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# INDUSTRIAL APPROACH ON PROCESS VALIDATION OF PARACETAMOL TABLETS 650 mg

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## ABSTRACT

The goal of the research project "A Process Validation of Paracetamol Tablet 650 mg" was to verify the method used in the production of 650 mg paracetamol tablets. A thorough validation process is essential to guarantee the quality, safety, and efficacy of the tablets of the commonly used analgesic and antipyretic drug paracetamol. The study used a methodical methodology to test each step of the manufacturing of tablets, including ingredient weighing and blending, granulation, compression and packing. To guarantee constant product quality, crucial process variables like blending time, compression force and drying conditions were closely monitored and managed. Several batches of paracetamol tablets were produced and tested under established validation procedures and legal requirements. Content homogeneity, dissolving rate, hardness, friability, weight change, and disintegration time were among the validation matrices. In order to do the production process's dependability and reproducibility, a statistical analysis was carried out. The research endeavor successfully showed that the production of Paracetamol 650 mg tablets regularly met the established quality standards. The tablets displayed constant weight, rapid disintegration, adequate hardness, little friability, and uniform drug content. The tablets' breakdown time fell within the acceptable range, guaranteeing optimal medication release. Patients will obtain a safe and effective product thanks to the proven process' assurance that the paracetamol tablets, 650 mg, can be produced consistently and reliably. The findings of this study add to the overall quality assurance and control in the pharmaceutical sector, reiterating the significance of process validation in guaranteeing the quality, safety, and efficacy of products. The results of this study can be used as a guide by pharmaceutical companies that make Paracetamol tablets or other similar dosage forms. The results of the research can also serve as a reference for regulatory agencies as they establish and enforce quality standards for the production of paracetamol tablets.

**KEYWORDS:** Process Validation, Paracetamol Tablets, Dosage strength, Manufacturing process, Quality control, Content uniformity, Hardness, Friability, Disintegration time, Dissolution rate.

## INTRODUCTION

Pharmaceutical validation refers to the process of establishing documented evidence, through a systematic approach, that a pharmaceutical process, system, or equipment consistently meets pre-defined requirements for quality, safety, and efficacy.[9,12,13] Validation is an important part of the pharmaceutical manufacturing and quality assurance process, and it is typically conducted under regulatory requirements and guidelines, such as those set forth by regulatory agencies like the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and other global regulatory bodies.[1]

There are four types of validation like process validation (prospective, concurrent, retrospectives and revalidation), System validation (air, water, computer, cleaning and steam) Analytical test method (for raw materials and for finished products) validation and Equipment validation (DQ, IQ, OQ and PQ).[8,9]

### Importance of process validation[3,4,9,12,21]

1. Compliance to Regulatory bodies 2. Assurance in quality 3. Optimization in the process 4. Reduced cost of production 5. Reduction in Batch failures, enhancement in efficiency and productivity 6. Lowering down time 7.

Reduced rejections 8. Increased output 9. Minimum complaints about process–related failures.

## AIM AND OBJECTIVE

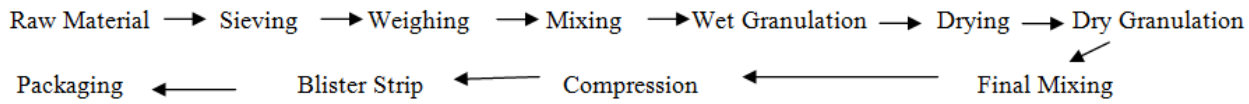
The study's goal is to use the Process Validation approach to develop and scale-up a pharmaceutical tablet dosage form of paracetamol tablet IP (650 mg). The use of Process Validation represents a significant improvement over the trial-and-error or accidental methods of Drug Delivery System development. We will identify and validate the key parameters of the main procedures used to manufacture tablet dosage forms. The latest statistical tools, such as sampling plans, process capability studies, analyses of variance, regression analyses, t-tests, control charts, histograms, Pareto charts, and experimental designs, will be used to optimize process variables. Based on those statistical analyses and interpretations, the validated process that has been built will be sufficiently robust to reliably generate items with pre-determined quality features throughout time. Validated procedures will also result in cost savings, increased productivity, shorter cycle times, fewer defects, fewer complaints and recalls, and lower inspection and testing expenses. A validated procedure will improve product quality and aid the pharmaceutical sector in boosting output, revenue, and client pleasure. The industrial community as well as consumers will gain a great deal from this idea.[12]

