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In Process Validation Of Oral Non Steroidal Anti-Inflammatory Drug: Ibuprofen 400 Mg Tablet

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Abstract: Documented evidence with a high degree of assurance that a process will consistently produce product, meeting its predetermined quality attributes is nothing but a process validation. In short process validation is checking of reproducibility of result. The critical process parameter was identified and evaluated by challenging its lower and upper release specification. The three process validation batches of same size, method, equipment and validation criteria was taken. The critical parameter involved in blending, compression, coating for our Ranitidine tablet were identified and evaluated as per the validation master plan. From the result we have found that in the same environmental condition there was no significant batch to batch variation and all the parameter studied were in accordance with the BMR also the scaleup didn't showed any significant deviations.
Keywords: Ibuprofen, Process validation, BMR.

INTRODUCTION[1-10]:

Act of establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes is said to be validation.According to Indian GMP validation is the essential part of GMP. Those required to be done as per the predetermined protocols. The validation is carried out during development stage by means of a risk analysis of the production process which is broken down into individual steps. This present work deals with identification of critical stage and their consequent evaluation by challenging its upper and lower specification. A written report summarizing results and conclusion should be recorded and prepared. The phase of validation includes-

1. Examination of equipment design
2. Determination of calibration
3. Adjustment requirements
4. Maintenance
5. Identifying critical equipment features that could affect the process and Product.
6. Operational qualification: Systems and equipment should operate correctly and their operation should be verified in accordance with an operational qualification protocol.

AIM :

The main purpose behind process validation is to provide documented evidence that the manufacturing process of Ibuprofen 400 mg coated tablet meets the predefined control parameters.

OBJECTIVE:

The objective of the study is to form a basis for written procedures for production and process control which are designed to assure that the drug Ibuprofen 400 mg coated tablet have the identity, strength, quality and purity they purport of are represented to possess.

- To check the critical steps in the manufacturing of Ibuprofen 400 mg coated tablet.
- To provide documented evidence, so that this would give high degree of assurance that this specific process will consistently produce Ibuprofen 400 mg coated tablets meeting its predetermined specification and quality characteristics.
- Quality, safety and efficacy would be designed and built into the product.
- To control each step of the manufacturing process to maximize the probability that the finished product meets all quality and design specifications.

EXPERIMENTAL[1-10]:

VALIDATION PROCEDURE:

Three consecutive batches of Ibuprofen 400 mg tablet shall be manufactured as per the Batch Manufacturing Record. Collect samples at different stages of processing as mentioned in the sampling plan for individual process. Send the samples to Quality Control Laboratory for analysis as per testing plan. Monitor and record the results of critical control variables and response variables as mentioned in the process parameter table for individual operation. During the processing of the batches, Current Good Manufacturing Practices shall be followed. Compression machine evaluation: Verify the tablets parameters at maximum and minimum speed of machine, then set the parameters for target speed and verify the parameters well within the limits, then check the physical parameters of the tablets. In case any deviation(s) observed they must be noted down in the deviation report immediately. The deviation must be noted in succession throughout the process along with the corrective action.A validation report shall be prepared upon the execution of this protocol and testing of the validation samples.

PHARMACEUTICAL INFORMATION OF DRUG :-

Drugs which are coming under the category of NSAIDs . All these drugs having analgesic, antipyretic and anti-inflammatory actions. They act through the mechanism of inhibiting the enzyme cyclooxygenase (COX-1 & COX-2) which is used in the synthesis of prostaglandins, prostacyclin and thromboxane from arachidonic acid.

IBUPROFEN

Category: Anti-inflammatory; analgesic.

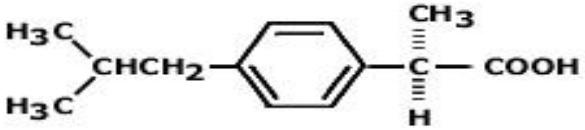
Description: White or almost white, crystalline powder or colourless crystals; odor, slight.

Solubility: Freely soluble in acetone, in chloroform, in ethanol (95%) and in ether; practically insoluble in water. It dissolves in dilute solutions of alkali hydroxides and carbonates.

Chemical Formula: Chemically it is *(RS)*-2-(4-isobutylphenyl) propionic acid.

Empirical formula of Ibuprofen: $C_{13}H_{18}O_2$.

Other ingredients used are Povidone , Alginic, Sodium lauryl Sulphate, Sodium starch glycolate, Magnesium stearate **,**Cellulose microcrystalline, Potato starch, Colloidal silica.



and enantiomer

Ibuprofen, Molecular Weight: 206.28

MATRIALS AND METHODS:

Product composition for three batches: The table 1 shows the quantity of API with other excipients per tablet and for total batch.

Coating material used for three batches:
The table 2 shows the quantity coating material per tablet and for total batch.

