PREPARATION AND PROCESS VALIDATION OF METFORMIN HYDROCHLORIDE TABLET

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ABSTRACT
The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently at the lowest possible cost. Validation is a concept that has evolved in States in 1978. The concept of validation has expanded through the years to embrace a widerange of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labeling or process control. Validation isfounded on, but not prescribed by regulatory requirements and is best viewed as an important andintegral part of cGMP. The basic concept has longbeen applied in other industries, often without formal recognition that such a concept was beingused. The end of the sequence that has been assigned to process validation is derived from the fact that the specific exercise of process validation should never be designed to fail. Failure in carrying out the process validation assignments often the result of incomplete or faulty understanding of the process’s capability, in other words, what the process can and cannot do under a given set of operational circumstances.

KEYWORDS: Metformin hydrochloride, sodium starch glycolate IP, starch IP, Purified water, polyvinyl pyrrolidone IP.

INTRODUCTION
Validation
The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever increasing interest in validation owing to their industry’s greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation. Validation is a...
The concept that has evolved in the United States in 1978. The concept of validation has expanded through the years to embrace a widerange of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labeling or process control. Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP. The word validation simply means assessment of validity or action of proving effectiveness [Sharma Kanchan et al, 2013].

**USFDA Defines Validation As:** “Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics. According to European commission: Validation is defined as “Action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results. Process validation establishes the flexibility and constraints in the manufacturing process controls in the attainment of desirable attributes in the drug product while preventing undesirable properties. This is an important concept, since it serves to support the underlying definition of validation, which is a systematic approach to identifying, measuring, evaluating, documenting, and reevaluating a series of critical steps in the manufacturing process that require control to ensure reproducible final product. A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes [FDA, 2001].

Process Validation Unfortunatly, there is still much confusion as to what process validation is and what constitutes process validation documentation. At the beginning of this introduction several different definitions for process validation were provided, which were taken from FDA guidelines and the CGMPs. Chapman calls process validation simply “organized, documented common sense”. Others has said that “it is more than three good manufactured batches” and should represent a lifetime commitment as long as the product is in production, which is pretty much analogous to the retrospective process validation concept [Nash R.A et al, 1993]. The big problem is that we use the term validation generically to cover the entire spectrum of CGMP concerns, most of which are essentially people, equipment, component, facility, methods and procedural qualification. The specific term
process validation should be reserved for the final stage(s) of the product/process development sequence. The essential or key steps or stages of a successfully completed product/process development program are presented [Schedule M]. The end of the sequence that has been assigned to process validation is derived from the fact that the specific exercise of process validation should never be designed to fail. Failure in carrying out the process validation assignments often the result of incomplete or faulty understanding of the process’s capability, in other words, what the process can and cannot do under a given set of operational circumstances. In a well-designed, well-run overall validation Program, most of the budget dollars should be spent on equipment, component, facility, methods qualification, and process demonstration, formerly called process qualification [Nash R.A et al, 1993].

**The Key Stages in the Product/Process**

1. Development Sequence
2. Development stage Pilot scale-up phase
3. Product design
4. Product characterization
5. Product selection
6. Process design
7. Product optimization
8. Process characterization
9. Process optimization
10. Process demonstration
11. Process validation program
12. Product/process certification

**Importance of Validation**

1. Assurance of quality
2. Time bound
3. Process optimization
4. Reduction of quality cost.
5. Nominal mix-ups, and bottle necks
6. Minimal batch failures, improved efficiently and productivity.
7. Reduction in rejections.
8. Increased output.
9. Avoidance of capital expenditures
10. Fewer complaints about process related failures.
11. Reduced testing in process and in finished goods.
12. More rapid and reliable start-up of new equipments

1. Easier scale-up form development work.
2. Easier maintenance of equipment.
3. Improved employee awareness of processes.
5. Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

Types of Validation
1. Prospective validation
2. Concurrent Validation
3. Retrospective Validation
4. Revalidation

1. **Prospective Validation:** The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product. In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase the production process should be broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorized protocol [Sumeet et al, 2013].

2. **Concurrent Validation:** It is a process where current production batches are used to monitor processing parameters. It gives an assurance regarding consistency of quality from batch to batch. Concurrent Validation means establishing documented evidence a process does what it is supposed to base on data generated during actual implementation of the process.
Concurrent validation may be the practical approach under certain circumstances. It is important in these cases when the systems and equipment to be used have been fully validated previously [Sumeet et al, 2013].

3. **Retrospective validation:** Concluded for a product already being marketed, and is based on extensive data accumulated over several lots and over time. Retrospective Validation may be used for older products which were not validated by the fabricator at the time that they were first marketed, and which is now to be validated to confirm to the requirement of division 2, Part C of the Regulation to be Food and Drugs Act. Retrospective Validation is only acceptable for well-established detailed processes and will be inappropriate where there have recent changes in the formulation of the products, operating procedures, equipment and facility [Sumeet et al, 2013].