### Plan of Research Work

1. Strategies of process validation to be planned.
2. Steps in validation to be outlined and development of preformulated tablets dosage form of paracetamol tablets 650 mg for the validation purpose. 3. Validation report 4. Prospective validation.[21]

## MATERIALS AND METHODS

Flow Diagram of Tablet Manufacturing




The amount of purified water required for the preparation of starch jelly is regulated based on the bulk density of paracetamol. An appropriate lot of paracetamol IP of greater or lower BD, respectively, may be combined proportionately with paracetamol IP with BD (bulk density) below or above the specified BD (0.6g/ml–0.7g/ml), as long as the BD of the final mixture falls within the specification. The QC department must provide the required proportion level for mixing purposes, which should be based on the actual BD of each lot, [Table 1]

1. Compression machine was set at lower and high thickness and samples were collected for dissolution.
2. After sampling, compression was carried out at optimum thickness.
3. Compression machine at three different speeds between 10 – 30 RPM (15, 20 & 25 RPM) of turret and samples were collected for Dissolution and Content uniformity testing at each speed. Also, physical parameters at each speed were done.

**Stability Studies:** A chemical intended for use as a drug should be assessed under storage circumstances (which should be adequate to cover storage, transportation, and future use). At the time of submission, the long-term testing should last for at least three primary batches for a minimum of 12 months, and it should be sustained for a length of time long enough to accommodate the proposed re-test period. It may be to decide whether long term stability studies are performed at 25°C ± 2°C/60% RH± 5% RH or at 30°C± 2°C/65% RH ±5% RH, [Table 4 and 18 to 23]

**Table 1 : Equipment used in Manufacturinf formula**

| Serial Number | Equipment |
|---|---|
| 1 | Vibro-Sifter (with standard ss sieve :40 mesh) |
| 2 | Oscillating granulator (with SS sieve No:12 mesh) |
| 3 | 1.Dial balance-<br>a)300kg capacity (100 g division)<br>a)100 kg capacity (200g division)<br>b)50 kg capacity (100g division) |
| 4 | Steam jacketed starch paste kettle |
| 5 | Rapid mixer cum granulator :400L CAPACTY |

| | |
|---|---|
| 6 | Multimill with circular ss sieves 2.5 mm diameter pores ,12.5 mm die pores) |
| 7 | Fluid bed drier: 200 kg capacity |
| 8 | Planetary mixer : 500 L |
| 9 | Compression machines<br>Double rotary 37 station Cad Press-II tableting machine. (With tablet Deduster)<br>Double rotary 45 station ADEPT D-D-45 tableting machine. with tablet Deduster& Metal Detector) |
| 10 | Punch is concave oblong with the word PARACETAMOL 650 embossed on upper set of punches and scoreline on the lower set of punch |
| 11 | Blister packaging machine (fitted with dust catcher) |
| 12 | Instruments for process control-<br>• Digital hygro-thermometer<br>• Moisture balance (halogen type with convection)<br>• Electronic balance single pan<br>• Tablet disintegration test apparatus<br>• Tablet hardness tester<br>• Friability tester<br>• Micrometer<br>• Leak test apparatus<br>• Electronic balance for secondary packaging |