1) METHOD:

1.1 SIFTING: Weighed all material separately by using calibrated weighing balance and all materials sifted or sieved by using sieve of 20#, for uniform distribution of particle size. After completion of sifting pooled sample of 100 gm from container.The acceptance criteria after sifting NMT 1% powder retained**.**Formula for acceptance criteria.

1.2 BLENDING (PRE LUBRICATION): The blending step involves mixing of additives using Double cone blender (DCB).] In this step transferred 281.250 kg of Ibuprofen drug powder, potato starch 54.838 kg, microcrystalline cellulose 60.531 kg, povidone 7.006 kg. In this step the lubricating agent is not added,then rotated the machine DCB at speed of 24 ± 1 RPM for 15 min.The sampling and testing plan for prelubrication is done from container 3 point pooled sampling 100 gm each ,Top: 1,Middle: 1,Bottom: 1,by using sampling rod.

Table 1: Details of material for core tablet

Sr. no.	Ingredients	Qty. mg/tab.	Std. Qty.(Kg)
1	Ibuprofen	400.00	125.00
2	Silica colloidal	7.08	2.212
3	Potato starch	87.74	27.42
4	Povidone	11.21	3.503
5	Microcrystalline cellulose	96.85	30.27
6	Alginic acid	10.62	3.320
7	Magnesium stearate	4.72	1.475
8	Sodium lauryl sulphate	2.36	0.737
9	Sodium starch glycolate	14.68	4.587
10	Crosscarmellose	4.72	1.475
	Total weight	**640.00**	**200.00**

Table 2: Material required for coating

Sr. no.	Ingredients	Qty. mg/tab.	Std. Qty.(kg)
1	Ibuprofen core tablets	400.00	200.00
2	PVAP Seal coat	19.81	6.190
3	Purified talcum powder	29.67	9.272
4	Granular sugar	102.5	34.75
5	Titanum dioxide	1.82	0.57
6	Calcium Carbonate	23.51	7.335
7	Gum Acacia	2.24	0.70
8	Carnauba wax	0.45	0.144
9	Purified water	…..	31 lit
	Total weight	**820.00**	**285.96**

1.3 BLENDING (LUBRICATION): In this step added alginic acid 6.638 kg, magnesium stearate (lubricant) 2.950 kg, colloidal silica 4.425 kg, sodium lauryl sulphate 1.475 kg, sodium starch glycolate 9.175 kg, Crosscarmellose 2.950 kg, in the previously blended non lubricated material. Then rotated the DCB for 3 min. at speed of 24 ± 1 RPM. sampling and testing plan for physical parameters after blending are pooled sample after completion blending.

The acceptance criteria after Blending (lubrication) is 100 ± 10 % (360 – 440 mg of Ibuprofen and relative standard deviation NMT 5%.

Sampling Location: Double Cone Blender: 12 - Point sampling. (Blend Uniformity Sample)

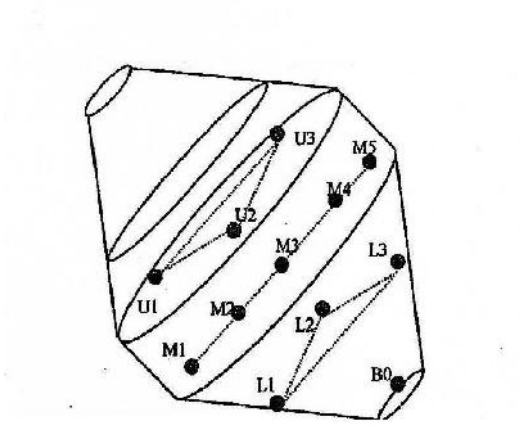
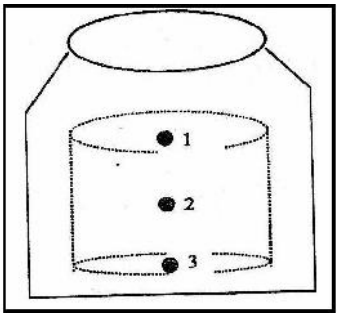


Fig.no.1. Double Cone Blender
Top samples : 3 (U_1, U_2, U_3)
Middle samples: 5 (M_1, M_2, M_3, M_4, M_5)
Lower sample : 3 (L_1, L_2, L_3)
Bottom sample : 1 (B_0)

1.4 SLUGGING, MILLING AND SIFTING:
In slugging process all blended material is transferred in Roll compactor, formation of large slugs or compact mass taking place.In milling the compact mass is passed through Multimill. Where cutting of large slugs into small granular particles takes place. During sifting the milled material is passed through different sieves for uniform distribution of particle size. This is done by using Vibro sifter.

Sampling Location: From HDPE Container.



