Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

PROCESS VALIDATION OF ZOLPIDEM TARTRATE 5 mg FILM COATED TABLETS

Parixit Rohitbhai Prajapati*, Ragini Kanaksinh Solanki, Vishalkumar Shashikant Modi, Tara Shankar Basuri

Department of Quality Assurance Techniques, SSR Collage of Pharmacy, Silvassa, U. T. of Dadra & Nagar Haveli -396230, India.

ABSTRACT

The purpose of research work was to study revalidation for Zolpidem tartrate 5 mg film coated tablets. Quality cannot be adequately assured by in-process and finished inspections and testing but it should be built in to the manufacturing process. These processes should be controlled in order or finished product meets all quality specifications. The critical process parameters were identified with the help of process capability and evaluated by challenging its lower and upper release specification. Three initial process validation batches (A, B, C) of same size, method, equipment and validation criteria were taken. The critical parameter involved in sifting , dry mixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication, compression stages and coating were identified and evaluated as per validation plan. Film coating of tablets were evaluated for coating uniformity, coating process efficiency and surface roughness. The spray rate, atomization air pressure, inlet air temperature, distance of nozzle from tablet bed, pan speed and pan differential pressure these affect the final film quality of coated tablets. Outcome indicated this process validation data provides high degree of assurance and manufacturing process produces product meeting its predetermined specifications and quality attributes.

Key words: Zolpidem tartrate, Coated tablet, Process validation, Process parameters.

INTRODUCTION

Definitions:

- Validation:

According to USFDA, "It is documented evidence which provide a high degree of assurance that a specific product will consistently produce a product meeting its predetermined specification and quality attributes".[1, 2]

- Process Validation:

According to USFDA (1987) "Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics".[3,4,5]

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."

Importance of Validation

1. Assurance of quality.
2. It is a time bound process.
3. Important tool for Process optimization.
4. It helps for Reduction of quality cost.

Corresponding Author :- **Parixit Rohitbhai Prajapati** Email:- parixitprajapati@gmail.com

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

5. It Causes in Minimal batch failures, improved efficiently and productivity.
6. It helps Reduction in rejections and hence increased output.
7. It has fewer complaints about process related failures.
8. It is More rapid and reliable start-up of new equipment [6].

Reasons for Process Validation

The possible reason of performing process validation includes:

1. New product or existing products as per SUPAC changes.
2. Change in site of manufacturing, batch size and equipment.
3. Change in process existing products, composition and components.
4. Change in the critical control parameters and specification on input material.
5. Change in the vendor of API or critical excipient. [7]

Types of Process Validation

1. Initial Process Validation:

- It was conducted prior to the distribution of a new product or a product made under a modified production process where the modifications are significant and affect the products characteristics. It is a preplanned approach and includes the initial stages of raw material specifications, formulation development, setting of process sampling plans, process development, designing of batch records, completion of pilot runs, transfer of technology from scale-up batches to commercial batch size, listing major process was executed and environmental controls.
- Initial Process Validation is the validation protocol in executed before the process is put into commercial use. The generally considered three consecutive batches/runs within the finally agreed parameters and giving product of the desired quality would constitute a proper validation of the process. On the basis of three commercial batches before marketing.

2. Concurrent Validation:

- A process where current production batches are used in monitor processing parameters. It gives a present batch was studied and offers for limited assurance regarding consistency of quality from batch to batch. Some concurrent validation examples are following:
- A limited numbers of batches are produced.
- A previous validated process was transferred to a third party contract manufacturer or to another site.
- Product is a different strength of a previously validated product with the same ratio of active / inactive ingredients.
- Product behavior and history will be reviewed based on developmental, scale up and test batches.
- A detailed procedure should be planned for handling of the marketed product if any adverse reactions observed in concurrent validation process.

3. Ongoing Process Verification during life cycle:

- Establishing documented evidence that a process does what it is supposed to do based on review and analysis of historical data. Some of the essential elements for Ongoing Process Verification during life cycle are t he following:
- A minimum of 10 last consecutive batches are manufactured for a defined period.
- The numbers of lots are released per year.
- Batch size, manufacturer, strength, year, period.
- Master manufacturing and packaging documents.
- List of process deviations, changes to manufacturing documents and corrective actions.

