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Research Article

Process Validation & Comparative Study of Haloperidol 5 Mg Tablet

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Abstract

It has always been known that facilities and processes involved in pharmaceutical production impact significantly on the quality of the products. The processes include raw material and equipment inspections as well as in-process controls. Process controls are mandatory in good manufacturing practice (GMP). The purpose is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it. Thus validation is an integral part of quality assurance. The purpose of research was to study prospective process validation Haloperidol 5mg tablet dosage formulation. The critical process parameter was identified with the help of process capability and evaluated by challenging its lower & upper release specification. Three initial process validation batches (PVB1, PVB2 & PVB3) of same size, method, equipment & validation criteria was taken. The critical parameter involved in sifting, dry mixing, lubrication & compression stages were identified and evaluated as per validation master plan. The outcome indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes as compare to previous manufacturing procedure.

Key words- Haloperidol, Prospective Process Validation, Uniformity of Content, NMT, NLT

Introduction

The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. To further enhance the effectiveness and safety of the drug product after approval, many regulatory agencies such as the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. For this reason, pharmaceutical validation and process controls are important in spite of the problems that may be encountered.[1] According to Indian GMP validation study is essential part of GMP. Those required to be done as per predetermined protocols. Prospective process validation is carried out during the development stage by means of risk analysis of the production process which is broken down into individual steps.[2] These are then evaluated on basis of past experience to determine whether they might lead to critical situation are identified, the risk is evaluated, the potential cause are investigated and assessed for probability & extent, the teal plan are drawn up, & priorities are set.[3] Unsatisfactory processes must be modified & improved until a validation exercise proves them to be satisfactory this form of validation is essential in order to limit the risk of error occurring on the production scale.[4]

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This present work deals with identification of critical stage and their consequent evaluation by challenging its upper and lower specifications.[5]

Material and Methods

Materials and Methods:

Haloperidol (B.P), Silac I (I.H), Sodium starch glycollate, Magnesium Stearate,Talc, Colloidal silicon dioxide (Aerosil) was used for this Formulation. All raw material used of BP grade and chemicals used in the analysis in the study were of analytical grade.

Dry granulation method is used for manufacturing.

Machineries:

Machineries and equipments used was as vibro sifter(20”), octagonal blender (350L, Aahan), compression machine 16 station single rotatory (Clit), U.V visible spectrophotometer (Shimadzu 1800), six stage dissolution rate test apparatus USP - I (Tab machine), Dr Schrödinger hardness tester (Electro lab), disintegration and friability test apparatus (Electro lab).

Dry Granulation:

Tablet was manufactured by dry granulation method using ingredients shown in table no 2. During manufacturing temperature NMT 25^{0}C & RH NMT 50% were maintained. After the dispensing of material they were sifted through Vibro sifter as shown in table no.2. Then sifted Aerosil with twice quantity of Silac I through vibro sifter as shown in table no. 2 then Haloperidol is geometrically mix with Silac I as shown in table no 3. Pre lubrication is done by adding aerosil & talc to geometrically mixed haloperidol & Silac I in octagonal blender at 14RPM, slow speed for 5min, 10min & 15min intervals. At different interval sample where collected for analysis as shown in table no. 4.Then lubrication is done by adding magnesium stearate to above pre lubricated blend in octagonal blender at 14RPM, for 3min as shown in table no.4.

Compression of Batches:

Tablets were compressed using 7.0 mm flat beveled round punch having break line on Upper punch & lower punch is plain. Each 140 mg tablet contains 5mg Haloperidol. The specification for tablet was Description (White, round, flat bevel edged uncoated scored tablet),Weight of 20 tabs(2.8 g±3%),average weight 140 mg(±5%) , hardness NLT 2kg/cm2, thickness 2.6 – 3.0 mm,friability NMT 1%w/w, DT NMT 10 Min, Assay 100%(± 5%), Dissolution NLT 80% of stated amount released in 60 min.

