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Research Paper

"Process Validation of Nimesulide Tablet"

AMIT SAH

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It is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. (FDA, 2011).

Importance of Validation

The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort where it involves people from various disciplines of the plant. (Nandhakumar et al., 2011)

- Assurance of quality
- Time bound
- Process optimization
- Reduction of quality cost.
- Nominal mix-ups, and bottle necks
- Minimal batch failures, improved efficiently and productivity.
- Reduction in rejections.
- Increased output.
- More rapid and reliable start-up of new equipment's
- Easier scale-up form development work.
- Easier maintenance of equipment.
- Improved employee awareness of processes.
- More rapid automation. (Singh RB, 2011)

ABSTRACT
The purpose of research was to study prospective process validation for Nimsulide 100 mg tablets dosage formulation. The critical process parameters were identified with the help of process capability and evaluated by challenging its lower & upper release specification. Three initial process validation batches (I, II & III) of same size, method, equipment & 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 & coating were identified and evaluated as per validation master plan.
In the present study the validation of product should be performed as per guideline. The protocol describes the process stages, control variables & measuring responses with justification, sampling plan, acceptance criteria & conclusion.
The Manufacturing of Nimesulide-100 mg tablets are validated considering the following Parameter. Dry mixing performed in Mass Mixer for 30 min, Drying is performed in fluid bed dryer with inlet temperature 50-60^{o}C and outlet temperature 25-30^{o}C temperature for 20 minutes. Lubricated granules mixed with Magnesium Stearate and Talc for 5 min, Compression performed on single rotary press at different level of Hopper, rpm, hardness and stage of compression, blister packing of tablet is done by setting sealing temperature as 140^{o}C.
All the analytical data and in process derived during process validation of Nimesulide-100mg tablets is complied with technical manufacturing document. 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. Hence process is validated.
Keywords: *Nimsulide, Prospective Process Validation, Validation.*

IN PROCESS CHECKS AND CONTROLS RESULTS: -
All three batches were manufactured as per the batch manufacturing record. Sampling and testing in each stage was carried out as per protocol and the results of each stage are recorded in below tables.

1 DATA PRESENTATION OF GRANULATION STAGES:
1.1 Dry mixing:
Load all sifted materials in to the Mass mixer and run the blades for 20 min.

Table 1: Dry Mixing

Sr. No.	Ingredient	Batch		
		Blending time (min)		
		1st	2nd	3rd
1. 2. 3.	Nimesulide Starch Lactose monohydrate	30 min	30 min	30 min

Table 2: Assay of Sample after Dry Mixing

Batch No.	Time (min)	Nimesulide, Assay limit: 90.0% - 110.0% RSD limit : NMT 6%.										RSD %
		Sampling Location ↓										
		TL	TC	TR	MR	ML	MC	BL	BC	BR	Composite	
1st	20	102.7	104.1	104.2	103.7	104.4	102.9	102.5	103.3	103.6	103.5	0.64
2nd	20	104.5	104.2	105.1	104.5	104.2	104.5	103.8	104.6	104.8	105.1	1.05
3rd	20	104.8	103.8	102.8	105.9	102.7	104.3	103.6	101.8	105.0	105.9	1.37

Discussion:
Parameter was well satisfied, within the specified limits of dry mixing. All samples comply with the specifications /meet the acceptance criteria.

1.3 Drying:
Transferthe wet granules from Mass mixer to FBD bowl. Dry the sifted granules in FBD at 50^0C- 60^0Ctill out let temperature reached to 25^0Cto 30^0Ccheck the LOD on moisture balance at 105^0 Cfor 5 min it should be in the range of 1.5 % to 2.5 % record the inlet and outlet temperature, LOD and time required for drying.

Table 3: LOD After drying

Batch No.	Inlet temperature (^{0}C)		Outlet temperature (^{0}C)		LOD% NMT 2.0 % Sampling Location Drying time in FBD Batch					Drying time in FBD Batch (Time)
	Std	Act	Std	Act	TC	MC	BC	ML	MR	
1st	50 – 60	59	25 - 30	30	1.60	1.95	1.6	1.87	1.76	20 min
2nd	50 - 60	60	25- 30	28	1.76	1.65	1.71	1.89	1.91	20 min
3rd	50 – 60	60	25- 30	30	1.78	1.56	1.68	1.87	1.56	20 min

Discussion:
As recommended that LOD for blend should not exceed 2% and observed within the specified limit. Hence obtained LOD is satisfactory.