4. **Revalidation:** Re-validation is usually performed to the confirmation of initial validation for a Periodic review. Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process. Re-validation becomes necessary in certain situations [Sumeet et al, 2013].

**Basic Concept of Process Validation**

1. Calibration, verification and maintenance of process equipment.
2. Prequalification or revalidation.
3. Establishing specifications and performance characteristics.
4. Selection of methods, process and equipment to ensure the product meets specifications.
5. Qualification or validation of process and equipment.
6. Testing the final product, using validated analytical methods, in order to meet specifications.
7. Challenging, auditing, monitoring or sampling the recognized critical key steps of the process.

**Phases in Process Validation** [Kaur Harpreet et al, 2013].
Phase 1
Pre-validation phase or the Qualification phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, Equipment qualification, Installation qualification, master production documents, Operational qualification, Process capability.

Phase 2
Process validation phase (Process Qualification phase) designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the “worst case” conditions.

Phase 3
Validation Maintenance phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures. At this stage the Validation Team also assures that there have been no changes/deviations that should have resulted in requalification and revalidation.

MATERIAL AND METHODS
Objective
The purpose of this work is to present an introduction and general overview on process validation of product metformin Tablets manufacturing process with special reference to the requirements stipulated by the US Food and Drug Administration (FDA). Quality is always an imperative prerequisite when we consider any product. Therefore, drugs must be manufactured to the highest quality levels. End-product testing by itself does not guarantee the quality of the product. Quality assurance techniques must be used to build the quality into the product at every step and not just tested for at the end. In pharmaceutical industry, Process Validation performs this task to build the quality into the product because according to ISO (International organization for standardization) 9000: 2000, it had proven to be an important tool for quality management of pharmaceuticals.

This process validation presentation describes the procedure, documentation, references, acceptance criteria & revalidation criteria to be used for proving the process validity of the product Cefixime-200 Tablets [Sarvani V et al, 2013].
Since validation activity is regulatory requirement to prove that system/ procedure is adequate to re-produce the results meeting pre-determined specification of product to ensure that drug is safe and adequate for its intended use. The critical process parameter was identified with the help of process capability and evaluated by challenging its lower & upper release specification. Three initial process validation batches (X, Y & Z) of same size, method, equipment & validation criteria was taken [WHO TRS, 2003].

**Research Envisaged**

Quality cannot be inspected or tested into the product; i.e. repeat testing and re sampling will not improve the quality. Quality comes through designing and proper controls of manufacturing parameters (build quality into product). Proper design and development of robust processes and tests with appropriate quality control checks will lead to a high quality product. Manufacturing quality into the product is essential and validation data will be indicative of the tendency to meet the specifications.

Validation is defined as the establishing of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the intended specified out comes. Validation studies verify the system under test under the extremes expected during the process to prove that the system remains in control.

**Drug Profile**

Drug: Metformin Hydrochloride  
Class: Antidiabetic  
Chemical Name: 1, 1-Dimethylbiguanide Monohydrochloride  
Molecular Formula: C4H11N5 • HCl  

Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. Its use in gestational diabetes has been limited by safety concerns. It is also used in the treatment of polycystic ovary syndrome, and has been investigated for other diseases where insulin resistance may be an important factor. Metformin works by suppressing glucose production by the liver. Metformin is a biguanide antihyperglycemic agent used for treating non-insulin-dependent diabetes mellitus (NIDDM).
Pharmacology

Indication: For use as an adjunct to diet and exercise in adult patients (18 years and older) with NIDDM. May also be used for the management of metabolic and reproductive abnormalities associated with polycystic ovary syndrome (PCOS). Jentadueto is for the treatment of patients when both linagliptin and metformin is appropriate.\[18\]

Pharmacodynamics: Metformin is an oral antihyperglycemic agent that improves glucose tolerance in patients with NIDDM, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other class of oral Antihyperglycemic agents. Unlike sulfonylureas, metformin does not produce hypoglycemia in neither patients with NIDDM or healthy subjects and does not cause hyperinsulinemia. Metformin does not affect insulin secretion [Kovacic S et al, 2003].