Process validation stage, control variables and measuring justification:

In sifting sieve integrity is check before and after operation. Geometric mixing done for uniformity, as shown in table no. 2 and analyzed. In Lubrication stage for uniformity of mixing at pre lubrication stage and lubrication stage the samples were withdrawn

as per fig 1 with predefined time interval (5, 10&15min) for pre blending and (3min) for lubrication and representative samples was studied for assay, particle size & BD. Also RPM of blender is validated for blending/ lubrication as shown in table no.4. At Compression stage speed challenge study was done by compression of 30% batch at minimum speed (22 RPM), 30% at maximum speed (25 RPM) & remaining at optimum speed (28RPM) & parameter evaluated were appearance, weight variation, thickness, hardness, DT, friability, assay & dissolution

Fig: 1 Illustrative diagram of octagonal blender and sampling locations

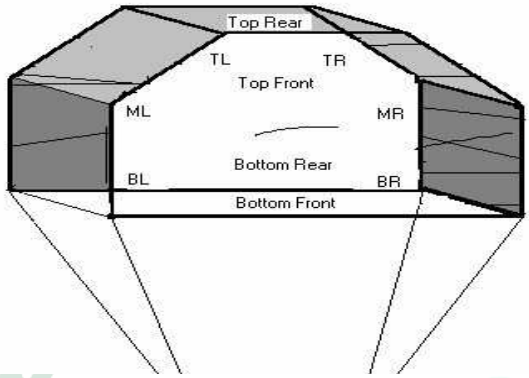

Table No.1 Experimental Design

Critical step	***Parameter of study***	***Key acceptance criteria***	
Sifting	Sieve integrity	It should ok before & after operation	
Lubrication	Assay of lubricated granules Bulk density, particle size	Assay of Haloperidol mg/g	95%-105% (33.93-37.50 mg/g)
		Bulk Density	To record
		Particle size	To record
Compression	Description Weight of 20 tablets Uniformity of weight Thickness Hardness Friability DT Dissolution	Description	White, round, flat bevel edged uncoated scored tablet
		Weight of 20 tabs	2.8 g±3% (2.716-2.884 g)
		Uniformity of weight	140 mg ± 5% (133.00-147.00 mg) (1222.2 to 1297.8 mg)
		Hardness	NLT 2 kg/cm^2
		Thickness	2.6-3.0 mm
		Friability	NMT 1.0 %
		Disintegration time	NMT 10 minutes
		Haloperidol / tablet	4.5-5.5 mg/tablet
		Dissolution	NLT 80 % of the labeled amount dissolved in 60 minutes

Table No 2: Geometric mixing of Haloperidol & Silac I.

Batch's	*Qty mix*			*Time Period Of Mixing*
	Haloperidol	*Silac I*	*Total mixture*	
PVB -1	Ist Part	Ist Part	IInd Part	5min
		IInd Part	IVth Part	5min
		IVth Part	VIIIth Part	5min
		VIIIth Part	XVIth Part	5min
PVB -2	Ist Part	Ist Part	IInd Part	5min
		IInd Part	IVth Part	5min
		IVth Part	VIIIth Part	5min
		VIIIth Part	XVIth Part	5min
PVB -3	Ist Part	Ist Part	IInd Part	5min
		IInd Part	IVth Part	5min
		IVth Part	VIIIth Part	5min
		VIIIth Part	XVIth Part	5min

Table no. 4: Blending Parameter

Parameter	*Specified*	*Batch no:*		
		0741101	*0741102*	*0741103*
Blending equipment name	Octagonal Blender (350 lit)	Octagonal Blender (350 lit)	Octagonal Blender (350 lit)	Octagonal Blender (350 lit)
Blending equipment ID No.	To be recorded	TM-160	TM-160	TM-160
Pre lubrication blending speed	13 RPM to 15 RPM	13 RPM	14 RPM	14 RPM
Pre lubrication blending time	15 minutes	15 minutes	15 minutes	15 minutes
Lubrication blending speed	13 RPM to 15 RPM	13 RPM	14 RPM	14 RPM
Lubrication blending time	3 minutes	3 minutes	3 minutes	3 minutes

