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FORMULATION AND VALIDATION OF SERTRALINE FILM COATED TABLET

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ABSTRACT

To survive in competitive market and to be successful, it is necessary to achieve high level of product quality validation is one of the important steps in achieving and maintaining the quality of the final product batch after batch. Without equipment, we cannot manufacture a product. Validation is one of the important steps in achieving and maintaining the quality of the final product. Each step of production process is validated we can assure that the final product is of the best quality of the product. Validation and quality assurance will go hand in hand, ensuring the quality for the products. This review provides information on objectives and benefits of Process validation, types of process validation, major phases in validation and regulatory aspects.

Keywords: Formulation, Process Validation, Sertraline, Film Coated, Tablet.

INTRODUCTION

The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control the drug substances and drug products to computerized systems for clinical trials and is the important step in gaining and maintaining the quality of the final product validation[1]. Validation can also be said as- The collection and assessment of data, from the process design stage all the way through production, which establishes logical indication that a process is capable of consistently delivering quality products[2]. Validation is a systematic approach to identifying, measuring, evaluating, documenting and reevaluating a series of critical step, in the manufacturing process that requires control to ensure a reproducible final product[3]. It has become a necessary step to ensure better quality of medicinal product, throughout manufacturing, storage, handling and distribution. Quality cannot be inspected or tested into finished product[4].

According to US FDA in 1978, A validation manufacturing process is one which has been proved to do what it purports or is represented to do[5]. 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[6]. Validation necessarily includes process qualification (the qualification of materials, equipment, system, building, personnel but it also includes the control on the entire process for repeated batches or runs[7].

USFDA defined process validation as establishing documented evidence which provides high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics[8].

MATERIAL AND METHODS

Sertraline Hydrochloride was Active pharmaceutical ingredient, Microcrystalline-cellulose, Hydroxypropyl cellulose, Sodium starch-Glycolate, Magnesium stearate, Purified Water, HPMC, Polyethylene glycol (Macrogol 400), Tween 80 and Titanium dioxide were used for experiment.

Process stages, control variables and measuring response / justifications

Following process parameters will be monitored during the manufacturing process of Sertraline Hydrochloride Tablets 50mg.

Table No. 1: 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 mixingand binding is completed in optimal mixing time.
		Mixing time	Granular composition and characteristic of the granules is affected by over mixing/under mixing
	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 ofblender.
		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,assays.
Coating	Coating solution preparation	Homogeneity of Coating solution	Surface smoothness and shade uniformityis affected by variation in particle size of insoluble colorant.
		Air pressure	Drop of air pressure causes dripping of coating solution hence cause sticking of tablets
	Spraying of coating solution	RPM of peristaltic pump	Uneven coating, spray rate may be causedby variation in peristaltic pump, RPM.
		Continuous spray of thecoating solution for the set time	Appearance, average weight, weight gain and uniformity of weight of coated tablets, yield.

RESULT AND DISCUSSION

Process validation is a key element in assuring that these principles and goals are met. In this study concurrent process validation was carried out for one product. In tablet dosage form, critical parameters were taken up for validation studies.

(a) Dry mixing: The dry-mixing step involves mixing of Sertraline with other additives using Rapid mixer granulator. The mixing of the active ingredient depends on the mixing time.

(b) Drying: The drying step involves drying of wet mass. Moisture in granules is important factor. If moisture is more in granules it will lead to poor flow and sticking problem. If moisture is less it will lead to capping height friability and chipping. During drying the LOD of granules should be taken in to consideration.The inlet temperature of the FBD is controlled during the drying process and the outlet temperature is monitored and correlated with the corresponding LOD of the granules under drying.

(c) Milling: Dried granules were than sifted and milled on Camilla the end of milling, composite sample was withdrawn and tested for particle size distribution, bulk density and LOD. Results obtained were found well within the limit and recorded.

(d) Blending/Lubrication: The blending of three batches was performed and the samples at the designated locations were drawn after 3 minutes of blending after transferring magnesium stearate to octagonal blender for determining the blend uniformity and RSD values .The RSD values meet the acceptance criteria. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous. Hence the blending time of 3 minutes after addition of magnesium stearate as validated.

