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Research Article

STUDIES IN PROCESS VALIDATION FOR IBUPROFEN 200mg AND METHOCARBAMOL 500mg CAPLETS DOSAGE FORMULATION

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ABSTRACT

The purpose of research was to study prospective process validationfor ibuprofen 200mg and methocarbamol 500mg caplets dosage formulation. The critical process parameterwas 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 was 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. 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.

Keywords: Ibuprofen, Methocarbamol, Bi-layered Caplets, Prospective process validation.

INTRODUCTION

According to Indian GMP validation study is essential part of GMP. Those required to be done as per predetermined protocols. Prospective process validation[1, 2]is carried out during the development stage by means of risk analysis of the production process which is broken down into individual steps. These are then evaluated on basis of past experience to determine whether they might lead to critical[3, 4] 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 The trial are then performed and evaluated & overall assessment is made. If at the end results[5] are acceptable the process is satisfactory. 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. This present work deals with identification of critical stage and their consequent evaluation by challenging its upper and lower specifications.

MATERIALS AND METHODS[4,5]

Ibuprofen, Micro crystalline cellulose (PH 101), Methyl cellulose, Sodium starch glycolate, Sodium lauryl sulphate, PVPK-30 (kollidon-30), Aerosil, Magnesium stearate, Talc, *Methocarbamol, Red oxide of Iron, FDC blue –No.2 AL Lake (PH 101) and Isopropyl alcohol (IPA) was used for this Formulation. All raw material used of USP grade and chemicals used in the analysis in the study were of analytical grade.

MACHINERIES[6]

Vibrosifter (50 to 300k, Saral-engineering), multimill (50 to 200kg, saral engineering), rapid mixing granulator [RMG] (150lts Saral engineering), fluid bed drier [FBD] (60kg,saral engineering), Mechanical Stirrer (Winmax enterprises), Conta Blender (200lts & 300lts bins, Saral engineering), compression machine (52,200 tab/ hr for bi-layer tablets , Gaylord, 29 stations, double rotator, automatic & continuous), disintegration and friability test apparatus (Electo lab), Auto coater (SCS 1050 – 80 to 110 kg/ batch & SCS 750 – 30 to 45 kg/ batch, Saral engineering), Analytical Balance(Sartorius), Hardness, Thickness & Diameter test apparatus (Pharma test), Friabilator(USP) (Electrolab), LOD Instrument(Ohaus).

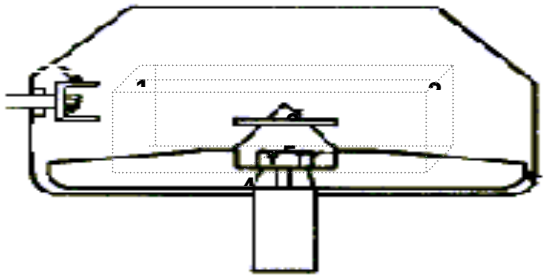

Fig. 1: Illustrative diagram of RMG and sampling locations

i. Top left ii. Top right, iii. Middle. iv. Bottom front, v. Bottom rear

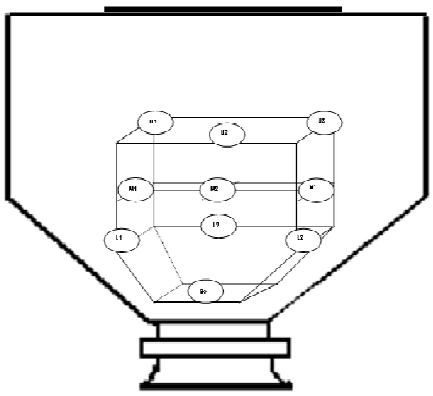

Fig. 2: Illustrative Diagram of Conta Blender and Sampling Locations

U1: Upper - Left – Rear, U2: Upper - Center – Front, U3: Upper - Right – Rear,
M1: Middle - Left – Center, M2: Middle - Center – Center,
M3: Middle - Right – Center, L1: Lower - Left – Front,
L2: Lower - Center – Rear, L3: Lower - Right – Front, Bo: Bottom – Center.