4. Re-Validation:

- Establishing documented evidence that changes in a process and /or the process environment that are introduced do not adversely affect product quality and process characteristics. When there is a change required in any critical process parameters, raw material fabricator, major equipment or premises, formulation, primary packaging components. Revalidation becomes very necessary in certain situations. The following some examples of planned and unplanned that may require re- validation:
- Changes in the raw materials including physical properties such as density, viscosity, particle size distribution, and moisture. That may have affected the process or product.
- Changes in packaging material such as a primary container and closure system.
- Changes in the process some example are mixing time, drying temperatures and batch size.[8,9].

Table 1. Stages of Process Validation

Stages	Intents	Typical Activities
Stage 1: Process Design	• The commercial process on knowledge gained through development and scale up activities. • The outcome is the design of a process suitable for routine manufacturing and that will consistently deliver product meets its critical quality attributes.	• A combination of product and process design (Quality by Design- QBD). • Experiments to determine process parameters, variability, necessary control and Risk assessments. • Other activities required to define the commercial Process.

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

		• Design experiment testing Facility design, Equipment & utilities qualification.
Stage 2: Process Qualification	To confirm the process design as capable of reproducible commercial manufacturing.	• Performance qualification (PQ). • Strong emphasis on the use of statistical analysis of process data to Performance and understand process consistency
Stage 3: Continued Process Verification	To provide ongoing assurance that process remains in a state of control during routine production through quality procedures through continuous improvement initiatives and quality procedures.	• Proceduralised data collection from every batch. • Statistical analysis product review and data trending. • Facility maintenance calibration and Equipment. • Production staffed back and Management review. • Improvement initiative through process experience.

Manufacturing process:

1. **Raw Material sifting:**

The required Quantities of Zolpidem tartrate, lactose monohydrate, Microcrystalline cellulose was sifted through 40# using vibratory sifter. Sifted Pregelantinised starch separately in a polybag.

2. **Binder preparation:**

12.500 L of purified water was taken in a clean SS vessel , heated to boiling and cool to maintain 35-40°. Added and dispersed Pregelantinised starch was added to the purified water under continuous stirring to form lump free slurry.

3. **Dry Mixing:**

The sifted raw materials were loaded into RMG and Mix for 10min at low speed mixing.

4. **Wet mixing:**

Binder solution was added RMG and mixed for 10 minutes impeller at slow speed and chopper off. Stop the mixing of raw materials and mixed for 1-2 minutes impeller at fast speed with chopper at slow speed. Mixing was continued till granulation end point was reached.

Determination of end point: One handful of wet mass was taken and pressed to form a lump, open the palm and break the lump by pressing the thumb at the center of the lump. The lump should break into small pieces.

5. **Wet mass sifting / wet milling (If required):**

The wet mass was milled using 10 mm SS Screen, Knives forward at optimum speed of multi- mill or sifting in vibratory sifter through 8.0 mm sieve.

6. **Drying:** The wet granules was dried at 50°c -60°c inlet air temperature till the loss on drying (LOD) of the granules was achieved between 2.0 to 3.5% (w/w).

7. **Sifting and sizing of dried granules:**

The dried granules was sifted through 30# using vibratory sifter and collected the retention. Mill the retention sample through Multimill using 1.0 mm SS Screen.

8. **Lubricants sifting:**

lubricants were sifted through 40# using vibratory sifter, sifted magnesium stearate separately and collected in a separate polybag.

9. **Lubrication:**

Load the sifted and sized granules were loaded octagonal blender and mix for 2 minutes at slow speed. Check loss on drying (LOD) of the mixed granules between 2.0 to 3.5% (w/w). Load the sifted lubricants except magnesium stearate in octagonal blender and mixed for 10 minutes at slow speed. Added magnesium stearate in octagonal blender and mixed for 2 minutes at slow speed.

10. **Compression:** Compressed the tablets using tablet compression machine.

