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FORMULATION AND PROCESS VALIDATION OF DICLOFENAC SODIUM AND PARACETAMOL COMBINATION TABLET

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ABSTRACT: A properly designed system will provide a high degree of assurance that every step, process, and change has been properly evaluated before its implementation. Validation is an important step carried out in order to control the entire process, and the process adapted to produce itself must assure that process will consistently produce the expected results and maintain the desired quality of the final product. Process validation is the validation of each and every step of the processes which involves series of activities carried out in order to have the assurance of the products manufactured. Each and every step should be scientifically planned, conducted and documented appropriately and for this one should have sound knowledge and understanding regarding the process as well as the product. So, the study here shows the research work done on the formulation and process validation of diclofenac sodium and paracetamol combination tablet, the critical process parameters involved in the manufacturing process and the consistency in the results of the three consecutive batches.

INTRODUCTION: Facilities are being constructed to manufacture ever more complex compounds. The traditional organic reaction compounds are being replaced with products from the fermentation of bacteria, algae, viruses and mammalian cells. Whether the product comes from reactors, extractors or fermenters the process falls under the scrutiny of the Food and Drug Administration (FDA). A primary rule of the FDA is that you must prove that the process you are using is under control. We satisfy that FDA requirement by validating the process.[1]

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The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals Assurance of product quality is derived from careful attention to number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in process and end product testing.[2]

Due to the complexity of the drug products, routine end-product testing alone is not sufficient due to several reasons. Furthermore, quality cannot be tested into the finished drug product but rather be built in the manufacturing processes and these processes should be controlled in order that the finished product meets all quality specifications. A careful design and validation of systems and process controls can establish a high degree of

confidence that all lots or batches produced will meet their intended specifications.[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]

Validation should thus be considered in the following situations,

- Totally new process,
- New Equipment,
- Process and equipment which have been altered to suit changing priorities,
- Process where the end-product test is poor and an unreliable indicator of product quality.[5]

Approach to process Validation:
For purposes of this guidance, process validation 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. This guidance describes process validation activities in three stages.

Stage 1 – Process Design:
The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification:
During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification:
Ongoing assurance is gained during routine production that the process remains in a state of control.[6]

Types of process Validation:
Prospective validation (pre marketing validation): Prospective validation is nothing but need of qualification for completion of experimental trails before the process is put into commercial use.

Retrospective validation:
The retrospective validation is an establishment processes that are stable and in routine use have not under gone a formally documented validation process. In this retrospective validation the manufacturing method has to remain in unchanged for period of time. Historical data is also useful for documentary evidence that the processes are validated.

Concurrent validation:
This validation involves in process monitoring of critical processing steps and product testing, this helps to generate the document evidence to show that the production process is in a state control.

Revalidation:
It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, equipment plan or site location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes.[7, 8]

MATERIALS & METHODS:

TABLE 1: THE FOLLOWING ARE THE MATERIALS USED

Materials	Paracetamol IP, Diclofenac sodium IP, Maize Starch IP, Dibasic Calcium Phosphate IP, PVPK-30 IP, Magnesium Stearate IP, Purified Talc IP, Colloidal Silicon Dioxide IP, Methyl Paraben IP, Propyl Paraben IP.
Pharmacopoeial Grade	I.P.

TABLE 2: PRODUCT DESIGN

Active Ingredient	Paracetamol & Diclofenac sodium
Strength	Paracetamol 325 mg Diclofenac sodium 50 mg
Description	White coloured, oval, biconvex, scored on one side, uncoated tablet.

Average Weight	900 mg
Shelf Life	36 months
Shape	Oval Shaped

TABLE 3: THE CRITICAL PROCESS PARAMETERS

S.No.	Mfg. Process Steps	Process Variables	Measured Responses
1.	Mixing	Mixing Time, Speed (Slow / Fast), and Ampere load.	Content Uniformity
2.	Drying	Drying Time, Inlet Temperature, Out let Temperature.	% LOD.
3.	Lubrication	Lubrication Time, RPM of Cage Blender, Volume occupied.	Content Uniformity of Blend.
4.	Compression	Hardness, RPM of Compression, Machine, Compaction Force.	Average Weight, Uniformity of weight, Disintegration Time, Thickness, Diameter, Friability.
5.	Primary Packing	Forming Temperature, Sealing Temperature, Speed of Packing M/C.	Appearance, Forming Roller temperature, Sealing Roller temperature, Leak Test.

