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# Process Validation and Evaluation of Critical Process Parameters of Atorvastatin 40mg

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**ABSTRACT**
**Pharmaceutical Process Validation is the most important and standard parameter of cGMPs. Validation means demonstration and objective evidence that consistently meets its pre-determined requirements. The main purpose of the process validation is to provide documented evidence that the manufacturing process of Atorvastatin 40 mg tablet is to the predefined control parameters. The objective of the study is to form a basis for procedures for production and process control which are considered to reassure that the drug Atorvastatin 40 mg tablet has to the identify, strength, quality, and purity they assert or are represented to possess. To control each step just as shifting, mixing, and granulation, of the manufacturing process to maximize the probability that the finished product to all provides documented evidence, that would give a high degree of assurance. Validation involves the collection and evaluation of data, throughout process stages, which are established scientific evidence that a process is competent of consistently delivering quality similar to the one with others in which the correlation study has been done.**



## INTRODUCTION:

Pharmaceutical process validation is one of the most important and recognized parameters of cGMPs. The requirement of process validation appears in the quality system (QS) regulation. The objective of a quality system is to consistently produce products for their intended use. Process validation is a key element in ensuring that these principles and goals are met. The creation of products that are suitable for their intended use is the main objective of quality assurance.[1]

- Drug Efficacy
- Computer system Output
- Safety of medical device
- Effectiveness of sterilizer
- Ability to manufacture the acceptable product

Process validations defined as the collection and evaluation of data, from the process design stage through commercial production, which are include the scientific evidence that a process is capable of consistently delivering quality product Process. This guidance describes the process .[2]

The main purpose of the third validation stage is numerous assurances that the process remains in a state of control (the validated state) during the commercial manufacturing process. A system or systems for detecting unintended departures from the process as designed is essential to accomplish this goal. A drug shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to the safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. [3]

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Re-validation provides 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 are the initial validation of the manufacturing process. Periodic review and trend analysis should be carried out at scheduled intervals. Re-validation becomes necessary in certain situations. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content, and its planning. The main elements of it are the listing inventory of the items to be validated and the planning schedule. [4]

## MATERIAL AND METHOD:

**Materials:**

The Atorvastatin standard was provided by Ajanta Pharma Ltd. Atorvastatin 40 mg tablets containing 40 mg of Atorvastatin and the excipients used in the drug matrix were obtained from the market.

**1. Dispensing: (Weighing & Measuring)**

- Dispensing can be done by purely manually scooping from primary containers and weighing each ingredient by hand on a weighing scale on mechanical devices according to BPR specifications.

**2. Sifting:**

- Size can also be a factor in the stability steps. Because of these significant roles, it is important to decide on a required size range, and hence to maintain and control it.

**Factors to be considered during sifting:**

- Check and record the temperature and relative humidity in the process area. The temperature should be 25+/-2ºc and RH 45+/-5%.
- Check and ensure visually all the equipment and equipment parts are cleaned, and record remarks if any.
- Check and record the integrity of the sieves before and after sifting throughout the processing activity.[5]

**3. Mixing:**

- Dry mixing is generally carried out in a Rapid Mixer Granulator. Dry mixing involves the mixing of ingredients before adding the granulation or binder solution.

**4. Granulation:**

- The granulation method can be divided into two parts-
- Wet granulation
- Dry granulation.

**Wet Granulation:**

- Agglomeration is the most common procedure in the pharmaceutical industry in the wet granulation method. The wet granulation process involves wet massing of the powder blend with a granulation liquid, wet sizing, and drying method.

**Important steps involved in the wet granulation:**

- Mixing of the drug(s) and excipients.
- Preparation of binder solution.
- Mixing of binder agent with powder mixture to form a wet mass.
- Wet mass using Coarse screening as a suitable sieve. (#6-12)
- Drying of moist granules.
- Screening of dry granules through a suitable sieve (#14-20)
- Mixing of screened granules with disintegrate, glidant, and lubricant.