**Table 2: Equipment used in Physical parameters to be checked during compression.**

| Serial Number | Ingredients | Standard | Quality Required |
|---|---|---|---|
| 01 | Paracetamol | IP | As Specified |
| 02 | Pregelatinized Starch | IP | As Specified |
| 03 | Povidone (PVP-30) | IP | As Specified |
| 04 | Croscarmellose Sodium | IP | As Specified |
| 05 | Starch | IP | As Specified |
| 06 | Talc | IP | As Specified |
| 07 | Magnesium Stearate | IP | As Specified |
| 08 | Purified Water | IP | As Specified |

**Table 3: Equipment used in intended storage condition as per ICH guidelines.**

| Serial No | Parameters | Standard | No. of Tablets taken for testing |
|---|---|---|---|
| 1 | Appearance | White uncoated tablets, plain on both sides | 20 tablets |
| 2 | Weight of 20 tablets | | 20 tablets |
| 3 | Hardness | 125 + 55 N | 6 tablets |
| 4 | Thickness | 5.20 mm-5.70mm | 10 tablets |
| 5 | Length | 16.40mm -16.60mm | 10 tablets |
| 6 | Width | 8.90mm-9.10mm | 10 tablets |
| 7 | Friability | NMT 1% W/W | 20 tablets |
| 8 | Disintegration Time | NMT 15 min | 6 tablets |
| 9 | Individual Weight Variation | 750.0 + 5.3 | 20 tablets |
| 10 | Group Weight Variation | | 20 tablets |

**Table 4: The content uniformity and RSD values after 5 minutes of Dry mixing.**

| Study | Storage Condition | Minimum time period covered by data at submission |
|---|---|---|
| Long term | 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH | 12 months |
| Accelerated | 40°C ± 2°C/75% RH ± 5% RH | 6 months |

**Table 5: Dry mix pooled sample results of B. No X, Y,Z.**

| **Dry mixing time** | | **5 Minutes** | |
|---|---|---|---|
| **Batch no** | **X** | Y | **Z** |
| Minimum | 94.03 | 93.33 | 94.18 |
| Maximum | 98.12 | 100.23 | 99.18 |
| Average | 96.13 | 95.89 | 96.24 |
| RSD | 1.38 | 2.24 | 1.9 |

**Table 6: Impeller reading.**

| **Batch Number** | **Final reading of Impeller (Ampere)** |
|---|---|
| X | Complies |
| Y | Complies |
| Z | Complies |

**Table 7: Impeller reading of RMG.**

| **Serial Number** | **Parameter** | **X** | **Y** | **Z** |
|---|---|---|---|---|
| 1 | % retains on #100 | complies | complies | complies |
| 2 | Tapped density (g/ml) | complies | complies | complies |
| 3 | Water Content (%w/w) | complies | complies | complies |

**Table 8: Inlet, Outlet Temperatures and LOD Results.**

| **Batch no** | **Inlet temperature ($^{o}$C)** | **Outlet temperature ($^{o}$C)** | **LOD (% w/w)** |
|---|---|---|---|
| X | 65 | 45 | 1.51 |
| Y | 65 | 46 | 1.52 |
| Z | 64 | 45 | 1.52 |

**Table 9: The Content Uniformity of paracetamol and RSD values after blending.**

| **Batch no** | **X** | | | **Y** | | | **Z** | | |
|---|---|---|---|---|---|---|---|---|---|
| Blending time (Minutes) | 15 | 25 | 35 | 15 | 25 | 35 | 15 | 25 | 35 |
| Minimum | 89.57 | 90.78 | 89.53 | 88.08 | 94.14 | 93.49 | 89.94 | 89.9 | 87.22 |
| Maximum | 102.41 | 98.48 | 99.5 | 98.72 | 100 | 100.3 | 99.29 | 98.29 | 100.29 |
| Average | 95.86 | 95.00 | 92.46 | 93.23 | 96.92 | 96.04 | 94.4 | 93.79 | 95.16 |
| RSD | 3.79 | 2.55 | 3.58 | 3.73 | 1.73 | 2.51 | 3.1 | 2.77 | 3.68 |