(e) Compression: The compression for all the three batches has been validated for minimum and maximum hardness, minimum and maximum speed and at optimum speed; initial stage, middle stage and end stage of compression. The results of physical parameters like appearance, thickness, length,width, hardness, friability, disintegration time, group weight, average weight, uniformity of weight and capability index, dissolution and assay of the tablets were well within the acceptable limits. The results are comparable among all the three batches.

(f) Blister packing: This process involves packing of tablets in clear thermoform able rigid PVC film and printed aluminium foil. Temperature of blister sealing rollers, forming rollers and speed of machine are critical variables. Adequate sealing roller temperature is essential to get proper sealing, less temperature will lead to improper sealing which cause leakage and higher temperature will result in burning or spoilage of PVC film or aluminum foil. Leak test and blister appearance are carried out to establish the above variables during blister packing operation.

Pre-formulation study

(a) Melting point: Melting point was determined on melting point apparatus**,** Melting point of Sertraline hydrochloride was found in the range of 243 - 245° C. Reported melting point of Sertraline hydrochloride is 244 - 245° C.

(b) Calibration Curve: The absorbance of the solutions were measured at 273 nm against 50% v/v aqueous methanol usedas blank and the results observed are as follows:

Table No. 2: Results of Calibration Curve

Concentration	2	4	6	8	10	12	14	16	18	20
Absorbance	0.020	0.045	0.072	0.110	0.150	0.180	0.210	0.250	0.300	0.350

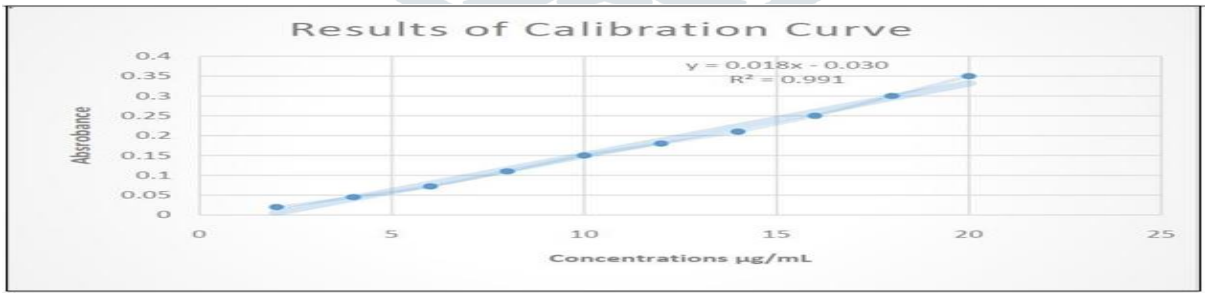

Figure 1: Graphical Representation of Calibration Curve

Evaluation of tablet

Bulk Density: Apparatus bulk density (pb) was determined by placing pre-sieved drug excipients blend into a graduated cylinder and the result was observed.

Tapped Density: Tapped density was determined and result was observed.

Loss on drying (LOD): The Loss on drying of the batches were observed

Blend Uniformity: Blend Uniformity was determined and result observed

Table No. 3: Results of pre-compression evaluation of blend granules

Batch	Untapped bulk density (g/ml)	Tapped bulk density (g/ml)	LOD (% w/w)	Avg. of Blend Uniformity
I	0.58	0.83	1.79 %	99.5 %
II	0.59	0.83	1.58%	98.3 %
III	0.59	0.84	1.75%	99.4 %
Acceptance Criteria	(0.50-0.70g/ml)	(0.80-0.90g/ml)	(NMT 3.0%)	90.0 - 110.0%