**Preparing the damp mass:**

- A binder agent is added to the powder mixture to support the adhesion of the powder particles good binder results in inappropriate tablet hardness and does not impact the release of the drug from the tablet.

**Determining the end point of granulation:**

- The determining endpoint is to compress a portion of the mass in the palm of the ball crumbles under moderate pressure; the mixture is ready for the next stage in processing, which is wet screening.
- The energy consumption by wet granulation (i.e.; the cumulative power consumption.) is converted completely into heating the mixer and its contents. The absorption of the kinetic energy of the particles results in heat. When growth by coalescence of agglomerates becomes significant, because of high agglomerates deformability the energy consumption will increase accordingly.
- The powder used by the mixer increases as the powder mass becomes increasingly wet. Power usage is often reflected in the readings of an ammeter or wattmeter mounted on the equipment and may be useful in helping to identify the proper endpoint for the wet granulation process.

**Screening the damp mass into Granules:**

- The screening is wet mass granulation of (usually no. # 6 or 8 mesh) to prepare the granules. This is special equipment, which prepares the granules, through perforations in the apparatus. The resultant granules are spread evenly on large pieces of paper in

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shallow trays and dried.

**Drying the Granules:**

- Granules may be dried in thermostatically controlled ovens, which constantly record the time, temperature, and humidity

**Sizing the Granulation by dry screening:**

- After drying, the granules are passed through a screen of a smaller mesh than used to prepare the original granulation. The degree to which the granules are reduced depends upon the size of the punches to be used. In general, the smaller the tablet to be produced, the smaller the granules used. Screens from 12 to 20 mesh sizes are generally used for this purpose. Sizing of the granules is necessary so that the die cavities for the free–flowing granulation. Voids or air spaces left by too large a granulation would result in the production of uneven tablets.

**Adding lubrication and blending:**

- After dry screening, a dry lubricant is dusted over the spread–out granulation through a fine mesh screen. Lubricants contribute to the preparation of compressed tablets in several ways.
- They improve the flow of the granulation in the hopper to the die cavity.
- They prevent the adhesion of the tablet formulation to the punches and dies during compression.
- They reduce friction between the tablet and the die wall during the tablet's ejection from the tablet machine.
- They give a sheen to the finished tablets.
- Powders/Granules intended for compression into tablets must possess two essential properties flow property and compressibility.
- Flow property/Fluidity is required to produce tablets of a consistent weight and uniform strength.
- Compressibility is required to form a stable, intact compact mass when pressure is applied. These two objectives are obtained by adding a binder to a tablet formulation and then preceding for granulation process.
- Other reasons for the granulation process are to improve appearance, mixing properties, to avoid dustiness, to density material, to reduce segregation, to improve the physical and chemical properties.

**Factors to be considered in Granulation:**

**Compressibility:**

- Compressibility is the ability of power to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. Determination of compressibility and flow by the Carr's Index.

% Compressibility = (Tapped density –Bulk density/Tapped density) X 100

**Flow properties:**

It is a very important parameter to be measured since it affects the mass of uniformity of the dose it is usually predicted from the Hausner Ratio and Angle of Repose measurement.

**Bulk density:**

The bulk density is obtained by dividing the weight obtained by the final volume in $cm^3$ of the sample contained in the cylinder.

**Mixing Time:**

The mixing time also determines the quality of the granules If the wet massing time is high → the tablet may fail the dissolution test. (Since drug release from hard granules is altered.)

**Impeller Movement:**

Adhesion of wetted mass to the vessel is less if impeller movement is helical. This gives a narrower granule size and few lumps.

**Drying:**

Drying is defined as the removal of a liquid from a material by the application of heat and is accomplished by the transfer of a liquid from a surface into an unsaturated vapor phase.