TABLE 4: NUMBER OF SAMPLES TAKEN

S.No.	Stage	No. of samples
1.	Dry Mixing	10
2.	Drying	9
3.	Lubrication & Blending	10
4.	Compression #	3* x 2**
5.	Primary Packing	1

(#) Quantity of samples taken is equivalent to no. of stations.
(*) Sampling is carried out at starting, middle and last of compression.
(**) For Double Rotary (LHS & RHS).

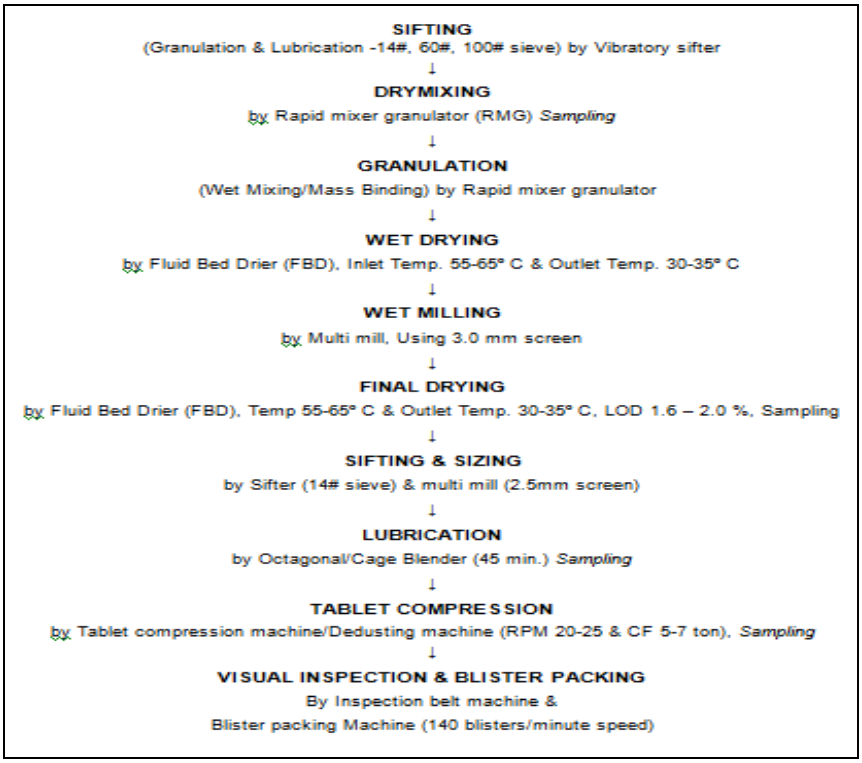

FIG.1: Manufacturing Procedure

RESULTS AND DISCUSSION:

Mixing:

TABLE 5: MIXING RESULT OF THREE BATCHES

S. No.	Attribute	Limit	Lot	Batch No.		
				B.No.01	B.No.02	B.No.03
1.	Dry mixing (Slow)	10 min	I	10min.	10min.	10min.
			II	10min.	10min.	10min.
			III	10min.	10min.	10min.
			IV	10min.	10min.	10min.
2.	Binder addition time	2-5 min	I	5min.	5min.	4min.
			II	5min.	3min.	5min.
			III	5min.	4min.	4min.
			IV	4min.	5min.	5min.
3.	Wet mixing					
	Slow (Impeller chopper)	14-16min	I	15min.	15min.	14min.
			II	14min.	16min.	15min.
			III	14min.	15min.	15min.
			IV	15min.	15min.	15min.
	Fast (Impeller chopper)	14-16min.	I	15min.	15min.	15min.
			II	16min.	15min.	15min.
			III	15min.	15min.	14min.
			IV	14min.	14min.	15min.
4.	Ampere Load	28-32amp	I	29amp.	31amp.	30amp.
			II	30amp.	30amp.	29amp.
			III	30amp.	30amp.	30amp.
			IV	30amp.	30amp.	30amp.
5.	Quantity of Extra Binder			Nil	Nil	Nil

The above **Table 5** shows that, the contents were Dry mixed slowly in Rapid Mixer Granulator under the predetermined specified parameter i.e. for 10 mins. for all the 3 batches. The Binder addition time, the Wet mixing time and the Ampere load was set to an optimum limit, which results in the uniform mixing of the contents and getting required consistency of dough mass. In wet mixing, the time of 15mins. shows excellent mixing consistency.