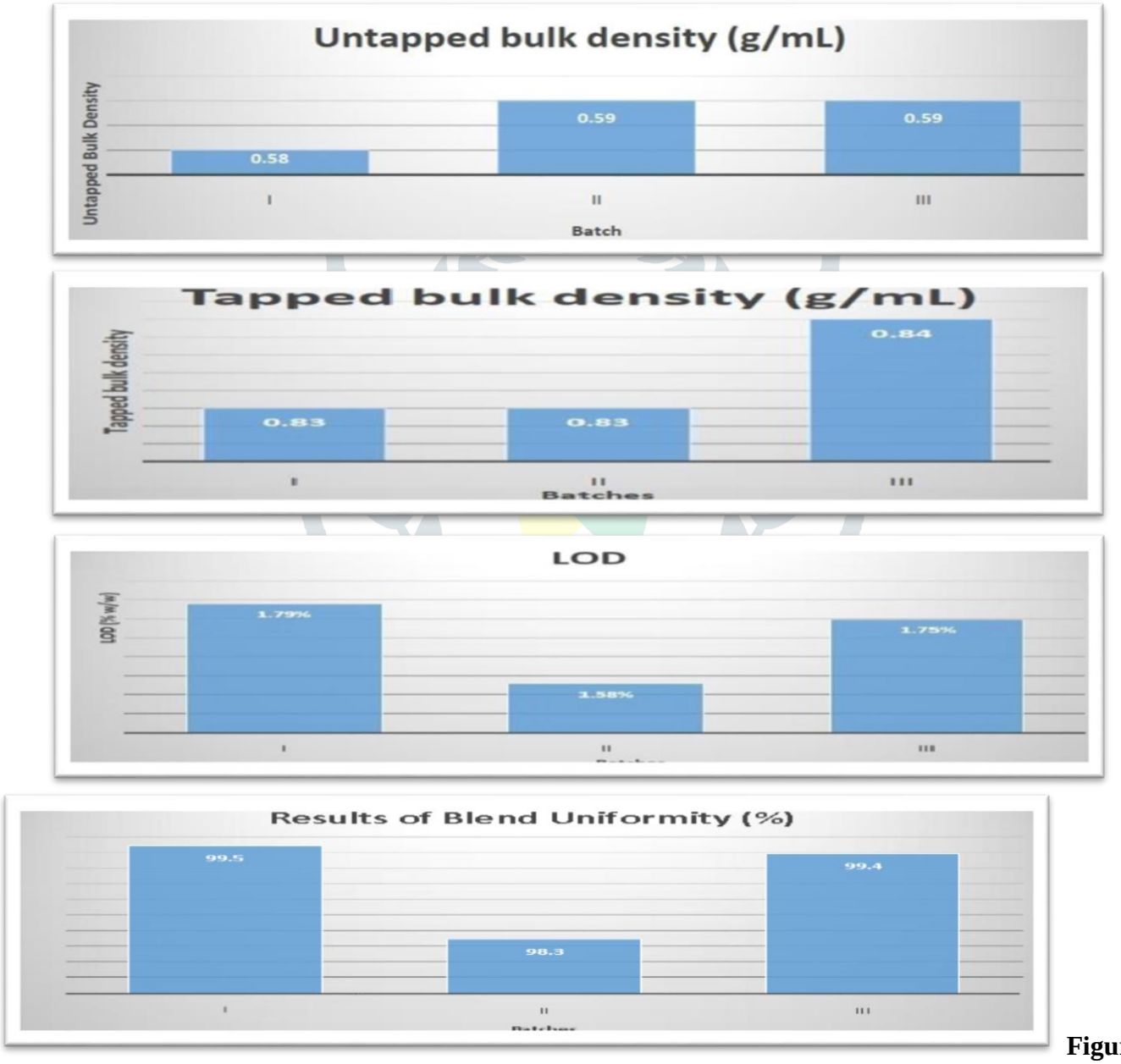

Figure 2: Graphical Representation of evaluation of blend granules

Particle size distribution: Particle size distribution was determined and result observed as:

Table No. 4: Results of Particle size distribution

Sieve Size	Acceptance Criteria	% w/w Retention		
		Batch I	Batch II	Batch III
20%	For information only	1.2%w/w	1.6% w/w	1.6% w/w
40%		13.0% w/w	27.2% w/w	27.0% w/w
60%		38.5% w/w	52.8% w/w	52.8% w/w
80%		50.0% w/w	64.3% w/w	63.6% w/w
100%		54.3% w/w	68.7% w/w	67.8% w/w
120%		60.0% w/w	74.4% w/w	73.8% w/w
% in pan		40.0% w/w	25.6% w/w	26.2% w/w

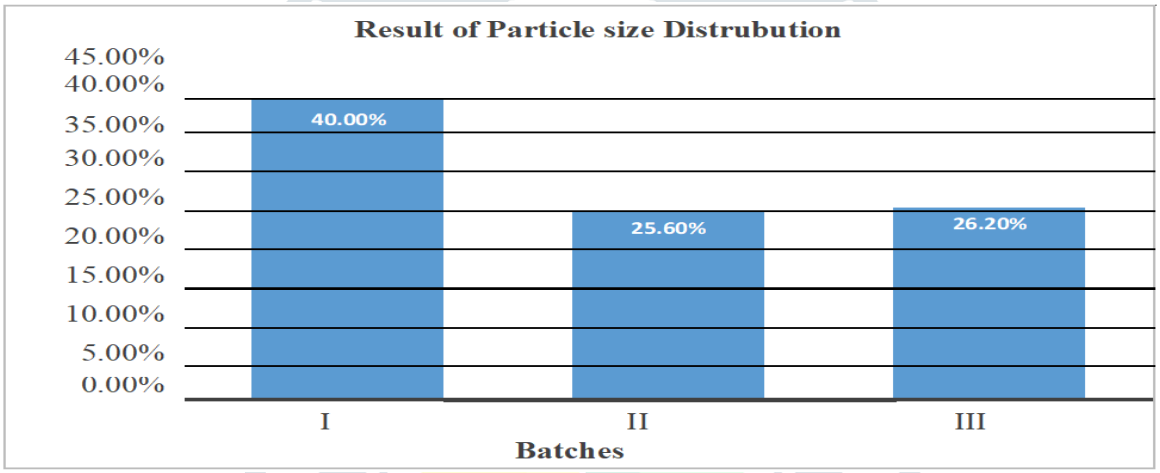

Figure 3: Graphical Representation of Particle Size Distrubution

Hardness: Hardness of in process tablet were as follows:

Table No. 5: Results of Hardness

Batch	Minimum	Maximum
Batch I	8.2 Kp	10.3 Kp
Batch II	8.0 Kp	11.1 Kp
Batch III	9.2 Kp	11.0 Kp
Acceptance Criteria	70 N – 160 N (7 Kp – 16 Kp)	

Figure 4: Graphical Representation of Hardness

Friability: Friability of in process tablet was as follows:

Tablet No. 6: Results of Friability

S .No	Friability (%w/w)
Batch I	0.06%w/w
Batch II	0.05%w/w
Batch III	0.06%w/w
Acceptance Criteria	**Not more than 1.0%w/w**