1.4 Lubrication:
Sifting of lubricants by 40# sieve and collect by separate poly bags.

1.4.1 Pre Lubrication
Load the above granules into blender and mix for 5 minutes.

Table 4: Assay of Sample after Final Lubrication

Batch No.	Time (min)	(Nimesulide) = Assay limit: 90.0% - 110.0% RSD limit: NMT 6%.									RSD %
		Sampling Location ↓									
		TL	**TC**	**TR**	**ML**	**MR**	**BL**	**BR**	**DP-1**	**Composite**	
1st	5	103.0	103.3	102.8	102.3	103.4	102.7	103.0	103.1	102.0	0.49
2nd	5	102.5	104.1	100.6	103.8	103.2	101.3	102.7	104.0	102.7	1.10
3rd	5	103.7	103.4	103.3	103.2	103.8	103.6	103.0	103.3	103.4	0.25

Discussion:

Unit dose sample were withdrawn from 10 different location of cone-blender at the end of final lubrication stage. All the individual results were observed within the range. The results are reproducible and consistent of all sampling locations. The blend homogeneity was found to be independent of location of sampling.

2.0 DATA PRESENTATION OF TABLET COMPRESSION:

Table 5: Description of tablets:

Test	Standard	RESULTS Batch Number		
		1st	2nd	3rd
Description	Yellow colored hexagonal , biconvex tablets	Yellow colored hexagonal , biconvex tablets	Yellow colored hexagonal , biconvex tablets	Yellow colored hexagonal , biconvex tablets

Compression of all three validation batches was as per batch manufacturing record. Results of the physical parameters at different speeds (RPMs), deferent hardness, and different powder level in the hopper and different stages of compression are given below.

Physical parameter of tablets compressed at different rpm

Table N0.:5

Appearance: Light yellow hexagonal flat uncoated tablet						
Sr. No.	**Batch No. 1st**					
	Unit in mg Limit: (319 to351)					
	06 RPM		**08 RPM**		**10 RPM**	
	LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
1	330	336	336	336	336	336
2	333	335	335	335	335	335
3	336	336	336	336	336	336
4	334	336	336	336	336	336
5	331	336	336	336	336	336
6	333	336	336	336	336	336
7	333	335	336	335	336	335
8	335	331	335	336	335	336
9	331	332	334	335	334	335
10	332	335	331	336	331	336
11	336	330	333	336	333	336
12	335	333	333	336	333	336
13	336	337	335	336	335	336
14	336	334	325	336	331	336
15	336	331	332	335	332	335
16	336	333	336	334	336	334
17	335	333	335	331	335	331
18	331	337	338	333	336	333
19	332	331	336	333	336	333
20	335	332	336	335	336	325

Weight variation ± 5.0% of avg. weight.	+1.19 -0.29	+0.59 -1.4	+0.29 -2.9	+1.19 -0.29	+1.19 -0.29	+0.29 -2.9
Thickness 4.032 mm-4.12 mm.	4.10	4.094	4.096	4.11	4.056	4.0987
Hardness NMT 7.0 kg/cm^2	5-6	8-10	5-8	5-7	5-7	6-7
Disintegration NMT 15 min	3'29"	5'56"	6'15"	4'10"	4'11"	6'10"
Friability NMT 1% w/w	0.40%	0.55%	0.49%	0.63%	0.41%	0.65%
Assay 90.0% to 110.0%	99.0%	100.1%	100.0%	98.8%	102.1%	99.8%

Physical parameter of tablets compressed at different rpm

Table N0.:6

Appearance: Light yellow hexagonal flat uncoated tablet						
Sr. No.	**Batch No. 2nd**					
	Unit in mg Limit: (319 to351)					
	06 RPM		**08 RPM**		**10 RPM**	
	LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
1	330	336	336	336	336	336
2	333	335	335	335	335	335
3	336	336	336	336	336	336
4	334	336	336	336	336	336
5	331	336	336	336	336	336
6	333	336	336	336	336	336
7	333	335	336	335	336	335
8	335	331	335	336	335	336
9	331	332	334	335	334	335
10	332	335	331	336	331	336
11	336	330	333	336	333	336
12	335	333	333	336	333	336
13	336	337	335	336	335	336
14	336	334	325	336	331	336
15	336	331	332	335	332	335
16	336	333	336	334	336	334
17	335	333	335	331	335	331
18	331	337	338	333	336	333
19	332	331	336	333	336	333
20	335	332	336	335	336	325
Weight variation ± 5.0% of avg. weight.	+1.19 -0.29	+0.59 -1.4	+0.29 -2.9	+1.19 -0.29	+1.19 -0.29	+0.29 -2.9
Thickness 4.032 mm-4.12 mm.	4.00	4.099	4.096	4.10	4.053	4.0987
Hardness NMT 7.0 kg/cm^2	5-6	8-10	5-8	5-7	5-7	6-7
Disintegration NMT 15 min	3'00"	5'50"	6'15"	4'16"	4'11"	6'00"
Friability NMT 1% w/w	0.80%	0.50%	0.49%	0.63%	0.45%	0.65%
Assay 90.0% to 110.0%	101.0%	100.1%	100.0%	98.8%	103.1%	100.8%