Top : 1, Middle: 1,
Bottom: 1, by using sampling rod.
Fig.no.2. Container (Pooled Sample)

1.5 COMPRESSION:
Compression is done by using machine Cadpress which is double rotary having 37 stations. Compression was carried as per BMR using standard concave shaped punches with hard chrome plated tips.
Number of stations : 37
Type of tooling : "D" type
Procedure is done for description, average weight, disintegration time, friability, thickness and hardness.

Testing parameters and acceptance criteria for core tablet:
The test required to be perform with their standard specification limit and no. of tablet to be required for the same is given in table No.3.

Coating parameters:
The parameter which are required to be maintained within the limit of coating machine is as per table No.4.

Finished product analysis and acceptance criteria for coated tablet:
The tablet after coating i.e. finished product is checked for different parameter that are given in table No.5 with their standard limits and No. of tablet required for the same.

Table 3: Testing of physical parameters for core tablet

Sr. No.	Parameter	Standards	No. of tablets to be taken for testing
1	Description	White circular, biconvex tablet, plane on both sides.	As per AQL.
2	Weight of 20 tablets	12.8 gm ± 5% (12.16 gm – 13.44 gm)	20 tablets
3	Average weight	640 mg ± 2.5%	20 tablets
4	Weight variation	640 mg ± 5%	20 tablets
5	Hardness	NLT 20 N (2.05 Kg/cm^2)	10 tablets
6	Thickness	6.70 – 7.10 mm	10 tablets
7	Disintegration time	NMT 15 min.	6 tablets
8	Friability	NMT 1 % w/w	20 tablets
9	Assay	380 – 420 mg 100 ± 5 %	10 tablets

Table 4: Coating parameters

Sr. No.	Parameter	Desired Settings
1.	Pan speed (RPM)	6 RPM
2.	Inlet air temperature	60 – 70 °C
3.	Outlet air temperature	45 – 55 °C
4.	Spray rate	40-50 gm/gun/min
5.	Number of guns used	6
6.	Distance of coating gun from bed	20 – 24 cm
7.	Atomizing air pressure	3-5 kg/cm^2

Table 5: Finished product analysis

Sr. No.	Parameter	Standards	No. of tablets to be taken for testing
1	Description	White, round, biconvex, Sugar Coated Tablet.	As per AQL.
2	Weight of 20 tablets	16.40 gm ± 5% (15.58 gm – 17.22 gm)	20 tablets
3	Average weight	820 mg ± 2.5% (799.50 to 840.50 mg)	20 tablets
4	Thickness	7.20 – 8.0 mm	10 tablets
5	Disintegration time	NMT 30 min	6 tablets
6	Weight Builds Up	160 – 190 mg	20 tablets
7	Assay	380 – 420 mg 100 ± 5 %	10 tablets

Sampling Location:
Sejong Coater: 5-Point sampling.

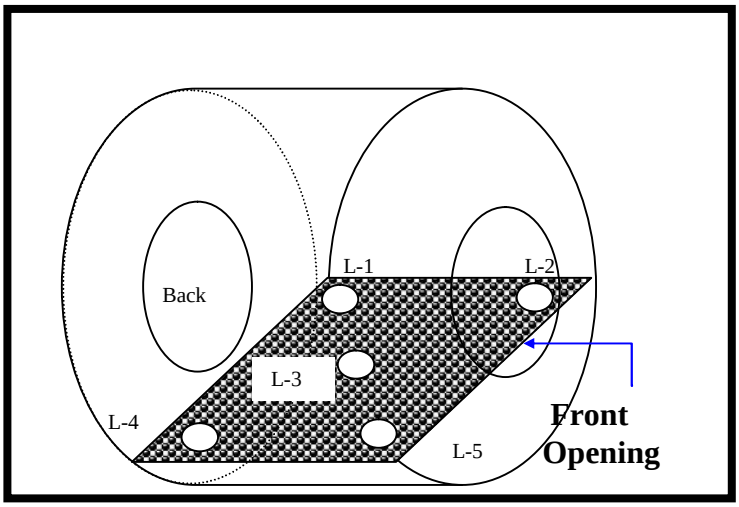


Fig. 3 Coating Pan with sampling location
L-1) Right Back side Layer; **L-2)** Right Front Side Layer; **L-3)** Middle Layer
L-4) Left Back Side Layer; **L-5)** Left Front Side Layer

1.7 BLISTER PACKING: This process involves packing of tablets in polythene lined aluminum foil and PVC blister pack. The leak test is performed by using blisters with rubber band dipped in solution of 1% methylene blue.Raised the pressure of vacuum 15 mmHg for 30 sec then released the pressure after 30 min.