Machineries:

Equipment and Instrument were used such as a Vibratory Sifter (Pharma fab), RMG (Sainath), FBD (ALLIANCE), Octagonal Blender (BACTOCHEM), Tablet Compression Machine (CADMACH), Metal Detector (Techno four electronics), Electronic Balance (Mettle Toledo), Disintegration Apparatus (Electro lab), Vernier Caliper (Mitutoyo), Friability Apparatus (Electro lab), Hardness tester (Dr. schleunger), Auto tester (Dr. Schleunger).

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

Table 2. List of Raw materials and their functions

Sr. No	Raw materials	Functions
1	Zolpidem tartrate	Active Pharmaceutical Ingredient
2	Lactose Monohydrate	Diluent
3	Microcrystalline-cellulose	Diluent, Disintegrate
4	Pregelantinised starch	Binder
5	Purified Water	Solvent
6	Sodium starch- Glycolate (Type-A)	Disintegrant
7	Silica colloidal-anhydrous	Disintegrate
8	Magnesium stearate	Lubricant
9	Hypromellose 5 cps	film former, Binder
10	Titanium dioxide	Opaquant agent
11	Purified Talc	Glidant
12	Macrogol 6000	plasticizer, lubricant

Process stages, control variables and measuring response / justifications

Following process parameters will be monitored during the manufacturing process

Table 3. Critical Process Parameter

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 is required so that mixing and binding is completed in optimal mixing time
		Mixing time	The granular composition of mix and characteristic of the granules. Ampere reading at end point consistency of wet mass.
	Drying	Inlet and outlet temperature	Control of inlet air temperature.
		Drying time	Granules are drying over or under of the Compression problems.
			LOD of dried granules.
	Lubrication	Mixing time	Blend uniformity and trouble free compression may be achieved by Control over mixing time and speed of mixer.
		Speed of Mixer	Uniformity of blend at Prelubrication and lubrication stage.
		Sequence of the addition of the 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	Variation in particle size of I insoluble colorant is affected by surface smoothness and shade uniformity.
	Spraying of coating solution	Air pressure	Any drop in the air pressure results in dripping of the coating solution. Which causes sticking of the tablets.

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

		RPM of peristaltic pump	Which results in uneven coating, Spraying rate in g/min or ml/min.
		Continuous spray of the coating solution for the set time	Clogging of Nozzle results in interruption of continuous spray.

Table 4. Sampling Plan

Process Step	Equipment	Sampling Plan	Monitoring/ Evaluation parameter
Dry Mixing	RMG	Collect 10 sample from different locations of RMG as mentioned in the sampling plan.	Content of Zolpidem tartrate in dry mix
Wet Mixing	RMG	Collect 10 sample from different locations of RMG as mentioned in the sampling plan.	Appearance of wet mass
			Ampere reading at the end of granulation end point
Wet Milling	Multi mill or Vibratory Sifter	-	Size of sieve and screen used
Drying	FBD	Collect 5 sample From different locations of FBD	Loss of drying
			Inlet and outlet temperature
			Total drying time
Sifting & Sizing	Vibratory Sifter & Multi mill	-	Size of sieve used
			Total sizing time
Lubrication	Octagonal Blender	2 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 20gm from all the 10 sampling points.	LOD, Sieve Analysis, Bulk density, Granules Flow Properties.
Compression	Compression Machine	Collect about 125 tablets from each side at minimum optimum and maximum speed of compression machine for following tests.	-
		10 Tablets from each side.	Thickness
		20 Tablets from each side.	Friability
		10 Tablets from each side.	Hardness
		20 Tablets from each side.	Average Weight
		50Tabletsfrom each side.	Uniformity of Weight
		6 Tablets from each side.	Disintegration time
Compression	Compression machine	Collect tablets 150 Tablets from each side at Initial, Middle and End Stage of compression.	-
		30 Tablets from each side.	Assay and Dissolution. rate in QC
		10 Tablets from each side.	Thickness
		20 Tablets from each side.	Friability
		10 Tablets from each side.	Hardness
		20 Tablets from each side.	Average Weight
		50 Tablets from each side.	Uniformity of Weight
		6 Tablets from each side.	Disintegration time
		Approximately 50 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 and dissolution profile.

