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Process Validation of Aripiprazole Tablets

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ABSTRACT:

The main aim of the present research work was to study prospective process validation of Aripiprazole Tablets, 30 mg which is an Antipsychotic drug. The Process Performance Qualification was carried out for three different batches having same batch size, manufacturing process, equipments, formula and validation criteria. The critical process parameters, and critical quality attributes involved in sifting, dry mixing, granulation, wet milling, drying, sifting & dry milling, blending and compression were identified and evaluated as per the approved validation protocol. All the in process parameters and process variables were checked and found well within acceptance criteria. The % LOD for dried granules after drying found out within 1.48-1.81 %. In process testing for compression (Avg. wt: 263 mg to 278 mg; hardness 4.4-7.3 Kp; thickness 3.26-3.47 mm; friability – nil; disintegration time 1min 8 sec to 1min 50sec) and finished product (Avg. wt: 270-272 mg; dissolution: 100.00 % to 103.00 %: assay 99.21- 100.96 %) validation found well within the limit. All the parameters and results were found within the acceptance limit as given in validation protocol. No deviation has taken place during manufacturing of these three batches. Considering all the parameters it was concluded that the manufacturing process and the equipments adopted were robust enough and are capable of producing consistent quality of product continuously. Hence the manufacturing process for Aripiprazole uncoated tablets stands validated and can be routinely used for commercial batches.

KEY WORDS: Process Validation, Aripiprazole, Critical Process Parameters, Validation Protocol.

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INTRODUCTION:

Process Validation

Definition:

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].

Process Validation: *New Paradigm* (FDA Guidance)

Process validation is now defined as the study of data, from the process design stage through commercial manufacturing, which establishes scientific proof that a process is capable of consistently producing quality drug product.

It involves a series of activities taking place over the lifecycle of the product and process

STAGES of Process Validation[2]:

Stage 1: Process Design

- Based on knowledge gained through product development and lab/pilot scale-up activities the commercial manufacturing process is defined at this stage.

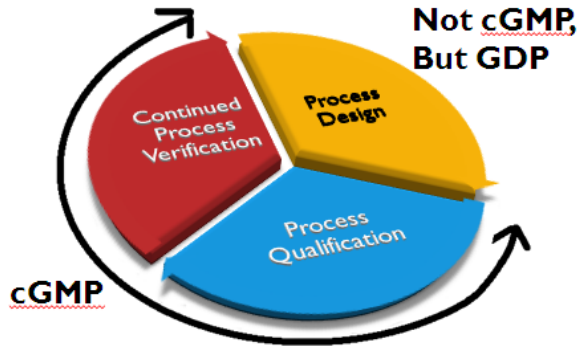
Stage 2: Process Qualification

- Evaluation of process design at this stage to determine if the process is capable of reproducible commercial production.

Stage 3: Continued Process Verification

- Ongoing assurance is gained during routine commercial batches for distribution confirming that the process remains in a state of control.

Figure 1 Process Validation Stages



Process Validation Stages

Process Validation: Major parameters MUST be considered[3]:

- ✓ Bio-batch Relationship
- ✓ Raw Materials
- ✓ Manufacturing Procedures and Equipment
- ✓ Granulation/Mix Analysis
- ✓ In-Process Controls
- ✓ Test Results with Validated Methods
- ✓ Investigations/Product Failures
- ✓ Site Review

Key concepts of successful validation program[4]:

- Understand the sources of variation
- Detect and measure sources of variation
- Access the impact of variability on the process and final product attributes
- Control the sources of variation commensurate with the risk they represent to the process and final product attributes

Concurrent Release of PPQ Batches:

- ❖ Drugs having a limited demand (e.g., orphan drugs)
- ❖ Short half-lives (e.g., radiopharmaceuticals, and positron emission tomography (PET) drugs).
- ❖ Medically necessary (e.g. epidemic situation)
- ❖ In agreement with Agency to overcome shortage of drugs in the market

Differences – EMA vs. USFDA[5]:

Table 1: Differences between EMA vs. USFDA for Process Validation Requirements

EMA	USFDA
It asks to enlist non-critical attributes and parameters in the process validation protocol.	Only requires the specification of critical quality attributes (CQAs) and critical process parameters (CPPs).
Three validation batches	Not specified
In Annex 15 three approaches are mentioned (traditional, continuous process verification, hybrid)	FDA Process Validation Guideline makes no distinction.
There is no such demand for an increased number of samples in the on-going process verification in Annex 15	FDA Guideline demands a higher number of samples till establishment of sufficient data to assess variability

Aripiprazole has an anti-psychotic category and insoluble in methanol and in water and the drug product is available in strengths 5 mg, 10 mg, 15 mg, 20 mg and 30 mg[6,7].

MATERIALS AND METHOD:

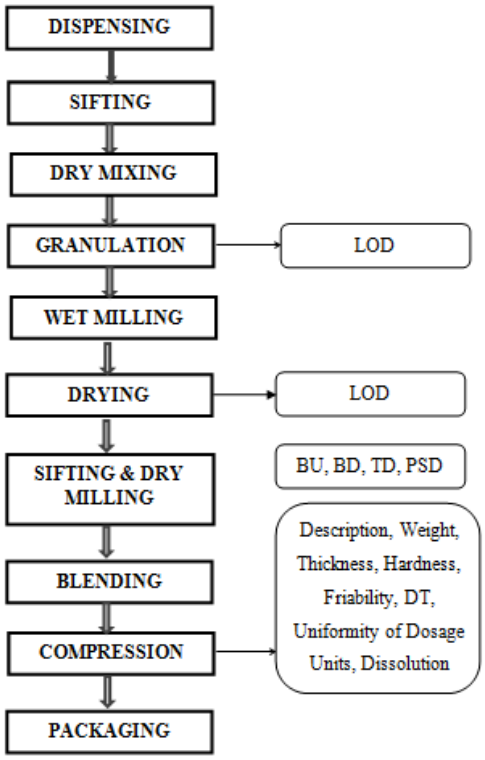
The drug substance Aripiprazole used for preparation of drug product was meeting all specification acceptance criteria as per USP monograph. The drug product was manufactured using wet-granulation process.

List of Equipments:

Table 2: List of Equipments

Equipment*	Capacity	Purpose
Rapid Mix Granulator (RMG)	400 L	Mixing & Granulation
Clit Mill	8.0 mm	Size reduction/ Comminuting/ Pulverizing
Fluid Bed Dryer (FBD)	120 kg	Drying (direct heating)
Octagonal Blender	600 L	Blending
High performance double rotary tablet press	61 station	Compression

Process Validation Flow Diagram:



Critical Process Parameters:

These parameters were controlled so as to minimize the variability of the finished drug product.

Table 3: List of Critical Process Parameters (CPPs) with Tests performed

Stage	Process Parameter	Tests to be Performed
Granulation (Wet mixing)	Load Size, Granulating Fluid Quantity Amperage Value	**LOD**
Wet Milling	Screen Size Speed of Machine	
Drying	Load Size Total Drying time Inlet/Outlet Temperature	**LOD**
Sifting & Dry Milling	Screen Size Feed Rate| Speed of Machine	
Blending	Total Mixing Time Loading/Mixing Pattern	**BU, BD, TD, PSD**
Compression	**Compression Force Tablet Filling Depth**	**Description, Weight, Thickness, Hardness, Friability, DT, Uniformity of Dosage Units, Dissolution**

RESULTS AND DISCUSSION:

Dry Mixing: This step is important to have uniform drug/excipients mixture prior to granulation stage. At this stage, it requires to ensure no overmixing of

materials to avoid demixing or segregation of materials.