Physical parameter of tablets compressed at different rpm

Table N0. 7

Appearance: Light yellow hexagonal flat uncoated tablet						
Sr. No.	**Batch No. 3rd**					
	Unit in mg Limit: (319 to351)					
	06 RPM		**08 RPM**		**10 RPM**	
	LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
1	330	336	336	336	336	336
2	333	335	335	335	335	335
3	336	336	336	336	336	336
4	334	336	336	336	336	336
5	331	336	336	336	336	336
6	333	336	336	336	336	336
7	333	335	336	335	336	335
8	335	331	335	336	335	336
9	331	332	334	335	334	335
10	332	335	331	336	331	336
11	336	330	333	336	333	336
12	335	333	333	336	333	336
13	336	337	335	336	335	336
14	336	334	325	336	331	336
15	336	331	332	335	332	335
16	336	333	336	334	336	334
17	335	333	335	331	335	331
18	331	337	338	333	336	333
19	332	331	336	333	336	333
20	335	332	336	335	336	325
Weight variation ± 5.0% of avg. weight.	+1.19 -0.29	+0.59 -1.4	+0.29 -2.9	+1.19 -0.29	+1.19 -0.29	+0.29 -2.9
Thickness 4.032 mm-4.12 mm.	4.10	4.094	4.096	4.11	4.056	4.0987
Hardness NMT 7.0 kg/cm^2	5-6	8-10	5-8	5-7	5-7	6-7
Disintegration NMT 15 min	3'26"	5'00"	6'15"	4'18"	4'11"	6'00"
Friability NMT 1% w/w	0.60%	0.55%	0.69%	0.63%	0.41%	0.45%
Assay 90.0% to 110.0%	99.0%	101.1%	101.0%	98.8%	100.1%	99.08%

Table No. 8: Physical parameter of tablets compressed at different Hardness (IPQA)

Appearance: Light yellow hexagonal flat uncoated tablet						
Sr. No.	**Batch No. 1st**					
	Unit in mg Limit: (319 to 351)					
	Low		**Optimum**		**High**	
	LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
1	330	336	336	336	336	336
2	333	335	335	335	335	335
3	336	336	336	336	336	336
4	334	336	336	336	336	336
5	331	336	336	336	336	336
6	333	336	336	336	336	336
7	333	335	336	335	336	335
8	335	331	335	336	335	336
9	331	332	334	335	334	335
10	332	335	331	336	331	336
11	336	330	333	336	333	336

12	335	333	333	336	333	336
13	336	337	335	336	335	336
14	336	334	325	336	331	336
15	336	331	332	335	332	335
16	336	333	336	334	336	334
17	335	333	335	331	335	331
18	331	337	338	333	336	333
19	332	331	336	333	336	333
20	335	332	336	335	336	325
Weight variation ± 5.0% of avg. weight.	+1.19 -0.29	+0.59 -1.4	+0.29 -2.9	+1.19 -0.29	+1.19 -0.29	+0.29 -2.9
Thickness 4.032 mm-4.12 mm.	4.12	4.10	4.03	4.02	4.056	4.0987
Hardness NLT 7.0 kg/cm^2	3-4	3-4	5-6	5-6	6-7	6-7
Disintegration NMT 15 min	3;22"	3'35"	4'15"	4'25"	6'50"	5'48"
Friability NMT 1% w/w	0.51%	0.48%	0.20%	0.28%	0.19%	0.15%
Assay 90.0% to 110.0%	97.0%	102.9%	100.8%	98.9%	99.7%	97.0%

Table No. 9: Physical parameter of tablets compressed at different Hardness (IPQA)