Mechanism of Action: Metformin’s mechanisms of action differ from other classes of oral ant hyperglycemic agents. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. These effects are mediated by the initial activation by metformin of AMP-activated protein kinase (AMPK), a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats. Activation of AMPK is required for metformin’s inhibitory effect on the production of glucose by liver cells. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors. Metformin administration also increases AMPK activity in skeletal muscle. AMPK is known to cause GLUT4 deployment to the plasma membrane, resulting in insulin-independent glucose. The rare side effect, lactic acidosis, is thought to be caused by decreased liver uptake of serum lactate, one of the substrates of gluconeogenesis. In those with healthy renal function, the slight excess is simply cleared. However, those with severe renal impairment may accumulate clinically significant serum lactic acid levels. Other conditions that may precipitate lactic acidosis include severe hepatic disease and acute/decompensated heart failure [Hardie DG et al, 2003].

Absorption: Absorbed over 6 hours, bioavailability is 50 to 60% under fasting conditions. Administration with food decreases and delays absorption. Some evidence indicates that the level of absorption is not dose-related, suggesting that absorption occurs through a saturable process. Limited data from animal and human cell cultures indicate that absorption occurs
through a passive, non-saturable process, possibly involving a paracellular route. Peak action occurs 3 hours after oral administration [Hardie DG et al, 2003].

**Medical Uses**

Metformin is primarily used for type 2 diabetes, but is increasingly being used in polycystic ovary syndrome, non-alcoholic fatty liver disease (NAFLD) and premature puberty,[15] three other diseases that feature insulin resistance; these indications are still considered experimental. The benefit of metformin in NAFLD has not been extensively studied and may be only temporary,[16] although some randomized controlled trials have found significant improvement with its use, the evidence is still insufficient. Metformin is used with a proper diet and exercise program and possibly with other medications to control high blood sugar.

**Experimental Work**

It is a protocol based study; Validation will be performed during following stages of manufacturing of Metformin Hydrochloride tablets:

1. Dry mixing (Dry mixing, Binding time & Stratified Sampling)
2. Drying (LOD)
3. Lubrication (Blending time, Stratified Sampling, Assay, Blend uniformity)
4. Compression (Speed of Compression machine, Hopper level, Different Hardness & Different interval)
5. Packing (Temperature, Machine speed) Protocol for Concurrent Process Validation of Metformin Hydrochloride Tablets Concurrent process validation protocol consists following contents:

   1. Sampling Plan
   2. Manufacturing Procedure and schematic diagram of Sample location
      a) Dry mixing
      b) Binding and Milling
      c) Drying
      d) Sifting & Sizing
      e) Lubrication
   3. Compression
   4. Blister strip packing machine setting and operation

**RESULT**

5.4.10. Observations & Acceptance Criteria of finished products
Table: Preparation and Process Validation of Metformin Hydrochloride Tablet.

Table No. 31: Acceptance Criteria of finished products.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Test</th>
<th>Acceptance Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Description</strong></td>
<td>White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.</td>
<td>White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Average Weight</strong></td>
<td>633mg ± 5%</td>
<td>634.9 mg</td>
</tr>
<tr>
<td>3</td>
<td><strong>Uniformity of Weight</strong></td>
<td>within ± 5% of the Average weight</td>
<td>Min. +0.30%</td>
</tr>
<tr>
<td>4</td>
<td><strong>Dimension</strong></td>
<td>9.75mm ±0.2mm</td>
<td>1. 9.83 5. 9.84 9. 9.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. 9.77 6. 9.80 10. 9.67</td>
<td>3. 9.69 7. 9.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. 9.68 8. 9.65</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><strong>Thickness</strong></td>
<td>4.50mm ±0.3mm</td>
<td>1. 4.52 5. 4.39 9. 4.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. 4.51 6. 4.52 10. 4.53</td>
<td>3. 4.56 7. 4.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. 4.49 8. 4.44</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><strong>Hardness :</strong></td>
<td>3.0Kg / cm²</td>
<td>1. 3.5 5. 4.0 9. 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. 3.0 6. 4.0 10. 3.5</td>
<td>3. 4.0 7. 3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. 3.5 8. 4.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><strong>Friability</strong></td>
<td>NMT 1.0 % w/w</td>
<td>0.29%</td>
</tr>
<tr>
<td>8</td>
<td><strong>Disintegration</strong></td>
<td>NMT 10 min</td>
<td><strong>01’28’’</strong></td>
</tr>
<tr>
<td>9</td>
<td><strong>LOD</strong></td>
<td>NMT 4% w/w (at 105°C for 3 hrs.)</td>
<td>2.89%</td>
</tr>
<tr>
<td>10</td>
<td><strong>Dissolution Assay:</strong></td>
<td>Not less than 70% of L.A.C4H11N5. HCl after 45min</td>
<td>86.51%</td>
</tr>
<tr>
<td>11</td>
<td><strong>Metformin 500.0 mg.</strong></td>
<td>90.0% - 110.0 % of L.A.</td>
<td>98.56%</td>
</tr>
<tr>
<td>12</td>
<td><strong>A TBC</strong></td>
<td>NMT 1000 CFU / g</td>
<td>10 CFU / g</td>
</tr>
<tr>
<td></td>
<td><strong>B Mould &amp; Yeast</strong></td>
<td>NMT 100 CFU / g</td>
<td>10 CFU / g</td>
</tr>
<tr>
<td></td>
<td><strong>C Pathogen</strong></td>
<td>Absent /g</td>
<td>Absent /g</td>
</tr>
</tbody>
</table>

Table No. 32: Acceptance Criteria of finished products.