WET GRANULATION[4, 5]

Caplet was manufactured by wet granulation method using ingredients shown in table no 1and 2. During manufacturing temperature 23±2 C and Relative humidity is 55±5%was maintained.. After dispensing of material they were sifted through sifter as shown in table no. 1 and table no.2. And prepare separately ibuprofen granu;les and methocarbamol granules.Transfer the sifted Methocarbamol, Microcrystalline cellulose (c), Methyl cellulose(b), Sodium starch glycolate(c), Sodium lauryl sulphate (c), FDC-blue-2 and Red oxide of iron to Rapid mixer Granulator and mix for 5 minutes. Add slowly (approximately 10 min) the binder solution into the dry mix blend in the Rapid Mixer Granulator. Then this material was wet milled with multi mill without mesh with impact forward slow speed. Load the milled granules in to FBD bowl and fix the bowl to FBD Set the inlet temperature to 60 $\pm$ 5 ^{o} C, product temperature to 55 $\pm$ 5 ^{o} C and outlet temperature to40±5°C and dry the granules up to getting the required LOD (Not More Than 1.0% w/w). Sizing was done by passing dried mass through 14 mesh sieve & retention generated passed through 1.5mm mesh of multimill knives forward, slow speed. Pree lubrication was done conta blender for 5 minutes at 10 rpm and lubrication was done in conta blender after geometric mixing of sifted lubricant with sized granules for 2 minutes at 10RPM. And by using methocarbamol formulation prepare the methecarbamol granules as ibuprofen granules.

COMPRESSION OF BATCHES[5]

Tablets were compressed using the size upper punch as 19.0mm and lower punch 7.9mm, IM embossing on Upper punch & lower Punches plain. Each 475.0 mg to 525.0 mg/ Methocarbamol contains 95.0 to 105.0% on label amount. Each 190.0 mg to 210.0 mg/tablet ibuprofen contains 95.0 to 105.0% on label amount The specification for tablet was average weight 840.0 mg $\pm$ 2% (823.2 to 856.8 mg), hardness NLT 3kg/cm2, thickness 7.0±0.3mm(6.7 to 7.3 mm), friability NMT 1%w/w, Assay 100 %(± 5%), Dissolution Not less than 80.0 %(Q) after 30 minutes.

PROCESS VALIDATION STAGE, CONTROL VARIABLES AND MEASURING JUSTIFICATION[6 - 14]

In sifting sieve integrity before and after. Dry mixing uniformity, the samples are withdrawn (5 min) and analyzed. Consistency of paste was evaluated in preparation of granulating agent. Wet mixing dough mass consistency was evaluated by studying speed of chopper & impeller, time of mixing and ampere reading. Drying stage LOD obtained within predefined interval of drying. Representative samples were selected for evaluation of LOD. Pre lubrication and Lubrication stage uniformity of mixing, the samples were withdrawn as per fig 2 with predefined time interval (n) and representative samples was studied for content uniformity. Compression stage speed challenge study was done by compression of 30% batch at minimum speed (10 RPM) parameter evaluated were appearance, weight variation, thickness, hardness, DT, friability, assay & dissolution.

Table 1

S.NO	RAW MATERIALS	SPECIFICATION	UNITS	STANDARD QUANTITY
1	Ibuprofen	USP	Kg	X
2	Micro crystalline cellulose (PH 101)	USP	Kg	X
3	Methyl cellulose	USP	Kg	X
4	Sodium starch glycolate (Type – B)	USP	Kg	X
5	Sodium lauryl sulphate	USP	Kg	X
6	PVPK-30 (kollidon-30)	USP	Kg	X
7	Aerosil	USP	Kg	X
8	Talc	USP	Kg	X
9	Magnesium stearate	USP	Kg	X
10	IPA	USP	Kg	X