**Table 10: Test Results for final mixing.**

| **Serial Number** | **Test** | | | |
|---|---|---|---|---|
| | **Performed** | **X** | **Y** | **Z** |
| 1 | Appearance | White granular powder | White granular powder | White granular powder |
| 2 | Identification | | | |
| | I) IR | Complies | complies | complies |
| | II)UV | Complies | complies | complies |
| | III)Chemical test | Complies | complies | complies |
| 3 | Assay | 645.74 mg/tab | 650.22 mg/tab | 643.60 mg/tab |
| 4 | Water content | 0.91% | 0.97% | 0.93% |
| 5 | Bulk density | Complies | Complies | Complies |

**Table 11: The Assay results after Blending.**

| **Batch no** | **X** | **Y** | **Z** |
|---|---|---|---|
| Assay (mg/tab) of Paracetamol | 645.74 mg/tab | 650.22 mg/tab | 643.60 mg/tab |

**Table 12: Acceptance Criteria of Tablet compression.**

| MEASURED RESPONSE | ACCEPTANCE CRITERIA |
|---|---|
| **Appearance** | **White capsule shaped, uncoated tablets plain on both sides** |
| **Avg. weight variation** | **15.0 g ± 0.106 g** |
| **Individual weight ariation** | **750.00mg ± 5%** |
| **Thickness** | **5.20 ± 5.70mm** |
| **Hardness** | **125 ±55 N** |
| **Friability** | **NMT 1.0% w/w** |
| **Disintegration time** | **NMT 15minutes** |

**Table 13: Individual weight variation of Paracetamol 650 mg.**

| | X | | Y | | Z | |
|---|---|---|---|---|---|---|
| **SL NO** | **LEFT** | **RIGHT** | **LEFT** | **RIGHT** | **LEFT** | **RIGHT** |
| **1.** | 750.17 | 751.15 | 725.00 | 750.17 | 750.20 | 750.25 |
| **2.** | 750.17 | 750.00 | 740.60 | 745.00 | 751.15 | 745.00 |
| **3.** | 750.17 | 751.15 | 715.20 | 715.18 | 715.20 | 751.15 |
| **4.** | 720.25 | 751.50 | 750.17 | 750.20 | 750.25 | 751.50 |
| **5.** | 740.66 | 740.60 | 751.15 | 755.65 | 740.60 | 740.60 |
| **6.** | 755.65 | 730.55 | 751.15 | 720.35 | 730.55 | 730.55 |
| **7.** | 720.35 | 752.50 | 751.15 | 740.52 | 752.50 | 751.15 |
| **8.** | 740.52 | 750.00 | 730.00 | 751.15 | 715.20 | 715.18 |
| **9.** | 750.60 | 751.15 | 715.20 | 715.18 | 751.15 | 752.50 |
| **10** | 751.15 | 715.20 | 715.18 | 735.25 | 715.20 | 750.00 |
| **11** | 751.50 | 750.17 | 751.15 | 715.20 | 715.18 | 751.15 |
| **12** | 740.60 | 750.17 | 750.17 | 750.20 | 750.25 | 715.20 |
| **13** | 730.55 | 750.17 | 751.15 | 740.80 | 750.55 | 750.17 |
| **14** | 752.50 | 750.17 | 751.50 | 751.15 | 715.20 | 715.18 |
| **15** | 750.00 | 750.17 | 740.60 | 751.15 | 725.00 | 750.00 |
| **16** | 720.20 | 750.17 | 730.55 | 751.15 | 740.60 | 751.15 |
| **17** | 730.00 | 720.25 | 751.15 | 751.15 | 715.20 | 715.20 |
| **18** | 751.15 | 715.20 | 715.18 | 735.25 | 750.17 | 750.17 |
| **19** | 750.00 | 751.00 | 730.50 | 751.15 | 715.20 | 750.17 |
| **20** | 750.17 | 750.20 | 750.25 | 725.00 | 745.00 | 730.00 |
| Maximum | **755.65** | **752.50** | **751.50** | **755.65** | **752.52** | **752.50** |
| Minimum | **720.20** | **715.20** | **715.18** | **715.18** | **715.18** | **715.18** |
| Average | **742.818** | **744.0735** | **738.35** | **740.0425** | **734.7175** | **740.8135** |

