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# Process Validation for Famciclovir

**Vishal Patil*, Deepak Kumar Gupta, Raju Choukse and Rakesh Patel**
School of Pharmacy, Dr. APJ Abdul Kalam University, Indore (M.P.) - India

## 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.

*** Corresponding Author**
**E.mail:** cemoon06@gmail.com

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) □ Stages of | □ Pocket Formation□ Quality of overprinted text |

## 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$^{0}$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** | | **RESULLlILTLTS** | | | | | |
|---|---|---|---|---|---|---|---|
| **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 $\pm$ 2.0 % |
| **3** | Average Weight | 30 tablets | 660.0 mg $\pm$ 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 $\pm$ 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**<br>(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<br>92<br>94<br>95<br>96<br>95 | 96<br>89<br>93<br>91<br>96<br>92 | 100<br>98<br>98<br>98<br>96<br>98 |
| 12. | **Assay** (By HPLC) Famciclovir [$C_{14}H_{19}N_5O_4$] mg / tablet % label claim | 475.0 to 525.0<br>95.0 to 105.0 | 494.319<br>98.9 | 496.178<br>99.2 | 494.932<br>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**<br><br>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".<br>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<br><br>50 sec | 11 min<br><br>10 sec | 14 min<br><br>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<br>101<br>100<br>101<br>100 | 96<br>98<br>102<br>96<br>98 | 97<br>101<br>103<br>100<br>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)**<br>Monohydroxy impurity<br>Any other individual impurity<br>**Total impurities** | Not more than 0.15<br><br>Not more than 0.10<br><br>Not more than 0.70 | 0.063<br><br>Below Limit<br><br>0.063 | 0.042<br><br>Below Limit<br><br>0.042 | 0.038<br><br>Below Limit<br><br>0.038 |
| 9.0 | **Assay (By HPLC) Famciclovir [C14H19N5O4]**<br>**- mg / tablet**<br>**- % label claim** | 475.0 to 525.0<br><br>95.0 to 105.0 | 493.60<br><br>98.7 | 496.45<br><br>99.3 | 497.99<br><br>99.6 |
| 10.0 | **Residual Solvents** | Should comply with option 2 of<br><br>USP residual solvents <467> | Complies | Complies | Complies |
| 11.0 | **Polymorphism (By XRD)**<br>**A. Identification of polymorphic form I and form II**<br>**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<br><br>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 |

**Result:** The batch passes the AQL criteria

**Table 5.53 Identification of Defects**

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

**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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