Table 2

S.NO	RAW MATERIALS	SPECIFICATION	UNITS	STANDARD QUANTITY
1	Methocarbamol	USP	Kg	X
2	Micro crystalline cellulose (PH 101)	USP	Kg	X
3	Methyl cellulose	USP	Kg	X
4	Sodium starch glycolate (Type – B)	USP	Kg	X
5	Sodium lauryl sulphate	USP	Kg	X
6	Red oxide of Iron	USP	Kg	X
7	FDC blue –No.2 AL Lake	USP	Kg	X
8	PVPK-30 (kollidon-30)	USP	Kg	X
9	Magnesium Stearate	USP	Kg	X
10	IPA	USP	Kg	X

Table 3

Sample location	Dry mixing - Content Uniformity (95.0 – 105.0%) for Ibuprofen		
Batch No:	I	II	III
Top Left	98.0%	100.1%	99.0%
Top Right	97.1%	100.8%	99.6%
Middle	99.2%	100.4%	99.6%
Bottom front	98.4%	100.5%	100.0%
Bottom rear	98.8%	101.0%	100.6%
Mean	98.3%	100.5%	99.6%
SD	0.0080	0.350	0.589
%RSD (NMT 5.0%)	**0.82**	**0.35**	**0.60**

Table 4

Sample location	Dry mixing - Content of Uniformity (95.0 – 105.0%) for Methocarbamol								
Batch No:	I			II			III		
Lot No's	I	II	III	I	II	III	I	II	III
Top Left	98.5	98.2	98.1	97.4	97.1	98.7	99.9	99.4	100.3
Top Right	97.9	98.6	97.9	97.6	97.8	99.1	99.9	98.1	98.9
Middle	97.2	98.5	97.2	97.7	98.2	99.0	99.8	99.0	99.4
Bottom front	98.2	98.3	97.7	97.6	97.6	98.5	99.6	98.6	99.0
Bottom rear	97.8	99.9	97.0	97.2	96.6	98.5	99.8	99.1	98.9
Mean	97.9	98.7	97.6	97.5	97.5	98.8	99.8	98.8	99.3
SD	0.486	0.689	0.465	0.2	0.622	0.279	0.122	0.502	0.595
%RSD (NMT 5.0%)	**0.5**	**0.7**	**0.5**	**0.2**	**0.7**	**0.3**	**0.1**	**0.5**	**0.6**

Table 5

Batch No.		I	II	III
Parameters	**Acceptance criteria**			
Impeller speed	70±5% RPM	70 RPM	70 RPM	70 RPM
Chopper speed	NA	NA	NA	NA
Time	5 min	5 min	5 min	5 min

Table 6: LOD% of Ibuprofen

Batch No.	I	II	III
LOD (NMT 1.0% w / w)	0.25%	0.25%	0.37%

Table 7: LOD% of Methocarbamol

	Batch No.	I	II	III
LOD (NMT – 1.0 % w / w)	**Lot-I**	0.29	0.42	0.40
	Lot-II	0.39	0.35	0.25
	Lot-III	0.29	0.38	0.41

Table 8

Sample location	**Lubrication- Content of Uniformity (95.0 – 105.0%) For Ibuprofen**		
Batch No:	**I**	**II**	**III**
U1 **(Upper left rear)**	100.5%	100.0%	97.4%
U2 (Upper centre front)	100.6%	98.9%	97.6%
U3 (Upper right rear)	97.6%	98.3%	97.4%
M1(Middle left centre)	98.7%	97.7%	97.0%
M2(Middle centrecentre)	99.1%	98.2%	96.5%
M3 (Middle right centre)	98.1%	98.1%	97.0%
L1(Lower left front)	100.0%	99.1%	98.0%
L2 (Lower centre rear)	96.2%	101.8%	98.6%
L3 (Lower right front)	95.9%	101.1%	98.1%
BO (Bottom centre)	97.6%	99.6%	98.4%
Mean	98.4%	99.3%	97.6%
SD	1.66%	1.353	0.671
%RSD (NMT 5.0%)	**1.7**	**1.4**	**0.7**