Content Uniformity (Dry Mixing):

TABLE 6: CONTENT UNIFORMITY OF DRY MIXING

B.No.	B.No. 01				B.No. 02				B.No. 03			
Lot	I	II	III	IV	I	II	III	IV	I	II	III	IV
API	Paracetamol				Paracetamol				Paracetamol			
Mean (T3+M4+B3/10) 90.0 – 110.0%	98.69	98.60	98.58	98.65	98.79	98.75	98.62	98.66	98.58	98.66	98.68	98.59
% RSD (NMT 2%)	0.7601	0.7065	0.6898	0.7118	0.6614	0.7133	0.6798	0.7424	0.7136	0.6923	0.7329	0.6271

B.No.	B.No. 01	B.No. 02	B.No. 03
API	Diclofenac Sodium	Diclofenac Sodium	Diclofenac Sodium
Mean (T3+M4+B3/10) 90.0 – 110.0%	98.52	98.57	98.50
% RSD (NMT 2%)	0.6919	0.6531	0.6717

In the above **Table 6**, samples of dry mixing were collected from 10 different locations i.e T3+M4+B3 and analyzed for Blend uniformity as per procedure. And from the analytical results, it is clear that the drug distribution pattern in the blend is almost homogeneous for both Paracetamol and Diclofenac sodium granules which shows that mixing is done in a controlled manner. Although the % content of all the three batches are under limits but, batch no. 2 shows good % content. The RSD values meet the acceptance criteria for all the 3 batches.

Drying:

TABLE 7: DRYING TEMPERATURES OF THREE BATCHES

S.No.	Attribute	Limit	Lot	Observation								
				B.No.01			B.No.02			B.No.03		
1.	In Let Temperature	55 - 65 °C	I	60 °C			60 °C			60 °C		
			II	60 °C			60 °C			60 °C		
			III	60 °C			60 °C			60 °C		
			IV	60 °C			60 °C			60 °C		
2.	Out Let Temperature	30 - 35 ° C	I	32 °C			32 °C			32 °C		
			II	32 °C			32 °C			32 °C		
			III	32 °C			32 °C			32 °C		
			IV	32 °C			32 °C			32 °C		
3.	Final Drying (Time)	27–33 min.	I	28min.			30min.			30min.		
			II	30min.			29min.			32min.		
			III	32min.			30min.			28min.		
			IV	30min.			31min.			30min.		
4.	Location			T	M	B	T	M	B	T	M	B
5.	LOD	1.6 -2.0%	I	1.8	2.0	2.0	1.8	2.0	1.8	1.8	1.8	2.0
			II	2.0	1.8	1.6	2.0	1.8	2.0	1.6	1.8	1.8
			III	1.8	1.6	1.8	1.6	1.8	1.8	2.0	2.0	1.8
			IV	1.7	1.8	2.0	1.8	1.8	1.8	1.8	1.8	1.6

Table 7 shows that, the drying was carried out in Fluidised Bed Drier at optimum temperature. The Inlet temperature, outlet temperature, LOD were within the limits for all the three batches which shows good consistency of drying and hence these parameters are reproducible. If the granules are over dried then the action of the fluid bed dryer may cause the attrition of granules, thus creating undesirable fines that can damage the formulation due to hydration changes in some actives and excipients. Conversely, if the granules are insufficiently dried then the product may not flow properly, which may cause problems with downstream processing, including product sticking to the faces of the tablet press punches and problems with product stability during storage.

Sifting and Sizing:

TABLE 8: SCREEN AND SIEVE SIZE USED FOR SIFTING AND SIZING

S.No.	Attribute	Observation		
		B.No.01	B.No.02	B.No.03
1.	Screen Size (mm)	2.5	2.5	2.5
2.	Sieve size (No.)	14#	14#	14#

In above **Table 8**, the screen size and sieve size is same for all the three batches i.e. 14# and 2.5mm screen. The uniformity of granules and yield is good for sifting and sizing, using these sizes.

Lubrication:

TABLE 9: LUBRICATION TIME AND RPM OF CONTA BLENDER OF THREE BATCHES

S.No.	Attribute	Observation		
		B.No.01	B.No.02	B.No.03
1.	Lubrication time	45min.	45min.	45min.
2.	RPM of Conta Blender RPM 7-9	7	8	8

In this **Table 9**, Lubrication time of 45 minutes in Conta blender at 7-9 RPM is considered satisfactory to get the uniform blend characteristics. But, the optimum RPM of 8 is considered to be excellent for making the blend uniform and also the yield loss is minimum. All 3 batches was carried out under the predetermined specified parameters.