***Loss on Drying:***

LOD is an expression of moisture content on a wet-weight bases, which is calculated as

$$\% \text{ LOD} = \frac{\text{Wt. of water in sample}}{\text{Total wt. of the wet sample}} \times 100$$

The moisture in a solid can be expressed on a wet–weight or dry–weight basis. On wet – weight basis, the water content of a material is calculated as the percentage of the weight of the wet solid, whereas on dry – weight basis, the water is expressed as a percentage of the weight of the dry solid.

**Moisture Content:**

Measurement of the moisture in wet a solid is calculated on a dry–weight basis

$$\% \text{ MC} = \frac{\text{wt. of water in sample}}{\text{Wt. of dry sample}} \times 100$$

**Milling:**

Milling is the mechanical process of reducing the particle size of solids. [8]

Milling equipment is usually classified as

| | |
|---|---|
| COARSE | # 20 mesh |
| INTERMEDIATE | # 20 -200 mesh |
| FINE MILLING | < # 200 mesh |

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**Dry Granulation:**
In the granulation process, the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granule. Two methods are used for dry granulation. [6]

**Blending:**
Each process of mixing has an optimum mixing time and so prolonged mixing may result in an undesired product. So, the optimum mixing time and mixing speed are to be evaluated. The blending step before compression is normally achieved in a simple tumble blender. The blender may be a mixed blender into which the powder is charged, blended, and discharged. In special cases of mixing a lubricant, over-mixing should be particularly monitored.[7]

**Tablet Compression:**
After the preparation of granules (in case of wet granulation) or slugs (in case of dry granulation) or mixing of ingredients (in case of direct compression), they are compressed to the final product.

There are several types of tablet presses or tableting machines, each varying in productivity but similar in basic function and operation. They all compress a tablet formulation within a steel die cavity by the pressure exerted by the movement of two steel punches, a lower punch, and an upper punch. It 'squeezes' the ingredient into the required tablet shape with extreme precision. It can make the tablet in many shapes, although they are usually round or oval.[8]

The operation of a single punch describes the basic mechanical process.
Stages occurring during compression:

- Stage 1: Top punch is withdrawn from the die by the upper cam. The bottom punch is low in the die so the powder falls in through the hole and fills the die.
- Stage 2: Bottom punch moves up to adjust the powder weight it raises and expels some powder.
- Stage 3: Top punch is driven into the die by the upper cam. The bottom punch is raised by the lower cam. Both punch heads pass between heavy rollers to compress the powder.
- Stage 4: The upper cam withdraws the top punch. The lower punch is pushed up and expels the tablet. The tablet is removed from the die surface-by-surface plate.
- Stage 5: Return to Stage 1.

Rotary tablet machines are equipped with multiple punches and operate through the continuous rotating movement of the punches. [9] A single rotary press with 16 stations (16 sets of punches and dies) may produce up to 1150 tablets per minute. Double rotary tablet presses with 27,33,37,41, or 49 sets of punches and dies are capable of producing 2 tablets for each data.[9]