**Table 14: The Assay result of Paracetamol 650 tablet after compression.**

| SL No | Test Performed | Specifications | X | Y | Z |
|---|---|---|---|---|---|
| 1 | Appearance | White, biconvex oblong One face and paracetamol engraved on the other face | complies | complies | complies |
| 2 | color | White | complies | complies | complies |
| 3 | odor | odorless | complies | complies | complies |
| 4 | Identification | | | | |
| | i)IR | IR spectrum of sample was compared withPARACETAMOL IP | complies | complies | complies |
| | ii)chemical test | As per IP specification | complies | complies | complies |
| **5.** | Related substances | 4-chloroacetanilide – NMT 10 ppm Any other impurity | complies | complies | complies |
| | | NMT 0.25% | | | |
| 6 | Dissolution | NLT 80 % in Minutes | 30complies | complies | complies |
| 7 | Loss of drying | 0.8% - 1.6% w/w | 1.30% w/w | 1.25 % w/w | 1.28 % w/w |

| | | | | | |
|---|---|---|---|---|---|
| 8 | DT | NMT 15 min | 4.5 min | 5 min | 4.9 min |
| 9 | Paracetamol | 617.5 – 682.5 mg per tablet | 651.20 mg | 650.35 mg | 650.95 mg |
| 10 | Thickness | 5.20 – 5.70 mm | 5.42 mm | 5.55 mm | 5.48 mm |
| 11 | Hardness | 70 – 180 N | 132 N | 123 N | 130 N |
| 12 | Friability | NMT 1.0 % w/w | 0.24 % w/w | 0.35 % w/w | 0.29 % w/w |
| 13 | Microbial limit | i)Total Aerobic viable | 35 CFU/gm | 34 CFU/gm | 36 CFU/ gm |
| | | count (TAC): NMT | | | |
| | | 2000 CFU/gm | | | |
| | | ii)Total fungal count(TFC): NMT 200 CFU / gm | Absent per gm | Absent per gm | Absent per gm |
| | | iii)Pathogens | Absent | Absent | Absent |
| | | (Escherichia coli, | | | |
| | | Salmonella, Pseudomonas | | | |
| | | Aeruginosa Staphylococcus aureus) | | | |

**Table 15: Yield results.**

| **Batch no** | | **X** | **Y** | **Z** |
|---|---|---|---|---|
| **Paracetamol** | **650 mg** | 645.74 mg/tab | 650.22 mg/tab | 643.60 mg/tab |

**Table 16: Finished Product result.**

| **Stage** | **Batch No** | | |
|---|---|---|---|
| | **X** | **Y** | **Z** |
| **Control sample** | 90 | 90 | 90 |
| **% of packed yield** | 99.36% | 99.35% | 99.37% |
| **% of final yield** | 99.64% | 99.65% | 99.67% |

**Table 17: IR spectral analysis.**

| **BATCH NO** | **SPECIFICATION** | **RESULT** |
|---|---|---|
| X | Specified | complies |
| Y | Specified | complies |
| Z | Specified | complies |