Content Uniformity (Lubrication & Blending):

TABLE10: CONTENT UNIFORMITY OF THREE BATCHES

B.No.	B.No. 01		B.No. 02		B.No. 03	
API	Paracetamol	Diclofenac Sodium	Paracetamol	Diclofenac Sodium	Paracetamol	Diclofenac Sodium
Mean (T3+M4+B3/10) 90.0 – 110.0%	98.59	98.39	98.55	98.46	98.62	98.36
% RSD (NMT 2%)	0.8202	0.7535	0.8107	0.7163	0.8258	0.7506

Above **Table 10** shows that, the Lubrication and blending samples were collected from 10 different locations and analyzed for Blend Uniformity as per procedure. The results of 10 samples from each batches are shown that the blend is homogenous. The RSD values meet the acceptance criteria for the all the 3 batches, and which shows that the intermediate processing steps like sifting and sizing operations were satisfactory, this makes the flow properties good.

Compression:

TABLE 11: COMPRESSION PARAMETERS OF THREE BATCHES

S.No.	Parameters	Acceptance Criteria	Observations Against Variables		
			B.No		
			B.No.01	B.No.02	B.No.03
1.	RPM of Compression m/c	20-25 RPM	22	23	24
2.	Compaction Force	5-7 ton	6	6	7
3.	Average weight	900mg	897.80	901.49	905.67
4.	Weight variation	±5% of Average weight	-1.48% to +1.14%	-0.93% to + 1.40%	-1.06% to +1.07%
5.	Disintegration time	NMT 15 minute	03 minute 52 seconds	03 minute 45seconds	03 minute 48seconds
6.	Thickness	6.20–6.70 mm	6.33	6.37	6.31
7.	Diameter	12.45–12.65mm	12.52	12.50	12.53
8.	Friability	NMT1.0% w/w	0.36	0.38	0.45
9.	Hardness	NLT4.0Kg/cm^2	6.10	5.71	5.56
10.	Assay	Paracetamol 90% to110%	98.47%	98.57%	98.50%
		Diclofenac sodium 90% to 110%	98.27%	98.32%	98.15%

The **Table 11** shows that the compression was carried out between the speed limits, and physical parameters of the tablets were studied at this speed. The parameters checked were average weight, weight variation, thickness of tablets, hardness of tablet, tablet friability and tablet disintegration time. The parameters are well within the limits of acceptance criteria at the speeds studied. Although, in above table the results of batch no.2 is optimum comparing to other batches. Hence, the compression stage is consistent and reproducible when the compression was carried out at the speeds of 20-25 rpm of the turret.

Primary Packing:

TABLE 12: PACKING SPEED AND TEMPERATURE FOR PACKING OF THREE BATCHES

S.No.	Attribute	Limit	Observations		
			B.No		
			B.No.01	B.No.02	B.No.03
1.	Speed	140 blister per minute	138	140	138
2.	Forming Roller temp.	140-160 ^{0}C	153^{0}C	150^{0}C	151^{0}C
3.	Sealing Roller temp.	170-190 ^{0}C	178^{0}C	178^{0}C	178^{0}C
4.	Leak Test	Pass	Pass	Pass	Pass

In **Table 12**, parameters like speed and roller temperature for packing of 3 batches was controlled under specified temperatures for proper sealed packing, resulting least defects in packaging as shown above in the table by applying the leak test which is satisfactory for all the batches. The batch no.2 and batch no. 3 shows optimum temperatures for packing, which is consistent.

Yield:

TABLE 13: % YIELD OF THREE BATCHES

S. No.	Stage	Yield (Informative)		
		B.No.		
		B.No.01	B.No.02	B.No.03
1.	Lubrication & Blending	99.60	99.61	99.55
2.	Compression	99.27	99.37	99.35
3.	Packing	98.11	98.21	98.20

The **Table 13** shows the overall process percentage yield for 3 batches, which was found to be under predetermined specified parameters. Batch no.2 and Batch no. 3 showed good % yield and, which shows that the process undergone was done in a controlled manner, resulting in the consistency and reproducibility of the process.

CONCLUSION: This report summarizes the overall data of the three batches (Batch No. 1,2 and 3). At each of the stages for the specified parameters, it is summarized and concluded that with process validation for the Diclofenac Sodium and Paracetamol combination tablet produces the batches with no significant deviation, and reported documented evidence that process can effectively produce a product with all required characteristics and uniformity in final dosage form, from batches to batches.

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