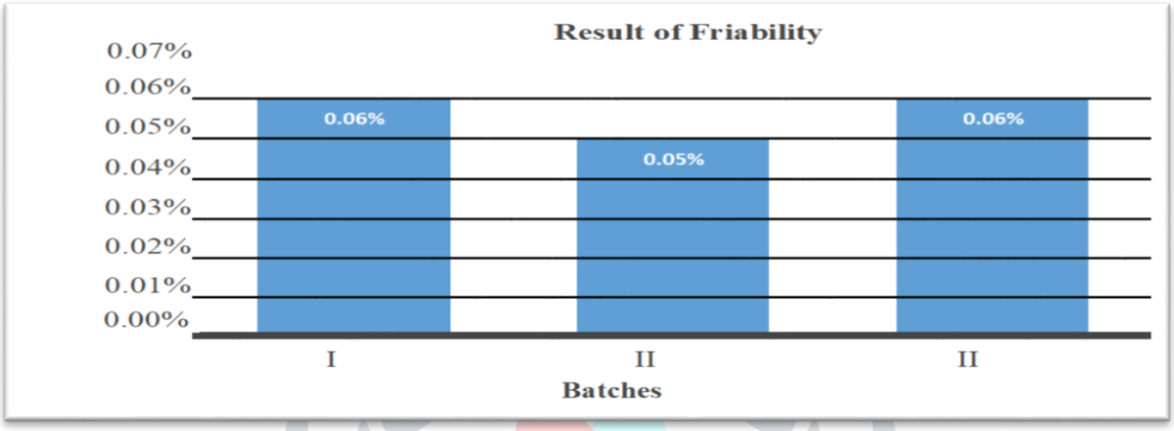

Figure 5: Graphical Representation of Friability

Assay: Observed results of assay are as follow:

Table No. 7: Results of Assay

Batch	Assay (% w/w)
I	**99.0 %**
II	**99.0%**
III	**98.5%**
Acceptance Criteria	**95.0 – 105.0 % of stated amount**

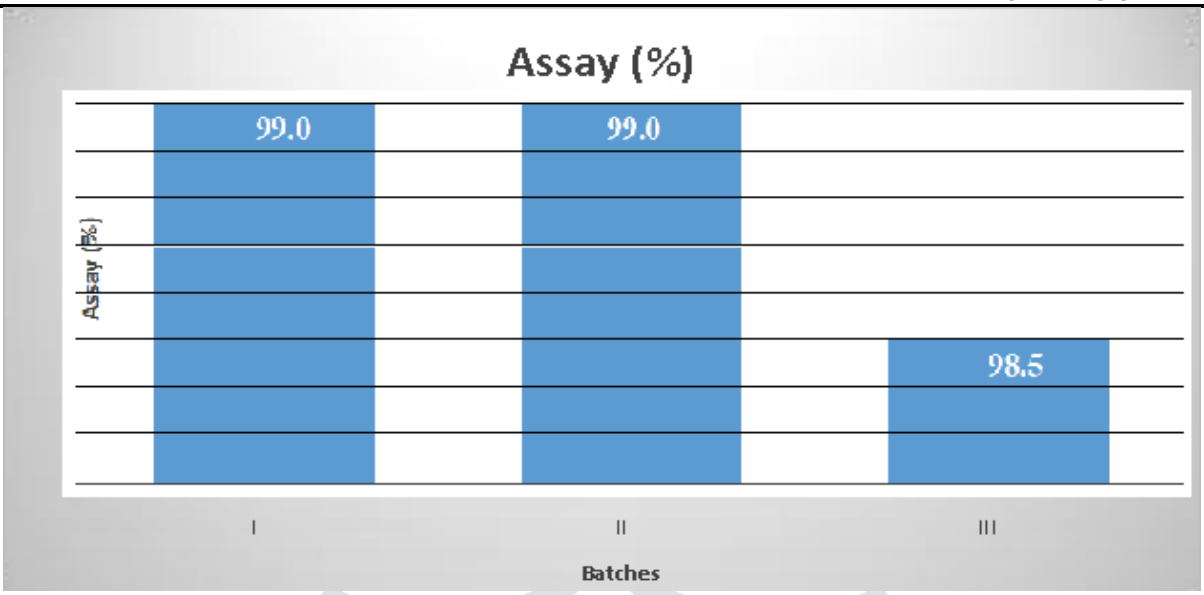

Figure 6: Graphical Representation of Assay

Weight variation:

Table No. 8: Results of Weight variation

No of tablets	Observation			Acceptance criteria
	Batch I	Batch II	Batch III	
Tablet -1	99.6	100.0	99.2	The AV value should benot more than 15.0 **(90.0-110.0%)**
Tablet -2	99.0	98.8	99.3	
Tablet -3	99.1	99.4	100.2	
Tablet -4	100.2	98.8	98.7	
Tablet -5	100.2	100.1	100.2	
Tablet -6	98.7	99.0	99.7	
Tablet -7	100.2	99.2	98.7	
Tablet -8	99.5	98.8	99.2	
Tablet -9	98.9	100.1	98.9	
Tablet -10	100.1	99.6	100.1	
Min	98.7	98.8	98.7	
Max	100.2	100.1	100.2	
AVG	99.5	98.3	99.4	