Appearance: Light yellow hexagonal flat uncoated tablet						
Sr. No.	**Batch No. 2nd**					
	Unit in mg Limit: (319 to 351)					
	Low		**Optimum**		**High**	
	LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
1	330	336	336	336	336	336
2	333	335	335	335	335	335
3	336	336	336	336	336	336
4	334	336	336	336	336	336
5	331	336	336	336	336	336
6	333	336	336	336	336	336
7	333	335	336	335	336	335
8	335	331	335	336	335	336
9	331	332	334	335	334	335
10	332	335	331	336	331	336
11	336	330	333	336	333	336
12	335	333	333	336	333	336
13	336	337	335	336	335	336
14	336	334	325	336	331	336
15	336	331	332	335	332	335
16	336	333	336	334	336	334
17	335	333	335	331	335	331
18	331	337	338	333	336	333
19	332	331	336	333	336	333
20	335	332	336	335	336	325
Weight variation ± 5.0% of avg. weight.	+1.19 -0.29	+0.59 -1.4	+0.29 -2.9	+1.19 -0.29	+1.19 -0.29	+0.29 -2.9
Thickness 4.032 mm-4.12 mm.	4.10	4.094	4.096	4.11	4.056	4.032

Hardness NLT 7.0 kg/cm^2	3-4	3-4	5-6	5-6	6-7	6-7
Disintegration NMT 15 min	3;22"	3'35"	4'15"	4'25"	6'50"	5'48"
Friability NMT 1% w/w	0.51%	0.48%	0.20%	0.28%	0.19%	0.15%
Assay 90.0% to 110.0%	99.0%	99.9%	99.8%	98.9%	99.7%	100.0%

Table No. 10: Physical parameter of tablets compressed at different Hardness (IPQA)

Appearance: Light yellow hexagonal flat uncoated tablet						
Sr. No.	**Batch No. 3rd**					
	Unit in mg Limit: (319 to 351)					
	Low		**Optimum**		**High**	
	LHS	**RHS**	**LHS**	**RHS**	**LHS**	**RHS**
1	330	336	336	336	336	336
2	333	335	335	335	335	335
3	336	336	336	336	336	336
4	334	336	336	336	336	336
5	331	336	336	336	336	336
6	333	336	336	336	336	336
7	333	335	336	335	336	335
8	335	331	335	336	335	336
9	331	332	334	335	334	335
10	332	335	331	336	331	336
11	336	330	333	336	333	336
12	335	333	333	336	333	336
13	336	337	335	336	335	336
14	336	334	325	336	331	336
15	336	331	332	335	332	335
16	336	333	336	334	336	334
17	335	333	335	331	335	331
18	331	337	338	333	336	333
19	332	331	336	333	336	333
20	335	332	336	335	336	325
Weight variation ± 5.0% of avg. weight.	+1.19 -0.29	+0.59 -1.4	+0.29 -2.9	+1.19 -0.29	+1.19 -0.29	+0.29 -2.9
Thickness 4.032 mm-4.12 mm.	4.10	4.094	4.096	4.11	4.056	4.04
Hardness NLT 7.0 kg/cm^2	3-4	3-4	5-6	5-6	6-7	6-7
Disintegration NMT 15 min	3;22"	3'35"	4'15"	4'25"	6'50"	7'48"
Friability NMT 1% w/w	0.51%	0.48%	0.20%	0.28%	0.19%	0.15%
Assay 90.0% to 110.0%	98.0%	99.9%	1OO.8%	98.9%	99.7%	1OO.0%

3.0 Discussion: (effect of hopper/ compression/ hardness**)**

For study the effect of hopper, three different levels were selected i.e. - full, half and almost empty hopper. As the experimental result obtained it clearly observed that full hopper were selected throughout the process. As the result obtained full and half hopper were selected for the process. Hence its parameters are more satisfactory as recommended.

For study the effect of compression machine three different rpm levels were selected i.e. - high, optimum and low speed. As the experimental result obtained it clearly observed that there was no significant effect of machine speed over specified parameter. Hence its parameters are more satisfactory as recommended.

For study the effect of hardness, three different levels were selected i.e. - high, optimum and low hardness. As the experimental result obtained it clearly observed that optimum hardness was selected throughout the process. As the result obtained optimum hardness were selected for the process. Hence its parameters are more satisfactory as recommended.

For study the effect of the tablets sampled at the different stages of compression is satisfactory and conforms to the acceptance criteria. All the individual parameters were observed found to be complying as per the acceptance criteria with respect to the parameters evaluated. Hence all parameters are well satisfied within the specified range.