**Table 18: Stability Report For All The Three Batches Studied Under Specified Conditions: Shelf life: 36 Months Stability Study- X for Accelerated Stability Studies. Label Claim: PARACETAMOL 650 mg.Storage conditions: 40 ± 2 °C / 75 % ± 5 % RH.**

| S.no | Description | Average Weight | Disintegration time | Hardness | Water (% w/w) | Dissolution | Related substances | Assay | Microbial<br>A. Bacteria<br>B. Fungi<br>C. Pathogens<br>limits |
|---|---|---|---|---|---|---|---|---|---|
| | White biconvex oblong tablet with scoreline on | 750.0 8.4 mg | NMT 15 min | 70 – 180 N | 0.8% - 1.6% w/w | NLT 80 % in 30 Minutes | complies | NLT 95% & | i)Total Aerobic viable count (TAC): NMT 2000 CFU/gm |
| | One face and | | | | | | | NMT | ii)Total fungal count |
| Specification | Paracetamol engraved on the | | | | | | | 105% | (TFC): NMT 200 CFU/gm |
| | other face | | | | | | | | iii)Pathogens: NA |
| Stage Initial | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | complies |
| 1M | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | NA |
| 2M | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | NA |
| 3M | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | NA |

**Table 19: Stability Study-X, (Long-term storage condition) Label Claim: Paracetamol 650 mg, Storage conditions: 25 ± 2 ºC / 60 % ± 5 % RH.**

| S.no | Description | Average Weight | Disintegration time | Hardness | Water % w/w | Dissolution | Related Substances | Assay % | Microbial limit.<br>A. Bacteria B. Fungi C. Pathogens |
|---|---|---|---|---|---|---|---|---|---|
| Specification | white biconvex oblong tablet and paracetamol engraved on the other face | 750.0 ± 8.4 mg | NMT 15 min | 70 – 180 N | 0.8% - 1.6% w/w | NLT 80 % in 30 minutes | complies | NLT 95% & NMT 105% | i)Total Aerobic viable count (TAC): NMT 2000CFU/gm<br>ii)Total fungal count (TFC): NMT 200 CFU/gm<br>iii)Pathogens: Absence |
| **Stage:**Initial | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies |
| 3M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 6 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 9 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 12 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 18 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 24 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 36 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 48 M | Ongoing Process | Ongoing Process | Ongoing Process | Ongoing Process | Ongoing Process | Ongoing Process | Ongoing Process | Ongoing Process | Ongoing Process |

**Table 20: Stability Study- Y for Accelerated Stability Studies, Shelf life: 36 Months Label Claim: PARACETAMOL 650 mgStorage conditions: 40 ± 2°C / 75 % ± 5 % RH.**

| Sl no. | Description | Average Weight | Disintegration time | Hardness | Water (% w/w) | Dissolution | Related substances | Assay | Microbial limit. a.Bacteriab.Fungic.Pathogens |
|---|---|---|---|---|---|---|---|---|---|
| Specification | white biconvex oblong tablet with screline one face and paracetamol engraved on the other face | 750.0 ± 8.4 mg | NMT 15 min | 70 – 180 N | 0.8% - 1.6% w/w | NLT 80 % in 30 minutes | complies | NLT 95% & NMT 105% | i)Total Aerobic viable count (TAC): NMT 2000 CFU/gm ii)Total fungal count (TFC): NMT 200 CFU/gm iii)Pathogens: NA |
| Stage | | | | | | | | | |
| Initial | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | complies |
| 3M | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | NA |
| 6 M | ON GOING STABILITY STUDY | | | | | | | | |

**Table 21: Stability Study-Y for Long-term storage conditionLabel Claim: Paracetamol 650 mg, Storage conditions: 25 ± 2 ºC / 60 % ± 5 % RH.**

| S.no | Description | Average Weight | Disintegration time | Hardness | Water % w/w | Dissolution | Related Substances | Assay % | Microbial limit. Bacteria B. Fungi C.Pathogens |
|---|---|---|---|---|---|---|---|---|---|
| Specification | white biconvex oblong tablet and paracetamol engraved on the other face | 750.0 ± 8.4 mg | NMT 15 min | 70 – 180 N | 0.8% - 1.6% w/w | NLT 80 % in 30 minutes | complies | NLT 95% & NMT 105% | i)Total Aerobic viable count (TAC): NMT 2000 CFU/gm ii)Total fungal count (TFC): NMT 200 CFU/gm iii)Pathogens: N.A. |
| **Stage :**Initial | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies |
| 3M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 6 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 9 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 12 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 18 M<br>24 M<br>36 M | ON GOING STABILITY STUDY | | | | | | | | |

