	Complies	Complies
End		Complies	Complies	Complies

Table 5.26 Results of Thickness

		Thickness					
Stage Of Sampling		**Batch no. A**		**Batch no. B**		**Batch no. C**	
		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	At Optimum Speed	5.55	5.62	5.50	5.55	5.56	5.64
Middle		5.51	5.60	5.50	5.55	5.52	5.65
End		5.50	5.58	5.49	5.54	5.55	5.61

Table 5.27 Results of Length and Width

Stage Of Sampling		Parameter	Batch no. A		Batch no. B		Batch no. C	
			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	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		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		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

Table 5.28 Results of Hardness

Stages of Sampling		Hardness (N)						Mean
								Batch No. A
Minimum Hardness		133	130	139	131	140	132	**134**
Maximum		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	At	157	160	162	163	159	158	**160**
Middle	Optimum	160	158	155	153	166	167	**160**
End		153	156	157	169	160	158	**159**
								Batch No. B
Minimum Hardness		129	131	130	140	135	130	**133**
Maximum		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	At Optimum	163	169	170	168	167	166	**167**
Middle	Speed	160	163	164	159	162	163	**162**
End		168	159	162	160	163	158	**162**
								Batch No. C
Minimum Hardness		127	138	140	132	129	133	**133**
Maximum		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	Optimum	168	163	158	154	165	170	**163**
Middle	Speed	172	158	165	161	169	161	**164**
End		160	163	172	169	170	165	**167**

Table 5.29 Results of Friability

Friability (% w/w)			
Stage Of Sampling	**Batch no. A**	**Batch no. B**	**Batch no. C**
Minimum Hardness	0.14	0.09	0.31
Maximum Hardness	0.09	0.10	0.12
Minimum Speed	0.21	0.24	0.23

Table 5.30 Results of Disintegration Time

Disintegration Time (minutes, determined at 37°C ± 2°C)

Stage Of Sampling		**Batch no. A**	**Batch no. B**	**Batch no. C**
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	At	10 min 09 sec	09 min 50 sec	10 min 26 sec
Middle	Optimum	09 min 50 sec	10 min 00 sec	10 min 19 sec
End	Speed	09 min 40 sec	10 min 11 sec	**Table 5.** in 54 Sec

Table 5.31 Results of Group Weight Group weight (g)

Stage Of Sampling	**Batch no. A**	**Batch no. B**	**Batch no. C**

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	At	19.856	19.858	19.826
Middle	Optimum	19.888	19.880	19.827
End	Speed	19.917	19.803	19.805

Table 5.32 Results of Average weight (mg)

		Average weight (mg)		
Stage Of Sampling		**Batch no. A**	**Batch no. B**	**Batch no. C**
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	Optimum	661.9	661.9	660.9
Middle	Speed	662.9	662.7	660.9
End		663.9	660.1	660.2

Table 5.37 Results of % Yield after Compression

Batch no.	% Yield	Limit*
A	**96.14**	***NLT 97.0%**
B	**96.68**	
C	**96.97**	

Yield Limit is tentative and will be finalized after 10 or more production batches

Table 5.38 In Process Analysis Report

Sr. No.	Tests	Specification	Batch No.(RESULTS)		
			A	**B**	**C**
1.	**Description**	White to off white, oval shaped, biconvex, uncoated tablets, engraved with "ML 72" on one side and plain on the other side.	Complies	Complies	Complies
2.	**Identification** (By HPLC)	The retention time of the principal peak in the chromatogram of sample preparation corresponds to that of the principal peak in the chromatogram of standard preparation as obtained in the "Assay".	Complies	Complies	Complies

3.	**Average weight** (mg)	660.0 ± 2.0 % (646.8 – 673.2)	658.81	659.37	659.83
4.	**Uniformity of weight**	660.0 mg ± 5 % (627.0– 693.0)	Min: 0.87 Max:0.88	Min: 0.86 Max:1.17	Min: 0.91 Max:1.11
5.	**Length** (mm)	18.0 ± 0.2 (17.8 – 18.2)	Min:18.02 Max:18.10	Min:18.03 Max:18.13	Min18.03 Max18.06
6.	**Width** (mm)	8.5 ± 0.2 (8.3 – 8.7)	Min:8.50 Max:8.60	Min:8.55 Max:8.56	Min:8.50 Max:8.60
7.	**Thickness** (mm)	5.5 ± 0.2 (5.3 – 5.7)	Min:5.52 Max:5.60	Min:5.51 Max:5.57	Min:5.53 Max:5.62
8.	**Hardness** (N)	120 to 220	Min:127 Max:161	Min:131.85 Max:156.78	Min:138.52 Max:165.49

9.	**Friability** (%	Not more than 1.0			
10.	**Disintegration Time** (min; determined at 37°C ± 2°C, with discs)	Not more than 15	12 min 12 sec	10 min 35 sec	09 min 06 sec
11.	**Dissolution** (In 0.1 N HCl; 900 mL; paddle, 50 rpm; by HPLC, % of labeled amount in 30 min)	Not less than 80 (Q)	95 92 94 95 96 95	96 89 93 91 96 92	100 98 98 98 96 98
12.	**Assay** (By HPLC) Famciclovir [$C_{14}H_{19}N_5O_4$] mg / tablet % label claim	475.0 to 525.0 95.0 to 105.0	494.319 98.9	496.178 99.2	494.932 99.0

COATING: On release of the Compressed Tablets by QA, the core Tablets are taken up for coating. During tablet coating stage, Tablets are coated in a Auto coater to validate the Coating process for Famciclovir tablet 500 mg Tablet, samples are collected for analysis for each Lot as defined in the sample summary. These validation samples shall be tested as per the sample summary, to meet the acceptance criteria specified therein.