4.0 DATA PRESENTATION OF PACKING STAGE:

4.1: Blister Packing:

Blister strip packing of all the three batches was carried out Blister packing machine. ***Printed Alu foil*** *and PVC* were used for the packing. Batch wise in process observations made during the strips are given below.

Table No. -11: Blister Packing

Sr. No	**Test**	**Acceptance criteria**
1	Temperature of Sealing Roller	140 ± 10^0C
2	Overprinting Quality	Should be good
3	Sealing Quality	Should be good
4	Cutting Quality	Should be good
5	Knurling Quality	Should be good
6	Leak Test	To comply
7	Strip Quality	Should be good

Table No. 12: Speed of strip Packing Machine = 30 cuts per min

Batch No.	Sealing Temp. (140 ± 10^0C)	Overprinting Quality	Sealing, Cutting & Knurling Quality	Leak Test	Strip Quality
1	142.1-143.5	Good	Good	Pass	Good
2	145.4-146.6	Good	Good	Pass	Good
3	143.4-145.4	Good	Good	Pass	Good

Table No. 13 Speed of strip Packing Machine = 40 cuts per min

Batch No.	Sealing Temp. (140 ± 10^0C)	Overprinting Quality	Sealing, Cutting & Knurling Quality	Leak Test	Strip Quality
1	144.5-145.8	Good	Good	Pass	Good
2	148.1-146.6	Good	Good	Pass	Good
3	143.5-144.8	Good	Good	Pass	Good

Table No. 14: Speed of strip Packing Machine = 50 cuts per min

Batch No.	Sealing Temp. (140 ± 10^0C)	Overprinting Quality	Sealing, Cutting & Knurling Quality	Leak Test	Strip Quality
1	146.5-147.3	Good	Good	Pass	Good
2	143.3-145.6	Good	Good	Pass	Good
3	146.7-146.6	Good	Good	Pass	Good

Table No. 15: Packing Data at different stages

Batch. No.		Sealing Temp. (140 ± 10^0C)	Overprinting Quality	Sealing, Cutting & Knurling Quality	Leak Test	Strip Quality
1	**Initial**	144.5-145.8	Good	Good	Pass	Good
	Middle	148.1-146.6	Good	Good	Pass	Good
	End	143.5-144.8	Good	Good	Pass	Good
2	**Initial**	146.5-147.3	Good	Good	Pass	Good
	Middle	143.3-145.6	Good	Good	Pass	Good
	End	146.7-146.6	Good	Good	Pass	Good
3	**Initial**	142.1-143.5	Good	Good	Pass	Good
	Middle	145.4-146.6	Good	Good	Pass	Good
	End	143.4-145.4	Good	Good	Pass	Good

5.0 SPESIFICATION AND RESULT OF FINISHED PRODUCT

Specification required for the finished product is mentioned along with the result of three (03) batches of Nimesulide-100mg Tablets.

Table No. 16: Specification and Result of Finished Product

S. No.	Test	Acceptance criteria	RESULTS		
			Batch		
			1st	2nd	3rd
1	Description	A printed carton containing 20 strips each contains 14 yellow colour hexagonal shaped, biconvex, uncoated tablets.	A printed carton containing 20 strips each contains 14 yellow colour hexagonal shaped, biconvex, uncoated tablets.	A printed carton containing 20 strips each contains 14 yellow colour hexagonal shaped, biconvex, uncoated tablets.	A printed carton containing 20 strips each contains 14 yellow colour hexagonal shaped, biconvex, uncoated tablets.
2	Identification	As per BP-2007	Complies	Complies	Complies
3	Weight of 20 tablets	6.700 g ± 5%	Complies	Complies	Complies
4	Avg. weight of tablets	335 mg ± 5% (between 319 mg to 351 mg)	336mg	331mg	335 mg
8	Thickness	4.08±1%	4.049	4.11	4.098
9	Disintegration Time	NMT 15 min	3'20"	5'59"	4'45"
10	Assay Nimesulide BP100 mg/ tablet	90.0 % to 110.0 %	99.9%	100.2%	100.1%
15	**Micro examination of non-sterile products** Microbial enumeration Test				
a	Total aerobic microbial count(TAMC)	Not more than 1000 cfu/g	20 cfu/g	20 cfu/g	20 cfu/g
b	Total yeast and mould count(TYMC)	Not more than 100 cfu/g	< 10 cfu/g	< 10 cfu/g	< 10 cfu/g
c	**Test for specified micro organisms**				
	Escherichia coli	Absent/g	Absent	Absent	Absent

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