| | |
|---|---|
| 48 M | |

**Table 22: Stability Study- Zfor Accelerated Stability Studies, Shelf life: 36 Months Label Claim: PARACETAMOL 650 mgStorage conditions: 40 ± 2°C / 75 % ± 5 % RH.**

| Sl no. | Description | Average Weight | Disintegration time | Hardness | Water (% w/w) | Dissolution | Related substances | Assay | Microbial limit. a.Bacteriab.Fungic.Pathogens |
|---|---|---|---|---|---|---|---|---|---|
| Specification | white biconvex oblong tablet with screline one face and paracetamol engraved on the other face | 750.0 ± 8.4 mg | NMT 15 min | 70 – 180 N | 0.8% - 1.6% w/w | NLT 80 % in 30 minutes | complies | NLT 95% & NMT 105% | i)Total Aerobic viable count (TAC): NMT 2000 CFU/gm ii)Total fungal count (TFC): NMT 200 CFU/gm iii)Pathogens: NA |
| Stage | | | | | | | | | |
| Initial | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | complies |
| 3M | Complies | Complies | Complies | Complies | Complies | Complies | complies | Complies | NA |
| 6 M | ON GOING STABILITY STUDY | | | | | | | | |

**Table 23: Stability Study-Z for Long-term storage conditionLabel Claim: Paracetamol 650 mg, Storage conditions: 25 ± 2 ºC / 60 % ± 5 % RH.**

| S.no | Description | Average Wt. | Disintegration time | Hardness | Water % w/w | Dissolution | Related Substances | Assay % | Microbial limit. C. Bacteria B. Fungi C.Pathogens |
|---|---|---|---|---|---|---|---|---|---|
| Specification | white biconvex oblong tablet and paracetamol engraved on the other face | 750.0 ± 8.4 mg | NMT 15 min | 70 – 180 N | 0.8% - 1.6% w/w | NLT 80 % in 30 minutes | complies | NLT 95% & NMT 105% | i)Total Aerobic viable count (TAC): NMT 2000 CFU/gm ii)Total fungal count (TFC): NMT 200CFU/gm iii)Pathogens: N.A. |
| **Stage:**Initial | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies |
| 3M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 6 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 9 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 12 M | Complies | Complies | Complies | Complies | Complies | Complies | Complies | Complies | N.A. |
| 18 M<br>24 M<br>36 M<br>48 M | ON GOING STABILITY STUDY | | | | | | | | |

**Result for process validation** [Table 2,3,5,6,7,8,9,10,11,12]

**Dry mixing**

Mixer name- Planetary mixer

Capacity – 500L, Lot size- 4,00,000 tabs, Variables considered for study- Mixing time

Measured response: Content uniformity and RSD; Acceptance criteria: 100 ± 15 % (RSD NMT 6.0%)

Time interval studies- 5 Minutes; Batch taken for studies- Three batches (X,Y,Z)

**Observation:** The mixing operation yields satisfactory results and the relevant parameters of the process complies with the desired acceptance.

**Results:** The results obtained from various parameters determined during the mixing operation are set as a standard acceptable value.

**Observations:** Sieve analysis, water content and tapped density values of three batches are comparable and are in closer homogeneity as per IH specifications.

**Conclusion:** The dry mixing time of 5 minutes is concluded as validated mixing time at fast speed.

**B. Granulation**

Fixed parameters: Lot size: 400000 tabs; Variables considered for study: Mixing time.

Acceptance criteria: Physical appearance granule, Measured response: Impeller reading, Chopper amperage Batch taken for study: X,Y,Z.

**Observation:** The above compilation data shows that uniform granules formation of all three batches was observed at the Impeller (Slow speed) amperage specified amps as per BMR (IP specifications).