Table No 5: Blending result before addition of lubrication

Assay in mg/gm of Haloperidol *Acceptance criteria: 95 to105% (33.93-37.50 mg/gm)*									
Blending time		*5min*		*10 min*			*15 min*		
Sample No.	*1st batch*	*2nd batch*	*3rd batch*	*1st batch*	*2nd batch*	*3rd batch*	*1st batch*	*2nd batch*	*3rd batch*
1	34.428	34.942	34.541	35.046	34.689	35.045	34.406	34.644	34.997
2	34.638	34.981	34.252	34.685	34.658	34.256	34.834	34.696	35.823
3	34.121	34.672	34.419	34.956	34.865	34.251	34.300	35.685	34.965
4	34.620	35.062	34.933	35.028	34.268	34.624	34.991	34.321	34.868
5	34.421	34.393	34.629	34.658	34.805	34.785	35.568	35.688	35.419
6	34.524	34.569	34.392	34.699	35.456	34.658	34.393	35.458	34.995
7	34.628	35.812	35.098	35.420	34.715	35.058	35.509	34.985	35.098
8	34.892	35.092	33.992	33.998	34.125	34.665	34.629	35.114	35.954
9	35.349	34.338	34.524	34.596	34.898	34.985	35.409	34.952	34.986
10	34.625	34.685	34.865	34.889	34.568	34.340	34.699	34.568	35.756
composite	34.624	34.854	34.564	34.791	34.704	34.665	34.873	35.011	35.286
Min	34.121	34.338	33.992	33.998	34.268	34.251	34.300	34.321	34.986

Max	35.349	35.092	35.098	35.420	34.898	35.058	35.568	35.688	35.954
Opt	34.735	34.715	34.545	34.709	34.583	34.654	34.934	35.233	35.470
Bulk density (gm/ml)	0.68	0.70	0.72	0.70	0.73	0.75	0.78	0.76	0.79
Particle size	79.84% #300 100% #1204	78.98% #300 100% #1204	82.41% #300 100% #1204	76.88% #300 100% #1204	78.68% #300 100% #1204	81.58% #300 100% #1204	80.59% #300 100% #1204	79.65% #300 100% #1204	81.61% #300 100% #1204
*Ok /Not Ok	Ok	Ok	Ok	Ok	Ok	Ok	Ok	Ok	Ok

***Complies / not complies = Ok \Not Ok**

Table No 6: Blending Result after Addition of Lubricants

Assay in mg/gm of Haloperidol Acceptance criteria: 95 to105% (33.93-37.50 mg/gm)			
Blending time 3 min			
Sample No.	***1st batch***	***2nd batch***	***3rd batch***
1	34.895	35.124	35.451
2	35.421	35.546	35.548
3	34.998	34.995	35.651
4	35.561	35.614	35.428
5	34.604	35.148	35.921
6	35.128	35.624	36.012
7	34.954	34.961	35.751
8	35.099	36.099	35.986
9	35.245	35.425	35.582
10	35.658	35.751	35.452
Composite	35.156	35.428	35.678
Minimum	34.604	34.961	35.428
Maximum	35.658	36.099	36.012
Optimum	35.131	35.530	35.720
Bulk density(gm/ml)	0.79	0.76	0.82
Particle size	80.45% #300 100% #1204	79.63% #300 100% #1204	81.45% #300 100% #1204
*Ok /Not Ok	Ok	Ok	Ok

***Complies / not complies = Ok \Not Ok**

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Table No. 7: Compression result

Parameters			***Description***	***Weight of 20 tablets***	***Thickness (mm)***	***Hardness (kg/cm)^2***	***Friability (%w/w)***	***D.T (min)***
Limits			(*)	2.716-2.884 gm	2.6-3.0 mm	NLT 2kg/cm^2	NMT 1%	NMT 10 min
Test	***RPM***	***Batch's***						
Start	**22**	**1st Batch**	Ok	2.776	2.73	4.5	0.39%	35 sec
		2nd Batch	Ok	2.792	2.76	4.0	0.41%	41 sec
		3rd Batch	Ok	2.798	2.80	4.7	0.35%	32sec
Middle	**25**	**1st Batch**	Ok	2.831	2.71	3.8	0.37%	39sec
		2nd Batch	Ok	2.789	2.78	4.2	0.40%	39sec
		3rd Batch	Ok	2.809	2.78	3.9	0.32%	41sec
End	**28**	**1st Batch**	Ok	2.806	2.73	4.4	0.35%	34sec
		2nd Batch	Ok	2.799	2.75	3.9	0.39%	40sec
		3rd Batch	Ok	2.816	2.80	3.7	0.33%	38sec