Table 9

SAMPLE LOCATION	**LUBRICATION CONTENT OF UNIFORMITY (95.0 – 105.0%) For Methocarbamol**		
Batch No:	**I**	**II**	**III**
U1 (Upper left rear)	99.1%	101.9%	99.1%
U2 (Upper centre front)	98.2%	98.6%	98.6%
U3 (Upper right rear)	99.8%	99.1%	98.5%
M1(Middle left centre)	97.7%	97.9%	98.5%
M2(Middle centrecentre)	98.7%	99.4%	98.1%
M3 (Middle right centre)	98.4%	100.0%	98.5%
L1(Lower left front)	98.3%	100.7%	99.6%
L2 (Lower centre rear)	99.7%	100.1%	99.4%
L3 (Lower right front)	99.3%	100.2%	99.6%
BO (Bottom centre)	98.8%	100.6%	99.1%
Mean	98.8%	99.9%	98.9%
SD	0.678	1.146	0.529
%RSD (NMT 5.0%)	**0.70**	**1.1**	**0.5**

RESULTS AND DISCUSSION

Integrity of sieve before and after was satisfactory for all PVBs. Uniformity of dry mixing was obtained is within the limits in table no 3, 4. Consistency of granulating agent was found excellent with given proportion. A dough mass consistency was excellent with respect to speed of beater & choppers as per table no 5. Drying stage LOD obtained at different time interval was shown in table no 6, 7. Uniformity of mixing in lubrication stage obtained by assay of 10 locations per batch & % RSD was calculated by mean assay of all locations. Compression stage speed challenge study showed in table no 8,9.

CONCLUSION

Uniformity of dry mixing is excellent because % RSD found within the specification (NMT 5). Granulatingagent were prepared of desired consistency. Dough mass was formed satisfactory within 7min wet mixing & ampere reading 10.5-13.0 Amp. Drying time 30 min is suitable for achieving LOD 1.0% w/w. Lubrication stage uniformity was achieved with 2 min because % RSD found wit in specification (NMT 5) and flow properties was satistisfactoty. Compression machines optimum speed (10RPM) 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 Ibuprofen 200 mg and Methocarbamol 500 mg Caplets 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.

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Table 10: Compression Stage Results

S. NO.	TEST	SPECIFICATION	RESULT		
	Batch No		I	II	III
1	**Appearance**	White /Blue colored, biconvex, bilayered film-coated caplet having 'IM' on one side and plain on other side.	Complies	Complies	Complies
2	**Identification By HPLC**	A) Retention time of the major peaks in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation. B) The UV scan of the sample preparation obtained from the PDA detector corresponds to that of the standard preparation	Complies	Complies	Complies
3	**Average mass**	850.0 mg ± 2% (833.0 to 867.0 mg)	846.88 mg	855.07 mg	857.74 mg
4	**Uniformity of mass**	± 5 % of the Average mass	-0.39 % to 1.40%	-3.67% to 1.69%	-4.6% to 4.3%
5	**Water by KF**	NMT 5.0% w/w	1.3%	1.4%	1.4%
6	**Disintegration time**	NMT 30 minutes	6 min 10 sec	8 min 05 sec	6 min 57 sec
7	**Hardness**	Not less than 200 N	158 N	159 N	175 N
9	**Dimensions**				
	Length	19.0 ± 0.2 mm (18.8 to 19.2 mm)	19.1 mm	19.1 mm	19.1 mm
	Thickness	7.0 ± 0.3 mm (6.7 to 7.3 mm)	7.1 mm	7.1 mm	7.1 mm
	Width	7.9 ± 0.2 mm (7.7 to 8.1 mm)	8.0 mm	8.0 mm	8.0 mm
10	**Dissolution**	Not less than 80.0 %(Q) after 30 minutes			
		Ibuprofen	96.6%	105.8%	99.3%
		Methocarbamol	98.2%	101.3%	93.2%
11	**Assay by HPLC:** Each film coated bilayered tablet contains				
	Methocarbamol USP	95.0 to 105.0% on label amount	95.4%	98.8 %	103.6%
	Ibuprofen USP	95.0 to 105.0% on label amount	99.5%	98.8%	97.9%
12	**Dissolution profile** Compare the dissolution profile of each validation batch with Bio lot by using f2 similar factor criteria				
	Ibuprofen 200 mg	50-100	57.1	69.5	55.8
	Methocarbamol 500 mg	50-100	69.0	86.7	53.8

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