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

RESULTS

Table 5. Observation & Acceptance criteria for speed challenge study

Batch No: A		Specification: xxx		
Test	**Acceptance criteria**	**Observation**		
		Minimum speed	**Average speed**	**Maximum speed**
Machine speed	Feeder speed	15 RPM	15 RPM	15 RPM
	Turrrent speed	11.60 RPM	22.30 RPM	29.30 RPM
Compression force	Pre compression force	-	-	-
	Main compression force	17.40 KN	18.50KN	17.62 KN
Appearance	White to almost white, round, biconvex uncoated tablets '5' embossing on one side and plain on the other side.	Complies	Complies	Complies
Average weight	65mg ± 7.5% (60.13 – 69.88mg)	63.5 mg	63.4mg	63.3mg
Weight of 20 tablets	1.20 mg – 1.40gm	1.30 gm	1.28gm	1.32 gm
Uniformity of weight	NMT 2/20 to exceed ± 10% and none to exceed ± 20%	Min–2.10 % Max: ±2.58%	Min–2.21% Max: ±3.00%	Min–2.21 % Max: ±2.37%
Diameter	5.0 -5.2 mm	5.02 – 5.08 mm	5.02 – 5.10 mm	5.02 – 5.08 mm
Thickness	2.3 – 2.9 mm	2.70 -2.73 mm	2.70 – 2.82 mm	2.70 – 2.80 mm
Hardness	30 – 90 N	54 - 64 N	55 - 66 N	55 – 61N
Friability	NMT 1.0% w/w	Nil	Nil	Nil
Disintegration	NMT 15 minutes	04min.02sec.	03min.52sec.	05min.02sec.

Table 6. Observations & Acceptance criteria for Hardness challenge study

Batch No: A		Specification: xxx	
Test	**Acceptance criteria**	**Observation**	
		Low Hardness	**High Hardness**
Appearance	White to almost white, round, biconvex, uncoated tablets '5' embossing on one side and plain on the other side.	Complies	Complies
Average weight	65mg ± 7.5% (60.13 – 69.88mg)	64.6 mg	60.4 mg
Weight of 20 tablets	1.20 – 1.40 gm	1.32 gm	1.32 gm
Uniformity of weight	NMT 2/20 to exceed ± 10% and none to exceed ± 20%.	Min: -2. 63% Max:+1.55%	Min: -2.15% Max:+3.30%
Diameter	5.0 – 5.2 mm	5.00 -5.06 mm	5.02 -5.09 mm
Thickness	2.3 -2.9 mm	2.77 – 2.83 mm	2.68 – 2.73 mm
Hardness	30 – 90N	52 – 65 N	52 – 61 N
Friability	NMT 1.0% w/w	Nil	Nil
Disintegration	NMT 15 minutes	04min.30sec	05min.10sec
Machine speed	Feeder speed	21RPM	15 RPM
	Turrent speed	22.30 RPM	22.30 RPM
Compression Force	Pre compression force	-	-
	Main compression force	18.84 KN	17.92 KN

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

Table 7. Yield of compressed tablets

Batch No: -	Batch No: A
Yield	98.96%

Table 8. Zolpidem Tartrate content in Dry Mix

Specification: xxx		Limit 90.0% to 110% of the labelled amount		
Batch No. Location		Batch A	Batch B	Batch C
Sample – 1	Top Left	102.6	102.5	104.2
Sample – 2	Top Right	104.0	103.4	102.8
Sample – 3	Top Front	103.6	102.1	101.3
Sample – 4	Top Rear	105.1	105.3	104.8
Sample – 5	Middle Left	105.1	102.3	104.4
Sample – 6	Middle Right	104.6	97.2	105.5
Sample – 7	Bottom Left	104.5	104.3	105.2
Sample – 8	Bottom Right	104.0	106.8	106.5
Sample – 9	Bottom Front	104.5	101.1	104.8
Sample – 10	Bottom Rear	104.8	102.4	105.3
Average		104.1	102.7	104.5
RSD (NMT 5%)		0.8	2.5	1.4

Drying:

Drying was carried out in FBD with inlet temperature 55 to 60˚C.