**Table 1:**

| Sr. No. | Item Code | Ingredients | Vendor/ Manufacturer Details | BMR/ BPR Qty. (kg) | Quantity issued in BMR & assigned BPR | | |
|---|---|---|---|---|---|---|---|
| | | | | | Batch No's.: | | |
| | | | | | A | B | C |
| A) | Active Pharmaceutical ingredients: | | | | | | |
| 1. | 1001404 | Atorvastatin Calcium USP (Process I) | Amoli Organics Pvt. Ltd. | 4.330*@ | 2.107 | 4.330 | 4.330 |
| 2. | 1000192 | Lactose BP | VRS Food Ltd. | 12.807 | 12.807 | 12.807 | 12.807 |
| 1. | 1000323 | Calcium carbonate BP | Canton Laboratories Pvt. Ltd. | 13.000 | 13.000 | 13.000 | 13.000 |
| 2. | 1000419 | Microcrystalline cellulose USPNF (Avicel PH 101) | DuPont Nutrition Ireland | 25.506**@@ | 0.584<br>24.888 | 25.506 | 25.506 |
| 3.<br>4. | 1000839 | Croscarmellose sodium USPNF (Ac-Di-Sol) | DuPont Nutrition Ireland | 1.500 | 1.500 | 1.500 | 1.500 |
| 5. | 1001775 | Hydroxypropylcellulose BP (Klucel-LF Pharma) | Ashland Specialty Ingredients | 1.500 | 1.500 | 1.500 | 1.500 |
| 6. | _ | Purified water$ | - | 23.000 L | 23.000 L | 23.000 L | 23.000 L |
| 7. | 1000839 | Croscarmellose sodium USPNF (Ac-Di-Sol) | DuPont Nutrition Ireland | 1.500 | 0.780<br>0.720 | 1.500 | 1.500 |
| 8. | 1000193 | Magnesium stearate BP | Nitika P'ceuticals Specialties Pvt. | 0.600 | 0.600 | 0.600 | 0.600 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Ltd. | | | | |
| 9. | _ | Purified water$ | -- | 23.690L | 11.846 | 11.846 | 11.846 |
| 10. | | | | *** | 11.846 | 11.846 | 11.846 |
| **For adjustment of API quantity for Assay and LOD. | | | | | | | |
| *43.298 mg of Atorvastatin calcium equivalent to Atorvastatin 40 mg. | | | | | | | |
| The molecular weight of Atorvastatin calcium Trihydrate is 1209.41 as mentioned in the USP monograph of Atorvastatin calcium. | | | | | | | |
| **3.0% extra quantity of Microcrystalline cellulose added to compensate for loss during drying. | | | | | | | |
| ***20.0% excess taken to compensate for loss during coating. | | | | | | | |
| $Purified Water conforms to the specification of IP/BP/USP/Ph. Eur. /IH. | | | | | | | |
| @Batch quantity of Atorvastatin calcium to be calculated on an anhydrous basis | | | | | | | |
| @@Amend the formula quantity of Microcrystalline cellulose USPNF (Avicel PH 101) for Excess amount of drug substances if used due to potency adjustment. | | | | | | | |

| Sr. No. | Stage | Acceptance Criteria/Limit | Unit | Batch No's.: | | |
|---|---|---|---|---|---|---|
| | | | | A | B | C |
| **Stage-wise Yield :** | | | | | | |
| 1. | **Lubricated blend:** | | | | | |
| | Accounted yield | 98.00% to 100.00% | % | 98.42 | 99.49 | 99.28 |
| 2. | **Compression tablets:** | | | | | |
| | Accounted yield | 98.00% to 100.00% | % | 98.04 | 98.48 | 98.41 |

## RESULT AND DISCUSSION:

In the present study, total 3 batches of Atorvastatin 40 mg tablets were manufactured and subjected to process validation. The validation was done at the various stage of manufacturing tablets such as lubrication, Compression, friability, Hardness, Uniformity of weight, disintegration, and thickness. Since the amount of the drug in the tablet is around 5 %, the critical process steps that can affect the distribution of drugs in the tablet were evaluated. Nonuniform drug distribution can affect the weight, dissolution, and assay. The result is presented below.

### 1. Result for Lubrication of Atorvastatin Tablets 40 mg:

To check the uniform distribution of the drug with granules, samples were collected from 10 different locations, 20 minutes before the lubrication and 3 minutes after the lubrication. All the collected samples were subjected for content uniformity and RSD is concise in the table 1 and 6. The tests were carried out for all three batches.

| Sr. No. | Parameters | Acceptance criteria | Unit | Batch No's.: | | |
|---|---|---|---|---|---|---|
| | | | | A | B | C |
| 1. | Blender speed | 10 | rpm | 10 | 10 | 10 |
| 2. | Blending time | 03 | Minute | 03 | 03 | 03 |
| 3. | Description | White to off-white colored, granular powder | NA | Off-white colored, granular powder | Off-white colored, granular powder | Off-white colored, granular powder |