Description: white to off white, round, flat bevel edged uncoated tablets with a score mark on one side tablet
(*) Description should be recorded ok or not ok

Overall result for compression:

Table No. 8: Overall result

Parameter	***Speed***	***1st Batch***	***2nd Batch***	***3rd Batch***
Description*	Minimum	Ok	Ok	Ok
	Maximum	Ok	Ok	Ok
	Optimum	Ok	Ok	Ok
Weight of 20 tablets (gm)	Minimum	2.750-2.770	2.748-2.780	2.750-2.780
	Maximum	2.770-2.820	2.780-2.830	2.780-2.820
	Optimum	2.768-2.800	2.778-2.810	2.768-2.800
Uniformity of weight	Minimum	±4.0	±4.2	±4.0
	Maximum	±4.2	±4.0	±4.4
	Optimum	±3.0	±2.8	±2.8
Thickness(mm)	Minimum	2.68	2.65	2.69
	Maximum	2.81	2.85	2.82
	Optimum	2.74	2.75	2.75
Hardness (kg/cm^2)	Minimum	2.5-3.0	2.8-3.2	2.5-3.0
	Maximum	3.0-6.0	3.2-6.0	3.0-6.2
	Optimum	2.8-5.8	3.0-5.6	2.8-6.0
Friability (%w/w)	Minimum	0.28	0.22	0.29
	Maximum	0.48	0.46	0.49
	Optimum	0.38	0.34	0.39
Disintegration time(min)	Minimum	30sec	28sec	30sec
	Maximum	48sec	45sec	44sec
	Optimum	39sec	36sec	37sec
Assay (%w/w)	Minimum	93.18%	93.31	94.08
	Maximum	103.55%	103.38%	102.48%
	Optimum	98.36%	98.34%	98.28%
Dissolution	Minimum	95.68%	97.09%	99.00%
	Maximum	102.30%	103.01%	100.80%
	Optimum	98.99%	100.05%	99.98%
Yield of batch's (%)		98.2%	97.6%	98.9%

Description: white to off white, round, flat bevel edged uncoated tablets with a score mark on one side tablet
(*) Description should be recorded ok or not ok

Comparative study:

Comparative study between old process & newly validated process is done as shown in table no.9 and results are shown graphically as in fig 3 & and fig 4.

Table No.9: Comparative table

Old one	*Old Result*	*New one*	*New Result*
Sifting all material done individually	Non-uniform mixing of aerosol in blend observed.	Sifting of aerosol done by mixing it with Silac I	Uniform mixing of aerosol in blend observed.
Geometric mixing is not present.	UOC is in lower side of limit (95 %to 105%) **UOC observed 95 % to 97%**	Geometric mixing of Haloperidol + Silac I is Present	Resulting in Uniform mixing of Haloperidol (Active) **UOC observed 99 % to 102%**
Blending time is more 20min also 750L of blender is used	More time & energy required give result of **UOC in lower side 96.8%.**	Blending time reduces to 15 min also 350L blender now used.	Time & energy reduces & gives result of UOC near to **Standard 99.9%.**
Blender Rpm is 13	More time required	Blender Rpm validated at 15	Les time with better results
Addition of Mg.stearate done along with other lubricants & bended for 5 min.	More time consume also UOC blend/tablet & dissolution of tablet is in lower side (dissolution NLT 80% in 60min) **UOC: 96.35% Disso: 91.50%**	Mg.stearate added at the end of blending & blended for 3min.	Time reduces also UOC blend/tablet & dissolution of tablet is observed near to standard (dissolution NLT 80% in 60min) **UOC: 99.95% Disso: 99.98%**

***UOC Uniformity of Content**

Graphical representation of comparative study:

- **Comparative graph for dissolution profile(in 60min) for three validation batch's**