**Conclusion:** The desired granular mass was obtained between impeller amperage specified amps. Resultant granules after drying and milling have desired flow properties. All the three batches resulted in granules with desired flow and compaction, which is evident from data of compression tablets. Hence the granules stage of PARACETAMOL 650 mg tablet is concluded as validated at impeller amperage of specified limit.

**Drying:** Fixed Parameters: Lot size: 400000 tabs, Variables considered for study: Drying time and Drying temperature.

Measured response: LOD (Loss on Drying).

**Acceptance criteria:** 1.1-1.8% w/w, Batches taken for study: X,Y,Z.

**Observation:** Drying was carried out as per BMR (IH specifications). During drying the desired LOD between 1.1-1.8% w/w was achieved at air drying for 15-25 minutes.

**Conclusion:** According to observations during drying for all three batches, it was concluded that only air drying the granular material after granulation is required till the LOD in between 1.1-1.8% w/w.

**Final Mixing:** Mixing speed: Slow Mixer; Load: 299.60 kg±1.4 kg.

Variables considered for study: mixing time; Time interval: 15,25,35 min.

Measured response: Uniformity of content and RSD and acceptance criteria: 100±15% (RSD NMT 6.0%)

Batches taken for study: X,Y,Z

**Observation:** It is observed from the compiled analytical data of the uniformity of content that the values of all the three batches are well within the acceptance criteria as per IH specifications.

**Observation:** The distribution of paracetamol is well acceptable at 25 minutes of blending and 5 minutes lubrication as shown by the samples analyzes. The results show closer homogeneity of drug distribution in the blend as per IH specification.

**Observation** Assay values of all three batches are comparable and are in closer homogeneity as per IH specifications.

**Conclusion:** The mixing time of 2 minutes is concluded as validated blending time at slow speed of blender for paracetamol 650 blending, when the process is performed in 500 liters capacity planetary mixer.

**Observation:** Individual weight variation is within the specified limits. All physical parameters, Dissolution, Uniformity of content and Assay of pool tablet values of paracetamol compressed tablets at different speeds are well within the limits and are complying with IP specification.

**Conclusion:** From the above results, we can conclude that the manufacturing process is in a state of control and capable of producing quality product uniformly.

**IR Spectrum Analysis Observation**: The IR spectrum of Paracetamol raw material was found to be identical with that of standard spectrum.

The spectral analysis for the pure sample of Paracetamol was performed to check the quality and purity of the raw materials used in the manufacturing of Paracetamol tablets. The results for the IR spectral analysis are as follows, [Table 17]

**Stability report:** For both long-term and accelerated storage circumstances, the stability reports were present for all three validation batches, X, Y and Z. As a result, it was determined that the stability research was valid.[4,6,15]Click or tap here to enter text.

## SUMMARY AND CONCLUSION

All the raw materials used in the manufacturing of Paracetamol 650mg

1. Tablets, were tested as per the given specifications and the results were within the limits. Hence the validation of raw materials was concluded.
2. The equipment used in the manufacturing of the Paracetamol 650 mg Tablets were checked for their Installation, Operation and Performance Qualification and concluded.
3. The dry mixing time of 5 minutes is concluded as validated mixing time at fast speed.
4. The desired granular mass was obtained between impeller amperage specified amps. Resultant granules after drying and milling have desired flow properties. All the three batches resulted in granules with desired flow and compaction, which is evident from data of compression tablets. Hence the granules stage of Paracetamol 650mg tablet is concluded as validated at impeller amperage of specified amps.
5. According to observations during drying for all three batches, it was concluded that only air drying the granular material after granulation is required till the LOD is NMT 1.0%.
6. The blending time of 4 minutes is concluded as validated blending time at slow speed of blender for Paracetamol 650 blending,
7. From the dissolution profile it was concluded that the compression process was validated.
8. From the finished product results, it was concluded that the process validation of Paracetamol 650mg Tablets is successfully performed and ready for commercial run.

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