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Research Article

Process Validation of Sertraline Hydrochloride 50 mg tablets

Parixit Rohitbhai Prajapati[*1], Deepika Natu Rathod[1], Vishalkumar Shashikant Modi[2] and Tarasankar Basuri[2]

[1]*Department of Quality Assurance Techniques, SSR Collage of Pharmacy, Silvassa, U. T. of Dadra & Nagar Haveli -396230, India*
[2]*Department of Pharmaceutical Chemistry, SSR College of Pharmacy, Sayli road, Silvassa-396230 India*

Abstract

The purpose of present research work wasto study Process Validation of Sertraline hydrochloride 50 mg tablet dosage form. As in a pharmaceutical product the quality cannot be directly incorporated or assured by in process and finished products inspections and testing rather it has to be incorporated in the manufacturing process itself. Process Validation helps in controlling all the parameters so that the finished product meets all the specifications and quality attributes. Various critical parameters involved in the process were identified with the help of process capability and thereby evaluating and challenging its lower and upper specifications. Three initial batches of same size, method, equipment and validation criteria were chosen. Other critical parameters involved in sifting, dry mixing, wet mixing, granulation, drying, sifting and sizing, lubrication, compression and coating stages were identified as per the Validation Master Plan. The outcome of the research work was that the process validation is providing the products that provide high degree of assurance that manufacturing process is producing products meeting its predetermined specifications and quality attributes.

Keywords: Sertraline hydrochloride, Process Validation, Prospective, Concurrent, Retrospective, Revalidation

1. Introduction

1.1 Validation [1]:

In 1978, According to USFDA, "A Validation process is one which has been proved to do what it purports or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continuing the production phase. Validation necessarily includes process qualification but it also includes the control on the entire process for repeated batches or runs."

1.1.1 Some definitions of Process Validation [2-4]:

According to USFDA (2008), "Process Validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products".

According to EMEA (2012), "Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medical product meeting its predetermined specifications and quality attributes."

According to ICH guidelines:"Process validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality."

The approaches for process validation according to EMA are asgiven below:

1. Traditional process validation
2. Continuous process verification
3. Hybrid approach
4. Continued process verification.

* Correspondence Info

Parixit Rohitbhai Prajapati,
Department of Quality Assurance Techniques,
SSR Collage of Pharmacy, Silvassa,
U. T. of Dadra & Nagar Haveli -396230, INDIA
E-mail: parixitprajapati@gmail.com

1.1.2 Objectives of Process Validation [5]:

It includes ensuring that:

- The process design used is evaluated to show that the process is reliable, reproducible, and robust.
- Assurance is gained on a continuous basis to show that the process remains in a state of control.
- The commercial manufacturing process defined, monitored and controlled.
- The validation covers all manufactured strengths of a product and the extent of validation at each manufacturing site should be based on risk assessment. On basis of appropriate risk assessment a matrix approach or bracketing may be acceptable.

1.1.3 Importance of Validation[6]:

- It gives assurance of quality.
- It is a time bound process.
- Important tool for process optimization
- It helps in reduction of quality cost.
- It causes minimal batch failures also the productivity is improved efficiently.
- It reduces chances of rejections and hence increased output.
- It avoids more use of capital expenditures and offers Easier scale-up formdevelopment work.
- Process related failures get reduced.
- Maintenance of equipment gets easier and also it provides more rapid and reliable start-up of new equipments.

1.1.4 Reason for Process Validation [7, 8]:

Various reasons for performing Process Validation include:

- New product or existing products as per SUPAC changes or batch size.
- Change in site of manufacturing, critical control parameters or equipment.
- Change in process existing products, composition or components.
- Change in vendor of API, critical excipient or specification on input material.
- Trend of out of specification or out of trend in consecutive batches.

1.2 Stages of Process Validation [9, 10]:

- Stage 1 — Process Design
- Stage 2 — Process Qualification
- Stage 3 — Continued Process Verification