Table 9. LOD of dried granules

% LOD of dried granules		Limit between 2.0 to 3.5% (w / w)		
Specification: xxx				
Batch No.		Batch A	Batch B	Batch C
Sample -1	Left	2.67	3.04	2.87
Sample -2	Right	2.83	2.26	3.07
Sample -3	Center	3.18	2.94	3.04
Sample -4	Front	2.74	3.08	2.76
Sample -5	Back	2.67	2.35	2.88

Table 10. Batch Yield of lubricated granules

Batch No.	Batch A	Batch B	Batch C
Yield	98.43%	99.5%	99.82%

Table 11. Zolpidem tartrate content in lubricated granules

Specification: xxx		Limit 90.0% to 110% of the labelled amount		
Batch No. Location		Batch A	Batch B	Batch C
Sample – 1	Top Left	104.4	102.0	103.9
Sample – 2	Top Right	102.2	105.4	102.2
Sample – 3	Top Front	100.7	102.6	103.8
Sample – 4	Top Rear	100.0	103.2	103.2
Sample – 5	Middle Left	103.9	101.9	102.8
Sample – 6	Middle Right	104.2	103.6	101.9
Sample – 7	Bottom Left	104.1	106.2	101.2
Sample – 8	Bottom Right	104.0	102.5	99.7
Sample – 9	Bottom Front	103.7	106.9	102.6

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

Sample – 10	Bottom Rear	102.9	103.0	103.1
Average		103.0	103.7	102.4
RSD (NMT 5.0%)		1.5	1.7	1.3

Table 12. Sieve Analysis

Batch No.	Batch A	Batch B	Batch C
Cumulative % Retained on			
# 40	29.52	29.74	29.90
# 60	29.93	29.13	29.20
# 80	29.94	29.13	29.20
# 100	29.94	29.13	29.20
% Passing Through			
# 60	70.07	70.87	70.80
# 100	70.06	70.87	70.80

Table 13. Bulk density and LOD

Batch No:	Batch A	Batch B	Batch C
P – Bulk density g/ml (untapped)	0.56	0.56	0.56
Pt - Bulk density g/ml (tapped)	0.71	0.71	0.72
LOD (Between 2.0 -3.5% (w/w)	2.95	2.43	2.83

Table 14. Hausner's Ratio

Batch No:	Batch A	Batch B	Batch C
Hausner's Ratio (Pt /P)	1.26	1.26	1.27

Table 15. % Compressibility

Batch No:	Batch A	Batch B	Batch C
% Compressibility (Pt-P) / Pt × 100	22	22	22

Table 16. Operating parameters of Auto - coater

Parameter	Observation		
Batch No: -	Batch A	Batch B	Batch C
Preheating of tablets at Approx.30 -40°C	40°C	40°C	40°C
Pan speed	2 – 6 RPM	3 – 6 RPM	2 – 7 RPM
Inlet Temperature (50 -60°C)	55.0 – 68.0°C	55.2 – 66.0°C	55.0 – 65.0°C
Exhaust Temperature (40 -45°C)	40.2 – 50.9°C	41.1 – 43.0°C	40.2 – 48.0°C
Bed Temperature (40 -45°C)	40.0 -52.0°C	42.0 – 45.0°C	40.5 – 50.0°C
Coating Mode	Auto	Auto	Auto
Cycle status	Continuous	Continuous	Continuous
Running Time	151 min	150 min	145 min
Pump Speed (Min & Max)	5 – 7 RPM	5 – 7 RPM	5 – 9 RPM
Spray Rate (Approx. 106.96 g/ml)	69.8 – 129.2 g/min	83.6 – 103.6 g/min	79.9 – 105.4 g/min
Spray Time (No. of coat)	126 min	120 min	85 min
Drying Time	15 min	15 min	15 min
Cooling Time	10min	10min	10min
Main Air pressure (3 - 4kg/cm^2)	4 kg / cm^2	4 kg / cm^2	4 kg / cm^2
Gun – 1 Atomizing pressure	4 kg / cm^2	4 kg / cm^2	4 kg / cm^2
Gun – 2 Atomizing pressure	4 kg / cm^2	4 kg / cm^2	4 kg / cm^2
Gun – 3 Atomizing pressure	4 kg / cm^2	4 kg / cm^2	4 kg / cm^2
Distance between bed time and gun 10''	10 inch	10 inch	10 inch
Weight gain (Approx. 2.0 mg)	2.0 mg	2.0 mg	2.1mg

Asian J. Pharm. Res. Vol 6, Issue 2, 68-77, 2016.