Table 5.39 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
Atomizing Pressure	3 ± 1 kg/cm²	3	3	3	3	3	3

Table 5.40 Individual In process Test Data during Coating:

Sr. 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)
8	Width**	8.60 mm ± 0.20 mm

Table 5.41 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

Table 5.42 Results of Thickness

Stage 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**

Table 5.43 Results of Length and Width

							Length & 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

Table 5.44 Results of Disintegration Time

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 min 59 sec	**Table 5.** min 02 sec

Table 5.45 Results of Group Weight

			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

Table 5.46 Results of Average Weight

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

Table 5.47 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

Table 5.48 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 5.49 Results of Dissolution Profile

Time Interval	CUMULATIVE % DRUG RELEASED (Famciclovir) Dissolution Medium: 0.1N Hydrochloric acid												B. No.: A	
													% MEAN	% RSD
10 min	50	40	44	37	40	35	37	34	38	39	48	35	40	12.9
15 min	74	61	66	58	62	74	54	56	54	47	64	72	62	13.5
20 min	88	80	82	75	78	92	70	75	77	63	81	87	79	10.3
30 min	100	101	100	96	102	103	93	96	98	86	98	99	98	4.9
45 min	99	102	102	104	105	103	104	100	98	100	99	98	101	2.4

Time Interval	CUMULATIVE % DRUG RELEASED (Famciclovir) Dissolution Medium0.1 N Hydrochloric acid												B. No.: B	
													% MEAN	% RSD
10 min	43	46	34	47	47	31	35	41	48	40	50	41	42	14.5
15 min	63	69	54	67	70	48	51	59	72	64	72	65	63	12.5
20 min	79	84	71	84	86	66	66	74	86	83	87	83	79	10.0
30 min	98	101	93	101	101	86	88	98	99	100	100	99	98	4.9
45 min	103	102	104	104	102	101	102	103	102	103	102	102	103	1.0

Time Interval	CUMULATIVE % DRUG RELEASED (Famciclovir) Dissolution Medium:0.1 N Hydrochloric acid												B. No.: C	
													% MEAN	% RSD
10 min	37	45	36	33	30	34	37	35	51	55	44	54	41	21.1
15 min	57	70	56	51	49	51	56	54	69	79	65	80	61	17.1
20 min	73	87	74	67	65	65	69	70	84	95	82	96	77	14.4
30 min	97	102	99	92	90	86	91	93	101	102	103	102	96	6.2
45 min	100	100	99	101	102	101	101	102	99	101	102	100	101	1.0

Table 5.50 Finished Product Analysis Report

Sr. 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	The R.T. 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	96 98 102 96 98	97 101 103 100 102
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	FormIat 2θ value of 15.5 and15.9 Form II at2θ value of 16.1 and 16.4 Below Limit	FormI at 2θ value of 15.5 and15.9 Form II at2θ value of 16.1 and 16.3 Below Limit	Form I at2θ value of 15.5 and 15.9 Form II at 2θ value of 16.1 and 16.4 Below Limit

Table 5.51 % Yield After Coating

Batch no.	% Yield	Limit*
A	**95.85**	***NLT 97.0%**
B	**96.41**	

C	**96.69**	

*Yield Limit is tentative and will be finalized after 10 or more production batches

5.10 INSPECTION

Table 5.52 Verification of inspected Tablet

Appearance	A	B	C
Stage Of Sampling	Complies	Complies	Complies
Minimum Hardness	Complies	Complies	Complies
Maximum Hardness	Complies	Complies	Complies
Minimum Speed	Complies	Complies	Complies
Maximum Speed	Complies	Complies	Complies
Initial(At opt)	Complies	Complies	Complies
Middle &end	Complies	Complies	Complies

Table 5.53 Identification of Defects

Critical	Qty	Major& Minor	Qty
Nil	**0**	**Nil**	**0**

Result: The batch passes the AQL criteria

Table 5.54 % Yield after Inspection

Batch no.	% Yield	Limit*
A	**95.81**	***NLT 96.5%**
B	**96.37**	
C	**96.65**	

PACKING:

Components:

Container Pack: Container, round white, HDPE, 40 cc, 33-400 neck finish
Closure, child resistant, with Pulp and heat seal Liner, 33 mm validated parameters:
Machine Speed: 20 ± 05 containers/minute

Container Pack

Table 5.55 Observation Of Tablet Counting Machine

B. No.	Frequency	Leak Test	Tablet Counting
A	Initial	Pass	30 tablets
	Middle	Pass	30 tablets
	End	Pass	30 tablets
B	Initial	Pass	30 tablets
	Middle	Pass	30 tablets
	End	Pass	30 tablets
C	Initial	Pass	30 tablets
	Middle	Pass	30 tablets
	End	Pass	30 tablets

* Vary the speed from minimum to maximum

Table 5.56 Cumulative Yield Data For Packing:

Conclusion

The project entitled "Process validation of Famciclovir 500 mg Tablets" was carried out at Macleods Pharmaceuticals as the validation batch met the specification of tablets.

Process validation study on three consecutive batches, Batch No. A, B,and C 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, coating and container packing. It shall also establish the suitability of equipments and area used for the production.

The process of manufacturing was carried as per the approved batch manufacturing card. The all process validation batches had been manufactured and validated in full compliance with cGMP requirement. Based on the results of the validation data of three consecutive batches, it shall be concluded that the manufacturing process used for Famciclovir 500 mg tablets 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

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