Table 4: Loss on Drying results of Wet Granules

Acceptance Criteria		Standard Deviation of the Results NMT 10		
Unit			%	
Batch No		Batch#1	Batch#2	Batch#3
Top	T1	27.50	26.67	26.29
	T2	27.36	26.51	26.47
Middle	M3	27.07	26.60	26.34
	M4	27.53	26.53	25.48
Bottom	B5	26.9	27.79	26.22
	B6	27.63	26.41	26.10
SD		0.29	0.52	0.35

Granulation: At this stage, it requires to control quantity of binder solution, granulation time and importantly endpoint of granulation. Wet granulation/Binding is required to get cohesive mass of granules that are free flowing after drying and of uniform particle size distribution. The end of granulation is achieved by constant amperage load and physical observation by pressing handful of granulated mass then breaking the same from center to have clear fracture, as well as no loose powdered mass is left unbounded after completion of granulation. Higher binder solution leads to over wetting of materials and prolongation of total drying time. Poor flow and compression properties are due to no proper mixing of granules and over mixing leads to low dissolution and harder granules.

Table 5 Loss on Drying results after Drying

Acceptance Criteria		Individual Sample: NMT 2.0 % w/w		
Unit			%	
Batch No		Batch#1	Batch#2	Batch#3
Top	T1	1.75	1.81	1.65
	T2	1.69	1.79	1.66
	T3	1.52	1.77	1.77
Middle	M4	1.63	1.77	1.62
	M5	1.59	1.70	1.56
	M6	1.65	1.79	1.52
Bottom	B7	1.67	1.73	1.58
	B8	1.63	1.79	1.58
	B9	1.52	1.75	1.48

Wet Milling: At this stage, it requires to consider equipment capacity, screen size, mill speed. Wet milling process ensures to achieve uniform size of wet granules by breaking up oversized granules and enhancing drying of the granules. Too small of screen size is responsible for over-heating of mill which leads to drying of granules; and high speed of mill is responsible for straining.

Discussion: At this stage, it is important to have moisture content within defined limit of wet granules & after drying step. This drying step is required for loss of moisture content from the wet granules. High moisture content leads to sticking or picking problems while over drying leads to friability and poor hardness.

Dry Milling: At this stage, it requires to ensure integrity of sieves before and after use. The milling step is required for uniform particle size distribution of granules which are responsible for properties like dissolution, disintegration, compressibility and flow.

Table 6 Blend Uniformity Analysis Test Specification and Results:

Specification	Mean value between 95.0–105.0 %, RSD <5.0 %		
Unit		%	
Batch No	Batch#1	Batch#2	Batch#3
1	98.2	97.7	100.3
2	98.0	98.5	100.2
3	97.8	97.7	100.7
4	98.2	98.2	100.9
5	98.0	97.8	103.0
6	98.2	98.3	98.9
7	98.0	98.3	100.5
8	98.2	100.0	99.7
9	97.4	98.1	100.5
10	97.5	96.6	98.2
Minimum	97.4	96.6	98.2
Maximum	98.2	100.0	103.0
Mean	98.0	98.1	100.3
RSD	0.30	0.87	1.27

DISCUSSION: At this stage, it requires to monitor optimum blending for consistent granules compressibility at compression stage. This stage is essential for uniformity of drug content throughout the blend. In process validation, vigorous sampling is required as per sampling plan to perform blend uniformity analysis. High or less blending results in poor lubricant or active substance distribution. Less or over drug content leads to poor efficacy and overdose/ safety issues respectively.

CONCLUSION:

The process validation of Aripiprazole Tablets has been performed for three batches (batch#1, batch#2, batch#3). The test data were evaluated for series of unit-operations. Input materials for its suppliers and quality, vendors for raw materials, quality of raw material, equipment qualification/ maintenance and cleaning, , quality of water used for manufacturing, environmental conditions and all critical process parameters were taken for consideration. No deviation has been reported during manufacturing of three batches. All the parameters and results were passed the specification acceptance criteria as defined in validation protocol. Evaluating of process controls and data, it is concluded that the manufacturing process and the equipments used were robust enough and are capable of producing consistent lot to lot quality of product. Hence the manufacturing process for Aripiprazole Tablets stands validated and can be routinely followed for commercial batches.

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