(B)Batch No.: Y

<table>
<thead>
<tr>
<th>S. No</th>
<th>Test</th>
<th>Acceptance Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Description</strong></td>
<td>White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a break line on one side.</td>
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</tr>
</tbody>
</table>
Table No. 33: Acceptance Criteria of finished products.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Test</th>
<th>Acceptance Criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
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<td>White to off white, oval, beveled edged uncoated tablets having M/500 embossing and a breakline on one side.</td>
</tr>
<tr>
<td>2</td>
<td>Average weight</td>
<td>633mg ± 5%</td>
<td>629.3 mg</td>
</tr>
<tr>
<td>3</td>
<td>Uniformity of weight</td>
<td>within ± 5% of the Average weight</td>
<td>Min. +0.17%</td>
</tr>
<tr>
<td>4</td>
<td>Dimension</td>
<td>9.75mm ±0.2mm</td>
<td>1. 9.73 1. 9.73 1. 9.73 2. 9.72 2. 9.72 3. 9.63 3. 9.69 4. 9.68 4. 9.68 4. 9.63</td>
</tr>
<tr>
<td>5</td>
<td>Thickness</td>
<td>4.50mm ±0.3mm</td>
<td>1. 4.66 1. 4.48 1. 4.52 2. 4.52 2. 4.51 1. 4.43 3. 4.56 3. 4.59 3. 4.58 4. 4.49 4. 4.49 4. 4.51</td>
</tr>
<tr>
<td>6</td>
<td>Hardness</td>
<td>3.0Kg / cm²</td>
<td>1. 3.0 1. 3.5 1. 4.5 2. 4.0 2. 3.5 2. 3.5 3. 4.0 3. 4.0 3. 4.0 4. 3.5 4. 3.5 4. 4.0</td>
</tr>
<tr>
<td>7</td>
<td>Friability</td>
<td>NMT 1.0 % w/w</td>
<td>0.35%</td>
</tr>
<tr>
<td>8</td>
<td>Disintegration</td>
<td>NMT 10 min</td>
<td>02’11’”</td>
</tr>
<tr>
<td>9</td>
<td>LOD</td>
<td>NMT 4% w/w (at 105°C for 3 hrs.)</td>
<td>2.59%</td>
</tr>
<tr>
<td>10</td>
<td>Dissolution Assay:</td>
<td>Not less than 70% of L.A. C₆H₁₁N₅HCl after 45min</td>
<td>89.33%</td>
</tr>
<tr>
<td>11</td>
<td>Metformin 500.0 mg.</td>
<td>90.0% - 110.0 % of L.A.</td>
<td>99.09%</td>
</tr>
<tr>
<td>12 A</td>
<td>TBC</td>
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<td>10 CFU / g</td>
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<td>NMT 100 CFU / g</td>
<td>10 CFU / g</td>
</tr>
<tr>
<td>C</td>
<td>Pathogen</td>
<td>Absent / g</td>
<td>Absent / g</td>
</tr>
</tbody>
</table>

(C) Batch No. : Z
<table>
<thead>
<tr>
<th></th>
<th>LOD</th>
<th>Dissolution Assay:</th>
<th>Metformin 500.0 mg.</th>
<th>TBC</th>
<th>Mould &amp; Yeast</th>
<th>Pathogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>NMT 4% w/w (at 105°C for 3 hrs.)</td>
<td>Not less than 70% of L.A.</td>
<td>98.0% - 103.0% of L.A.</td>
<td>NMT 1000 CFU / g</td>
<td>NMT 100 CFU / g</td>
<td>Absent / g</td>
</tr>
<tr>
<td>11</td>
<td>3.02%</td>
<td>90.83%</td>
<td>99.15%</td>
<td>10 CFU / g</td>
<td>10 CFU / g</td>
<td>Absent / g</td>
</tr>
</tbody>
</table>

CONCLUSION

All the analytical data review during process validation of Metformin Hydrochloride tablets found satisfactory hence process is validated.

REFERENCES

3. EU Guide to Good Manufacturing Practice, Qualification and validation, year -2002.
5. Health Products and Food Branch Inspectorate, Guidance Document Validation, Guidelines for Pharmaceutical Dosage Forms.