### 2. Stage-wise Yield of Atorvastatin Tablets 40 mg:

After the successful granulation process, granules were taken for compression. During the compression, process validation was done for all three batches (A, B, C) by exigent the parameters like maximum hardness, minimum hardness, initial stage optimum speed, middle stage optimum speed, and end-stage optimum speed. On the base of these parameters, various in-process tests were carried out such as description, average weight, diameter, friability, hardness, disintegration, thickness, uniformity of weight, and assay. Tablets were subjected to disintegration only for maximum and minimum compression hardness. From the result of all batches, it was experiential that compression force only pretentious the friability & disintegration time. As the compression hardness increased, friability was decreased whereas disintegration time was increased, this might be due to more compact tablets. All the test results have complied with the specifications in Table 3.

### 2. Result of Compressed Tablet at Compression Stage:

| Sr. No. | Test/ Parameter | Acceptance Criteria/Limit | Unit | | Batch No's.: | | |
|---|---|---|---|---|---|---|---|
| | | | | | A | B | C |
| 1. | Description | White to off-white, circular, biconvex-shaped, film-coated tablets, plain on both sides. | NA | | @ | @ | @ |
| 2. | Average weight | 180.0 mg ± 5.0% (171.000 to 189.000 mg) | mg | | 180.30 | 180.30 | 180.30 |
| 3. | Uniformity of weight | Not more than 2 of the individual weights deviate from the average weight | Min. | % | -2 | -2 | -2 |
| | | | Max. | % | 3 | 3 | 1 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | by more than ± 5 % and none deviate by more than ± 10 %. | | | | | |
| 4. | Disintegration Time | Not more than 15 minutes | Min. | | 02 Min. 20 Sec. | 01 Min. 13 Sec. | 01 Min. 15 Sec. |

@ Off-white circular, biconvex-shaped, film-coated tablets, plain on both sides.

**Table 4 (A) Critical Process Parameters (CPP) of tablets:**

| Sr. No. | Batch No. | Machine ID | Description (White to off-white, Circular, biconvex uncoated tablets | Turret speed (12 to 45 RPM) For Information | | Friability (NMT 1.00 % w/w) | |
|---|---|---|---|---|---|---|---|
| | | | | Min. | Max. | Min. | Max. |
| 1. | CP0202A | R/PR/TC/001 | Complies | 15.00 | 15.00 | 0.14 | 0.38 |
| 2. | CP0202A | R/PR/TC/001 | Complies | 15.00 | 15.00 | 0.03 | 0.32 |
| 3. | CP0202A | R/PR/TC/001 | Complies | 15.00 | 15.00 | 0.09 | 0.30 |

**Table 5 Critical Quality Attributes (CQA) of core tablets: (In-process data)**

| Sr. No. | Batch No. | Average weight 180.0 mg ± 5.0% (171.000 to 189.000 mg) | | | (Hardness) (2.0 Kp to 6.0 Kp) | | Thickness 3.50 ± 0.30 mm (3.20 to 3.80 mm) | | Diameter (7.90 mm to 8.20 mm) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Min | Max | Mean | Min | Max | Min | Max | Min | Max |
| 1. | A | 178.90 | 181.70 | 180.30 | 2.60 | 5.30 | 3.60 | 3.72 | 8.10 | 8.20 |
| 2. | B | 178.40 | 181.10 | 180.00 | 2.20 | 5.80 | 3.59 | 3.72 | 8.10 | 8.20 |
| 3. | C | 179.80 | 181.40 | 180.70 | 2.70 | 4.50 | 3.54 | 3.63 | 7.99 | 8.08 |

## CONCLUSION:

The concurrent process validation of the Atorvastatin 40mg tablet has been performed for three batches (batch A, batch B, batch C) and all the parameters and results were found within the acceptable limit. Based on the results of the validation data for three batches, it was concluded that the manufacturing process used for the formulation of the Atorvastatin 40mg tablet will constantly create a stable product congregation with its predetermined specifications and quality attributes. Hence, it can be concluded that the method in the manufacture of the given product is considered to be validated and can be routinely followed.

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