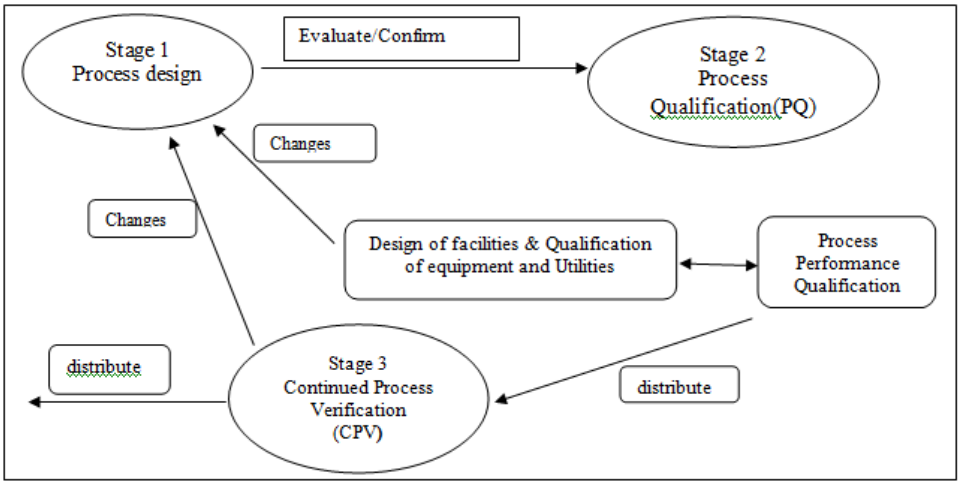

Figure 1: Three model of process validation according to FDA Guidance for Industry

1.3 Types of Process Validation[11, 12]:

1.3.1 Prospective Validation

Establishing documented evidence that a process will produce what it is supposed to produce based on thepre-planned protocol. Here validation protocol is implemented before the manufacturing process is put for commercial use. The production process is recognized in individual steps during the product development. On the

basis of experience or theoretical considerations each step should be evaluated to find out the critical parameters that may affect the quality of the finished product.

1.3.2 Retrospective Validation

Establishing documented evidence that a process does what it is supposed to do based on review and analysis of historical data. The sources of such data are production, QA and QC records. A minimum of ten consecutive batches produced is to be utilized in order to consider the acceptable data.

1.3.3 Concurrent Validation

Establishing documented evidence that a process does what it is supposed to do base on data generated during actual implementation of the process. It involves process monitoring of critical processing steps and product testing which in turn helps for generating document evidence to show that the production process is in a state of control that a minimum of three consecutive batches within the finally agreed critical parameters, which gives the product of the desired quality would be to utilized in order to consider the acceptable data.

1.3.4 Revalidation

Establishing documented evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Revalidation becomes very necessary in some situations.

2. Manufacturing process

2.1 Verification of raw materials:

The ingredients, item code, quantity of all ingredients to be dispensed were checked and verification of the batch no. of each ingredient from the BMR, then verified for release and the details were recorded.

2.2 Raw materials sifting:

The raw materials were shifted into a rapid mixer granulator (RMG) and mixed it for approximately 15 – 20 minutes at slow speed.

2.3 Wet mixing:

Purified water was added into RMG through paste window with slow speed impeller and mixed for 2-3 minutes with slow speed impeller, mixing was stopped and mixing was continued with chopper and impeller on at slow speed till granulation point was achieved.

2.4 Wet mass milling:

The wet mass was milled through multimill using 8/10 mm SS screen, knives forward at medium speed.

2.5 Drying:

The wet granules were dried at 60 °C to 65°C inlet air temperature till LOD was achieved NMT 3.5 % w/w. LOD was checked at the end of drying process. If LOD was not within the limit,redry the granules to achieve the LOD.

2.6 Sifting and sizing of dried granules:

Dried granules were sifted using 20 mesh size through vibratory sifter then retention was collected and retention was milled by multimill using 1.5 mm SS screen at knives forward medium speed.

2.7 Lubricant sifting:

The lubricants were sifted through 40 # sieve using vibratory sifter, except magnesium stearate sift separately.

2.8 Lubrication:

The sifted and sized granules were loaded into octagonal blender and mixed for 5-6 minutes at 14 RPM. The LOD of the mixed granules was checked. If LOD was not within the limit ready the granules. The sifted lubricants except magnesium stearate were loaded into octagonal blender and mixed for approximately 2 minutes at speed of 14 RPM then the LOD of lubricated granules was checked.

2.9 Compression:

The tablets were compressed at the average weight 165mg ± 3.0 % using single rotary compression machine.

2.10 Coating:

The tablets were coated to achieve desired average weight using coating pan.

2.11 Machineries:

Equipments and Instruments: Vibratory Sifter (Pharma Fab), RMG (Sainath), FBD (Alliance), Octagonal Blender (Bactochem), Tablet Compression Machine (Cadmach), Metal Detecter (Techno Four Electronics), Electronic balance (Mettletoledo), Disintegration Apparatus (Electrolab), Vernier Caliper(mitutoyo), Friability Apparatus (Electrolab),Hardness tester(Dr. Schleunger), Autotester (Dr. Schleunger).