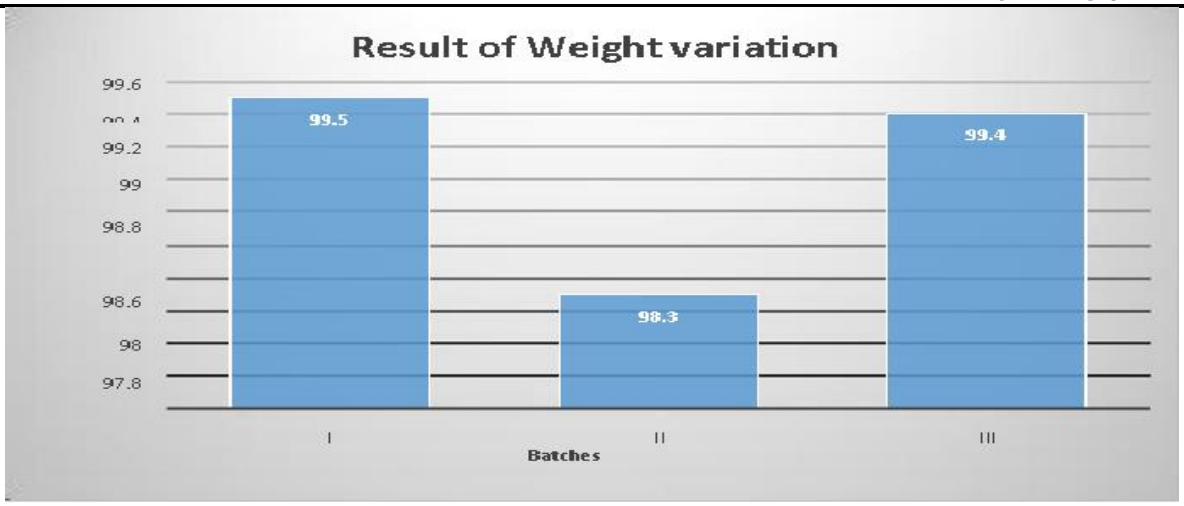

Figure 7: Graphical Representation of Weight Variation

***In-vitro* disintegration:**

Table No. 9: Results of *In-vitro* disintegration

Batches	Disintegration Time
I	6 min 10 sec
II	5 min 43 sec
III	07 min 10 sec
Acceptance Criteria	**Not more than 15 minutes**

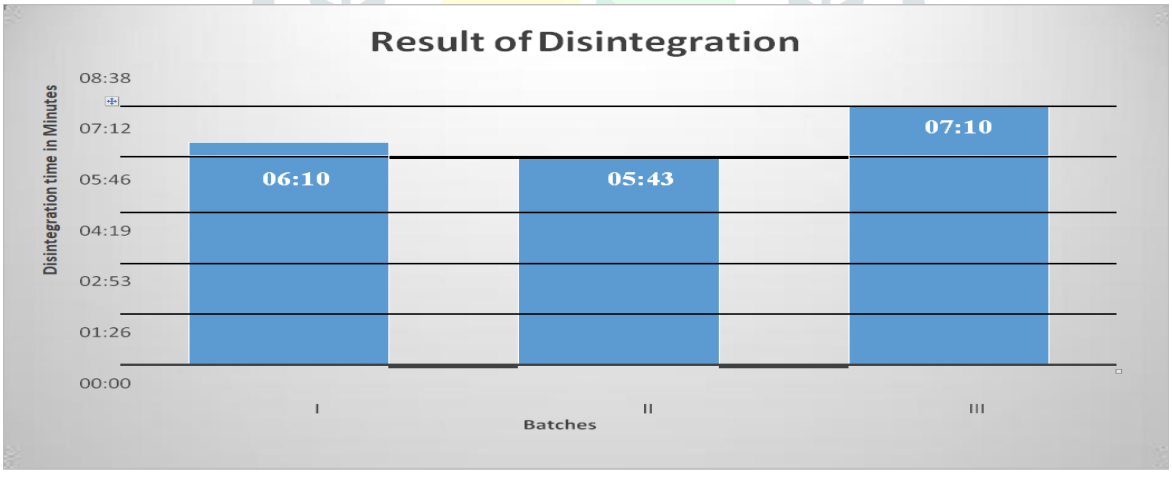

Figure 8: Graphical Representation of Disintegration

***In-vitro* dissolution:** Dissolution of different batches observed for different time interval and after 45 minutes following results observed:

Table No. 10: Results of Dissolution

Dissolution at 45 min		
Batches	**Min**	**Max**
I	91	99
II	88	99
III	92	100
Acceptance Criteria	Not Less than 85% (Q=80%)	

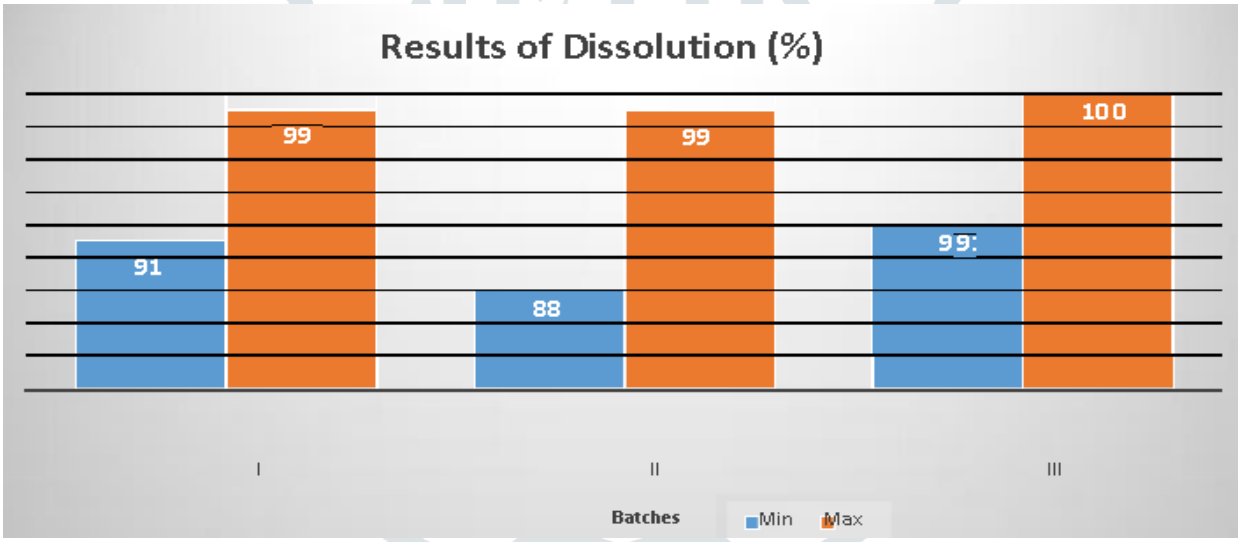

Figure 9: Graphical Representation of Dissolution

CONCLUSION

Process validation is major requirement of cGMP regulation for the process efficiency andsturdiness from the review validation data on pharmaceutical process validation and process controlvariables of tablets manufacturing processes in industry and it isthe full fledged quality attributingtool for the pharmaceutical industries. The main goal in qualifying laboratory equipment is toensure the validity of data. The current equipment qualification programs and procedures usedwithin the pharmaceutical industry are based on regulatory requirements, voluntary standards, vendor practices, and industry practices. 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 study includes the validation of critical steps of manufacturing such as blending, compression and blister packing all process

validation batches had been manufactured and validated in full compliance with cGMP requirement Based on the results of the validation data, it shall be concluded that the manufacturing process as it consistently produces the product of predetermined quality parameters. Hence it can be concluded that the manufacturing process of Sertraline hydrochloride 50 mg tablet was validatedand was approved for routine production.

CONFLICTS OF INTERESTS

There are no Conflicts of Interests

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