Table 17. Yield of coated tablets

Batch No: -	Batch A	Batch B	Batch C
Yield	98.09%	98.63%	95.23%

Table 18. Observations & Acceptance criteria for In - process Test

Batch A		Specification: xxx		
Test	Acceptance criteria	Observation		
		Initial	Middle	End
Appearance	White to almost white, round, biconvex, uncoated tablets '5' embossing on one side and plain on the other side.	Complies	Complies	Complies
Average weight	65mg ± 7.5% (60.13 – 69.88mg)	61.9 mg	63.8mg	63.7mg
Weight of 20 tablets	1.20 – 1.40gm	1.30gm	1.34gm	1.27gm
Uniformity of weight	NMT 2/20 to exceed ± 10% and none to exceed ± 20%.	Min: -2.10% Max: +2.58%	Min: -3.29% Max: +1.88%	Min: -3.17% Max: +2.38%
Diameter	5.0 – 5.2 mm	5.02 – 5.08 mm	5.00 -5.02 mm	5.00 -5.02 mm
Thickness	2.3 -2.9 mm	2.70 – 2.73 mm	2.71 – 2.77 mm	2.74 – 2.80 mm
Hardness	30 - 90N	54 - 64 N	55 – 65N	66 - 79N
Friability	NMT 1.0% w/w	Nil	Nil	Nil
Disintegration	NMT 15 minutes	04min.02Sec	04min.02Sec	04min.02Sec

Table 19. Observation and Acceptance criteria for In – process Test (QC)

Test	Observation			Acceptance criteria
Batch	A	B	C	
Assay	99.0%	99.0%	98.9%	95 – 105 % of stated amount (4.75 – 5.25 mg / tablet)
Dissolution	Min: 99% Max: 102%	Min: 99% Max: 100%	Min: 100% Max: 101%	NLT 75 % of stated amount in 45 minutes

CONCLUSION

On the basis of data generated from the three batches (Batch-A, Batch-B, Batch-C), it is concluded that the manufacturing process of Zolpidem tartrate 5 mg film coated tablets was capable of producing a product meeting its quality attributes and predetermined specification. The results of all stages were found within the standard specification and acceptance criteria mentioned in the process validation protocol and finished product specification. Hence it was concluded that the manufacturing process of Zolpidem tartrate 5 mg film coated tablets is considered validated and approved for routine production. Therefore, the Process Stands Validated.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

REFERENCES

1. Nash R, Wachter A. In Pharmaceutical Process Validation", 3rd Edition, Revised and Expanded, Marcel Dekker Inc., New York, 1993, 13-23.
2. Agalloco J, Carleton F. Validation of Pharmaceutical Processes", 3rd Edition, Marcel Dekker, Informa Healthcare, New York, 2008, 1-4.
3. Md. Alam S. Pharmaceutical Process Validation, An Overview". *Journal of Advanced Pharmacy Education & Research*, 2(4), 2012, 185-200.
4. Paula K, Cliff C. Note for Guidance on Process Validation. *Journal of GXP Compliance*, 16(4) 2001, CPMP/QWP/96, EMEA/CVMP/598/99 18-29.

5. Annex 3. Guidelines on good manufacturing practices, validation, Appendix 7, non-sterile process validation, WHO Expert Committee on Specifications for Pharmaceutical Preparations Forty-ninth report, 2011, 75-86.
6. Potdar MA. Pharmaceutical Quality Assurance", 2rd Edition, volume 1, Nirali Prakashan, Pune, 2007, 8.1-8.44.
7. Guidance on process Validation, Rev 1-EMA/CHMP/CVMP/QWP/7027/2012.
8. Guidelines for Process Validation of Pharmaceutical Dosage Forms. Saudi Food and Drug Authority, Kingdom of Saudi Arabia, 2010, 9-15.
9. Shruthi N, Gupta N, Raghunandan H, Kashyap U. USFDA Guidelines on Process Validation - A Review", *International Journal of Pharm Tech Research*, 6(3), 2014, 920-923.