Table 1: List of Raw Materials and their Functions

Sr. No.	Raw Material	Functions
1.	Sertraline tartarate	Active pharmaceutical ingredient
2.	Calcium hydrogen phosphate anhydrous	Diluent
3.	Microcrystalline-cellulose	Diluent
4.	Hydroxypropyl cellulose	Binder
5.	Sodium starch- Glycolate	Disintegrant
7.	Magnesium stearate	Lubricant
8.	Purified Water	Solvent
9.	HPMC	Coating agent, film-former
10.	Titanium dioxide	Opacifier, pigment
11.	Polyethylene glycol (Macrogol 400)	Plasticizer
12.	Tween 80	Non ionic surfactant and emulsifier

2.12 Process stages, control variables and measuring response / justifications

Following process parameters will be monitored during the manufacturing process

Table 2: Process stages, control variables and measuring response / justifications

Stage	Step	Control Variables	Measuring Response / Justifications
Granulation	Dry mixing	Time	Uniform distribution of active ingredients with excipients
	Wet mixing	Mixer speed	Proper mixer speed to ensure that mixing and binding is completed in optimal mixing time.
		Mixing time	Granular composition and characteristic of the granules is affected by over mixing / undermixing
	Drying	Inlet and outlet temperature	Drying of the granules.
		Drying time	Compression problems by over or under drying of the granules.
			LOD of dried granules.
	Lubrication	Mixing time	Blend uniformity and trouble free compression may be achieved by controlling mixing time and speed of blender.
		Speed of blender	Uniformity of blend at lubrication stage.
		Sequence of addition of lubricants	Yield of lubricated granules.
Compression	compression	Compression force and optimal speed of tablet press	Appearance, uniformity of weight, diameter, thickness, hardness, disintegration test, dissolution rate, assay, yield
Coating	Coating solution preparation	Homogeneity of coating solution	Surface smoothness and shade uniformity is affected by variation in particle size of insoluble colorant.
	Spraying of coating solution	Air pressure	Drop of air pressure causes dripping of coating solution hence cause sticking of tablets.
		RPM of peristaltic pump	Uneven coating, spray rate may be caused by variation in peristaltic pump, RPM.
		Continuous spray of the coating solution for the set time	Appearance, average weight, weight gain and uniformity of weight of coated tablets, yield.

Table 3: Sampling Plan

Process step	Equipment	Sampling plan	Monitoring/ evaluation parameter
Dry mixing	RMG	1 to 3 time of unit dose sample quantity from 10 1ocations on completion of dry mixing process.	Content of active ingredients in dry mix.
Wet mixing	RMG	As per requirement.	Appearance of wet mass
			Ampere reading at the end of granulation end point.
Drying	FBD	5 sample of different locations of FBD	Loss of drying
			Inlet and outlet temperature
			Total drying time
Sifting & sizing	Vibratory sifter & multi mill	As per requirement.	Size of sieve used
			Total sizing time
Lubrication	Octagonal blender	1 to 3 times of unit dose sample quantity from 10 locations on completion of lubrication process.	Content of active ingredients in lubricated granules.
		Composite sample of approximately 20g from all the 10 sampling points.	LOD/sieve analysis, bulk density, granules flow properties.
Compression	Compression machine	Collect tablets from LHS & RHS at minimum optimium and maximum speed of compression machine for following tests.	-
		10 tablets	Thickness
		10 tablets	Friability
		10 tablets	Hardness
		20 tablets	Average weight
		80 tablets	Uniformity of weight
		6 tablets	Disintegration time
Compression	Compression machine	Collect tablets from LHS & RHS at low and high hardness	-
		10 tablets from each side.	Thickness
		10 tablets from each side.	Friability
		10 tablets from each side.	Hardness
		20 tablets from each side.	Average weight
		80 tablets from each side.	Uniformity of height
		6 tablets from each side.	Disintegration time
Compression	Compression machine	Collect tablets at initial, middle and end stage of compression	-
		30 tablets.	Assay and dissolution rate in QC
		10 tablets.	Thickness
		10 tablets.	Friability
		10 tablets.	Hardness
		20 tablets.	Average weight
		80 tablets.	Uniformity of weight
		6 tablets.	Disintegration test
		100 tablets (composite sample)	Complete analysis in QC
Coating	Coating pan	50 tablets	Disintegration test, Average weight, Uniformity of weight
		70 tablets	Complete analysis in QC in dissolution profile.