RESULTS AND DISCUSSION:

Three batches each of 3.12 lac were taken for the Process validation of Ibuprofen tablets. For each of three batches the critical steps were identified and variables studied. Sifting done by using 20# sieve and % sample retained of three batches are as 0.24,0.27 AND 0.25 respectively for batch A,B and C .The blending (prelubrication) shows bulk density for three batches was found to be .668, .663, .664 respectively for batch A,B, and C and tapped density three batches was found to be 0.886,0.876 and 0.880 for three batches .

The physical parameters of compressed tablets is as per table No.8 and weight variation at different speeds for batch A ,B and C is as in table no.7.

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Table no.6 The blend uniformity after lubrication

BATCH	SPECIFICATION	A	B	C
MINIMUM	Between 90 to 110 % of Ibuprofen with RSD not more than 5.0 %	95.13	96.42	95.24
MAXIMUM		100.54	100.14	100.20
AVERAGE		98.29	97.69	98.41
% RSD	NMT 5%	1.69	1.04	1.60

Table no.7 weight variation

BATCH	SPECIFICATION	1600	2000	2400
A	640 mg ± 5%	635.87	646.82	632.58
B		645.55	639.48	640.74
C		635.94	640.13	645.20

Table no.8. Physical parameters of batch A, B and C for validation.

			A			B			C		
Sr. no.	**Parameter**	**Specification**	**1600 Tab /min**	**2000 Tab /min**	**2400 Tab /min**	**1600 Tab/ min**	**2000 Tab/ min**	**2400 Tab/ min**	**1600 Tab/ min**	**2000 Tab/ min**	**2400 Tab/ min**
1	Appearance	White, biconvex tablet. Plain on both the sides.	C	C	C	C	C	C	C	C	C
2	Weight of 20 tablets	12.8 gm ± 5% (12.16 gm – 13.44 gm)	12.71	12.93	12.65	12.91	12.78	12.81	13.05	12.95	12.78
3	Average weight (mg)	640 mg ± 2.5% (624 to 656 mg)	635.87	646.82	632.58	645.5	639.4	640.8	635.6	640.	645
4	Thickness (mm) (Avg.)	6.70 – 7.10 mm	6.84	6.85	6.84	6.83	6.85	6.84	6.84	6.83	6.84
5	Hardness (kg/cm^2) (Avg.)	NLT 20 N (2.05 Kg/cm^2)	26.62	27.02	26.80	26.05	26.93	25.72	25.89	26.32	25.52
6	Friability (% w/w)	NMT 1 % w/w	0.21	0.16	0.19	0.22	0.26	0.18	0.23	0.22	0.17
7	Disintegration time	NMT 15.0 min	1.52	2.20	2.05	1.59	2.10	2.16	1.46	1.58	2.15

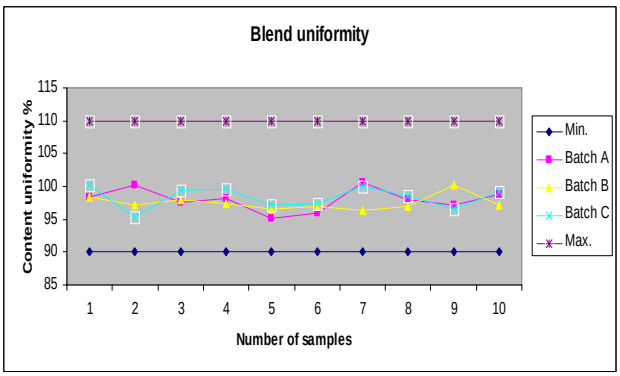
The compression was carried out at different speeds of machine 1600, 2000 and 2400 tablets/minute. The samples were collected at different speeds analyzed for all physical parameters and found that all parameters were within the limit. The samples were collected at full, middle, near end of the hopper, at the lower and higher thickness of tablet, at initial, middle, final cycles of compression and found that all parameters were within the limit given in table No.8

The coating was carried out as per BMR by using Sejong coater and also the coating parameters were mounted for three batches. One pooled sample from each batch of Ibuprofen 400 mg tablet was collected after completion of coating and analyzed as per finished product specifications and found that the following were well within the limit i.e. inlet temperature 60 to 70 °C, exhaust temperature 45 to 55 °C, pan speed 6 RPM, atomization speed pressure 3 to 5 kg/cm^2, spray rate 40 to 50 gm/gun/min, gun distance 20 to 24 cm.

The blister packing of tablets was found well within the limit i.e. blister forming roller temperature 140 to 160 °C, sealing roller temperature 175 to 180 °C and machine speed 70 to 100 cuts/min. Leak test is performed and it was found that the quality of sealing was satisfactory. Over printing details and blister appearance were also found to be satisfactory in the final blister pack .

DETAILS OF THREE BATCHES FOR BLEND UNIFORMITY

The three batch checked for blend uniformity and found within the limit. As shown in graph No.1



Graph 1 : Blend Uniformity of Batch A,B,C.

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