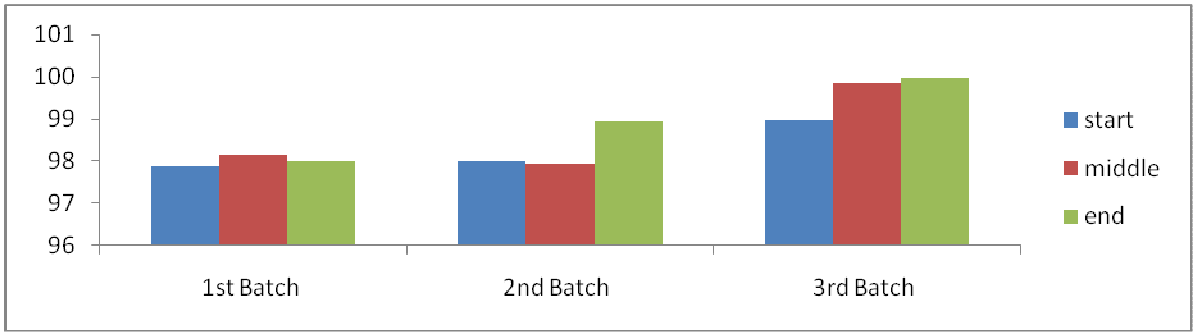

Fig 2: Comparative graph for dissolution profile (in 60min) for three validation batches

- **Comparative graph for dissolution profile(in 60min) for tablet produce by Old & New Process**

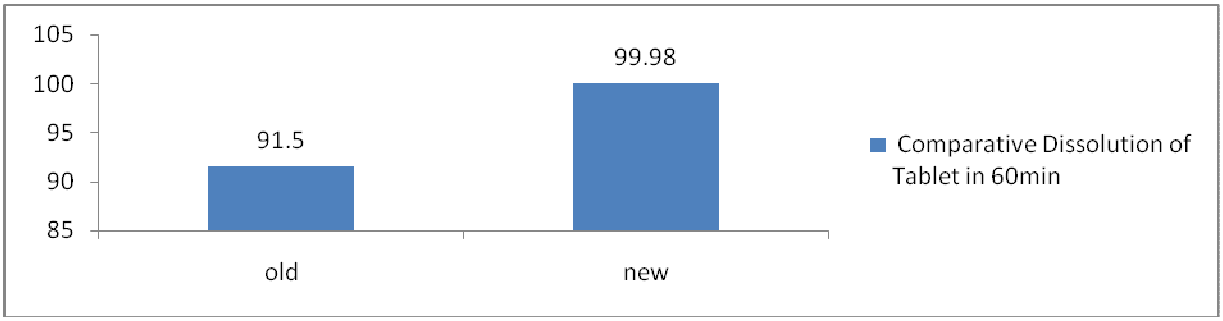

Fig 3: Comparative graph for dissolution profile (in 60min) for tablet produce by Old & New Process

Result & Discussion

Integrity of sieve before and after was satisfactory for all PVBs. Blending process was carried out in two steps (pre-lubrication and lubrication). The pre-lubrication was completed within specified pre-lubrication time of 15 minutes at pre-lubrication speed of 13 RPM to 15 RPM. After completion of pre-lubrication, the lubrication was completed using 'Magnesium Stearate' within specified lubrication time of 3.0 minutes at lubrication speed of 13 RPM to 15 RPM. Samples were collected from Blender as per sampling location shown in fig 1& are analyzed for description, identification, blend uniformity, assay, Bulk density and Particle size were found to be complying with respect to standards of blend. Compression stage speed challenge study showed in table no 7& 8. Comparative study is done and its result is as shown in table no. 9 and fig 2&3

Conclusion

The selected sieve was suitable for sifting. By study result of three batches'(for blending stage) we concluded that best results obtains with blending time of 15min with blending RPM of 14.Compression machines optimum speed (25RPM) was satisfactory for effective compression. Therefore based on results PVBs at each of the stages for the specified parameters it is summarized and concluded that with the prospective process validation for the Haloperidol 5mg tablet produces the batches with no significant deviation and reported documented evidence, that process can be effectively produce a product which complies with the present specification & reproducible quality standards**.**

Through Comparative study we observed that Now the Validated process of manufacturing has following advantages:

- Time reduces
- Cost of Manufacturing reduces
- Also Quality Product is Produced

Overall I concluded through my study that validation results in

- Quality Product
- Cost effective Product
- Productivity Increase
- And Also Reduces Manpower

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