3. Results

Table 4: Observations and Acceptance Criteria for Speed Challenge Study

Batch No. A		Specification: YYY		
Test	**Acceptance criteria**	**Observation**		
		Min speed	Optimum speed	Max speed
Machine speed	Feeder speed	12 RPM	18 RPM	18 RPM
	Turrent speed	12 RPM	30 RPM	50 RPM
Compression force	Pre compression force	-	-	-
	Main compression force	4.83 kN	6.23 kN	5.51 kN
Appearance	white to off white, caplet shaped, biconvex, uncoated tablets with breakline on one side	Complies	Complies	Complies
Average weight	165.5 mg ± 3 % (160.54 – 170.47 mg)	165.2 mg	165.0 mg	165.3 mg
Uniformity of weight	Within ± 5 % of average weight	Min: -2.12 % Max: +2.48 %	Min: -2.49 % Max:+3.22 %	Min: -2.40 % Max: +2.36 %
Dimension	10.4 * 4.2 ± 0.2 mm	10.42 * 4.22 mm 10.42 * 4.23 mm	10.41 * 4.23 mm 10.42 * 4.24 mm	10.42 * 4.24 mm 10.43 * 4.24 mm
Thickness	3.3 ± 0.3 mm	3.26 – 3.31 mm	3.19 – 3.24 mm	3.28 – 3.33 mm
Hardness	NLT 30 N	69 – 100 N	96 – 125 N	68 – 105 N
Friability	NMT 1.0 % w/w	0.06 % w/w	0.05 % w/w	0.06 % w/w
Disintegration time	NMT 15 minutes	03 min 05 secs	03 min 08 secs	03 min 10 secs

Table 5: Observations and Acceptance Criteria for Hardness Challenge Study

Batch No. A		Specification: YYY	
Test	**Acceptance criteria**	**Observation**	
Appearance	white to off white, caplet shaped, biconvex, uncoated tablets with breakline on one side	Complies	Complies
Average weight	165.5 mg ± 3 % (160.54 – 170.47 mg)	165.0 mg	166.2 mg
Uniformity of weight	Within ± 5 % of average weight	Min: -2.67 % Max: +2.43 %	Min: -2.88 % Max: +2.10 %
Dimension	10.4 * 4.2 ± 0.2 mm	10.42 * 4.21 mm 10.43 * 4.22 mm	10.41 * 4.22 mm 10.42 * 4.23 mm
Thickness	3.3 ± 0.3 mm	3.38 – 3.43 mm	3.15 – 3.25 mm
Hardness	NLT 30 N	45 – 78 N	124 – 131 N
Friability	NMT 1.0 % w/w	0.12 % w/w	0.04 % w/w
Disintegration time	NMT 15 minutes	02 min 30 secs	03 min 15 secs
Compression force	Pre compression force	-	-
	Main compression force	3.01 kN	12.19 kN

Table 6: Batch yield of compressed tablets

Batch No.	GQG5001	GQG5002	GQG5003
Yield	95.56 %	96.75 %	97.54 %

Table 7: Sertraline HCl content in dry mix:

Specification: YYY	**90 % to 110 % of the labeled amount Mean of individual test results : 95 % - 105 %**			
Batch No.		**A**	**B**	**C**
Location				
Sample 1	Top left	94.3	96.4	99.4
Sample 2	Top right	97.1	98.1	98.1
Sample 3	Top front	97.5	98.1	98.1
Sample 4	Top rear	96.7	98.2	98.2
Sample 5	Middle left	96.4	99.3	99.3
Sample 6	Middle right	96.3	97.3	98.5
Sample 7	Bottom left	97.0	96.9	99.3
Sample 8	Bottom right	94.9	96.4	98.4
Sample 9	Bottom front	97.4	97.1	98.7
Sample 10	Bottom rear	96.4	97.4	97.6
	Average	96.4	97.2	98.6
	RSD NMT (5 %)	1.1	0.9	0.6

Drying:

Drying was carried out in FBD with inlet temperature 60 to 65^{0}C

Table 8: LOD of dried granules:

% LOD of dried granules			**Limit : NMT 3.5 % w/w**	
Specification : YYY				
Batch No.		**A**	**B**	**C**
Sample 1	Left	1.28 % w/w	1.31 % w/w	2.05 % w/w
Sample 2	Right	2.80 % w/w	1.18 % w/w	1.68 % w/w
Sample 3	Centre	1.25 % w/w	1.15 % w/w	1.67 % w/w
Sample 4	Front	3.03 % w/w	1.23 % w/w	1.67 % w/w
Sample 5	Back	1.22 % w/w	1.19 % w/w	1.91 % w/w

Table 9: Batch yield of lubricated granules:

Batch No.	**A**	**B**	**C**
Yield	98.61 %	98.71 %	98.58 %

Table 10: Sertraline HCl content in lubricated granules

Specification : YYY	**90 % to 110 % of the labeled amount Mean of individual test results : 95 % - 105 %**			
Batch No.		**A**	**B**	**C**
Location				
Sample 1	Top left	98.3	99.5	101.0
Sample 2	Top right	98.3	98.8	99.8
Sample 3	Top front	99.6	99.4	103.7
Sample 4	Top rear	98.5	98.9	101.6
Sample 5	Middle left	98.2	100.1	102.6
Sample 6	Middle right	96.7	98.5	100.7
Sample 7	Bottom left	96.6	98.8	101.0
Sample 8	Bottom right	96.9	99.3	101.0
Sample 9	Bottom front	98.1	100.2	102.4
Sample 10	Bottom rear	98.1	98.2	101.3
	Average	97.9	99.2	101.5
	RSD NMT (5 %)	1.0	0.7	1.1

Table 11: Sieve analysis:

Batch No.	A	B	C
Cumulative % retained on			
# 40	27.88	27.79	32.72
# 60	30.96	31.92	32.77
# 80	52.66	49.95	56.88
# 100	56.73	52.64	63.13
% passing through			
# 60	69.04	68.08	67.23
# 100	43.27	47.36	36.87

Table 12: Bulk density and LOD:

Batch No.	A	B	C
P – bulk density g/ml (untapped)	0.59	0.63	0.77
Pt – bulk density g/ml (tapped)	0.83	0.83	0.84
LOD (NMT 3.5 % w/w)	1.64 % w/w	1.56 % w/w	1.44 % w/w

Table 13: Hausner's ratio:

Batch No.	A	B	C
Hausner's ratio (Pt / P)	1.42	1.33	1.08

Table 14:% Compressibility:

Batch No.	A	B	C
% Compressibility = $\frac{(pt-p)}{pt} * 100$	29	25	8

Table 15: Observations and Acceptance Criteria for in process test (QC)

Test	Observation			Acceptance criteria
Batch	**A**	**B**	**C**	
Assay	99.0 %	99.0 %	98.5 %	95 – 105 % of stated amount (47.5 – 52.5 mg / tablet)
Dissolution	Min: 91.0 % Max: 99.0 %	Min: 88.0 % Max: 99.0 %	Min: 92.0 % Max: 100.0 %	NLT 75 % of stated amount in 45 minutes

Table 16: Observations and Acceptance Criteria for in process test (QC) for tablet

Specification: YYY				
Test	**Observation**			**Acceptance Criteria**
Batch	**A**	**B**	**C**	
Appearance	**Conforms**	**Conforms**	**Conforms**	white to off white, caplet shaped, biconvex, uncoated tablets with breakline on one side
Average weight	167.30 mg	165.72 mg	163.92 mg	165.5 mg ± 3 %
Uniformity of weight	Min: -1.91 % Max: +1.43 %	Min: -1.70 % Max: +1.44 %	Min: -1.35 % Max: +2.00 %	Within ± 5 % of average weight
Dimension	10.43 * 4.21 mm 10.51 * 4.25 mm	10.41 * 4.19 mm 10.51 * 4.27 mm	10.43 * 4.20 mm 10.47*4.21 mm	10.4 * 4.2 ± 0.2 mm
Thickness	3.18-3.21 mm	3.21-3.28 mm	3.22-3.27 mm	3.3 ± 0.3 mm
Hardness	74-88 N	73-98 N	46-67 N	NLT 30 N
Friability	0.20 % w/w	0.06 % w/w	0.07 % w/w	NMT 1.0 % w/w
Disintegration time	06 min 10 secs	05 min 43 secs	07 min 10 secs	NMT 15 min
Assay	99.5 %	99.6 %	99.0 %	95-105 % of stated amount.
Dissolution	Min: 93.0 % Max: 97.0 %	Min: 93.0 % Max: 99.0 %	Min: 95.0 % Max: 98.0 %	Min: 95.0 % Max: 98.0 %

4. Conclusion

From the various data generated from the three consecutive batches it can be concluded that the manufacturing process of Sertraline hydrochloride 50 mg tablet was capable of producing the products meeting its predetermined specifications and quality attributes. The results were collected at all stage and it was observed that all the results obtained were found within the specified standards and acceptance criteria which were mentioned in the process validation protocol and were according to the finished products specifications. Hence it can be concluded that the manufacturing process of Sertraline hydrochloride 50 mg tablet was validated and was approved for routine production.

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