AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Process Validation of Extra Power Pain Control Caplets

Prajapati PR[1]*, Desai N [1], Modi VS[1], Tarasankar Basuri[1]

1.SSR college of Pharmacy, Sayli road, Silvassa-396230

ABSTRACT

Process validation is an important step to maintain the quality of final product. This work presents the process validation of Extra Power Pain Control caplets at manufacturing plant Wockhardt ltd. Daman. Revalidation was performed to ensure corrective actions to deliver finished product that meet at intermediate stage, finished product stage and possess laid down specification till claimed shelf life. Three consecutive batches were taken for the validation study. It provides a documented evidence for manufacturing process, critical process parameter and sampling plans.

Keywords: Process Validation, Revalidation, Caplets, Quality.

*Corresponding Author Email: parixitprajapati@gmail.com

Received 15 September 2016, Accepted 21 September 2016

Please cite this article as: Prajapati PR *et al*., Process Validation of Extra Power Pain Control Caplets. American Journal of PharmTech Research 2016.

INTRODUCTION

Pharmaceutical Process Validation is an important and recognized parameters of cGMPs. The requirement of process validation appears of the quality system (QS) regulation. Process validation is a key element in assuring that these principles and goals are met.[1]

US Food and Drug Administration (FDA) defines Process Validation as "Establishing documentation evidence, which provides a high degree of assurance that a specific process, will consistently produce a product meeting its predetermined specifications and quality attributes".[2]

The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. Quality cannot be adequately assured by in-process and finished product inspection and testing but should be built into its manufacturing processes. These processes should be controlled in order that the finished products meet all quality specifications.

Therefore, building of the quality requires careful attention to a number of factors, such as the selection of quality components, product and process design, control of processes, in-process control, and finished product testing. [3]

Responsible authorities for validation [3]

Table 1: Responsible authorities for validation

Department/Designation	Responsibility
Manager production	Responsible for manufacturing of batches and review of protocol and report
Manager QC	Responsible for analysis of samples collected
Executive QC	Responsible for samples collection and submission to QC
Manager maintenance	Providing utilities and engineering support
Executive production	Responsible for preparation of protocol and manufacturing of validation batches
Manager QA	Responsible for protocol authorization and preparation of summary report

Types of process validation [4, 5, 6, 7]

Initial process validation

It is defined as the established documented evidence that a system does what it purports to do which is based on a pre-planned protocol. This validation usually carried out prior to distribution either of a new product.

Concurrent validation

It is similar to Prospective validation, except that the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.

Continuous Process Verification

It is an alternative approach to process validation in which process of manufacturing performance is continuously monitored and evaluated.

For the products developed by a quality by design approach, where scientifically established during development that the established control strategy provides a high degree of assurance of product quality, than continuous process verification.

The method by which the process will be verified should be defined.

There should be a science based strategy for the required attributes for incoming material, critical quality attributes and critical process parameters to confirm product realization. This should also include regular evaluation of the control strategy.

Revalidation

Revalidation must be performed on introduction of any changes affecting a manufacturing procedure having a bearing on the established product performance characteristics.

Re-validation provides the proof that changes in a process that are introduced do not adversely affect process characteristics and quality of the product. Revalidation becomes necessary in certain situations. Some of the changes that require validation are as follows:

- Changes in raw materials, source of active raw material manufacturer, packaging material.
- Changes in the process (e.g., mixing time, drying temperatures and batch size).
- Changes in the equipment (e.g., addition of automatic detection system).
- Changes in the plant/facility.

A decision not to perform revalidation studies must be fully justified and documented.

MATERIALS AND METHOD

Product detail

Table 2: Product detail

Product name	**Extra power pain control caplets**
Dosage form	Solid oral tablet
Shelf life	24 months
Label claim	Each film coated caplet contains Aspirin Ph. Eur. 300 mg Paracetamol Ph. Eur. 200 mg Caffeine Ph. Eur. 45 mg
Pack style	Blister pack

Manufacturing formula

Table 3: Product Composition (Core Caplets)

Sr. No.	Ingredients	Specification	Source of Ingredients
1	Paracetamol	Ph. Eur.	Farmson
2	Caffiene	Ph. Eur.	BASF south east Asia
3	Aspirin#	Ph. Eur.	Novice
4	Pre-gelatinized starch	Ph. Eur.	Cargill
5	Povidone (K-90 F)	Ph. Eur.	BASF
6	Maize starch(grade - 03401)	Ph. Eur.	Cargill
7	Hydroxyl propyl cellulose # (low substituted LH -21)	NF	Shin-Estu chemical Co. Ltd
8	Microcrystalline cellulose # (AvicelPh 102)	Ph. Eur.	FMC Bio Polymer
9	Stearic acid purified #	Ph. Eur	Made king Robinson
10	Purified water	Ph. Eur	In-house

Material to be dispensed in triple laminated aluminium bag kept in polythene bag to protect material from moisture.

Product composition (Coated caplets)

Table 4: Product composition (Coated caplets)

Sr. No.	Ingredients	Specification	Source of ingredients
1	Hydroxypropyl methyl cellulose 5 cps	Ph. Eur.	Dow chemical
2	Hydroxypropyl methyl cellulose 15 cps	Ph. Eur.	Dow chemical
3	Polyethylene glycol 4000	Ph. Eur.	Clariant
4	Purified water	Ph. Eur	In-house

Purpose of Revalidation

Revalidation performed to ensure that the corrective action recommended in GTS report: GTS/SR/003/15, are capable to deliver finished product are meeting at intermediates stage, finished product stage & possess laid down specification till claimed shelf life.

Due to degradation of aspirin to salicylic acid, brown spot observed in stability study Brown spots and browning of tablets was observed in the commercial batches manufactured at the location. The issue was reported to global technical services for assistance & investigation, GTS recommended controls in manufactory process was carried out according to the recommendation of GTS.

Minor process changes are made for improvement of finished product quality, as proposed in the GTS study report & new wet granulation area. No batch size change

Manufacturing process

Tablets were manufactured by wet granulation method. Paracetamol, pregelatinized starch, povidone, maize starch to be sifted through 20# sieve and caffeine through 30# sieve.Sift hydroxypropyl cellulose, microcrystalline cellulose, stearic acid through 40# sieve. Perform dry mixing using saizoner mixer lot wise. Perform wet mixing by adding purified water of standard quantity at this step and granulate the

batch keeping impeller fast and chopper off until small granules and few balls are visible. Transfer to FBD bowl for drying at 60 ^{0} C $\pm 5^{0}$ C until LOD is below 1.5% w/w. Mill the dried granules through multimill and then transfer the milled granules in octagonal blender . Now sift aspirin through 20# sieve and transfer the sifted aspirin to octagonal bender and mix for 10 minutes at 12 RPM. Transfer the sifted lubrication material to octagonal blender at this stage. Compress the approved blend into tablets using compression machine after adjusting specified parameters. Tablets were coated by using Hydroxypropyl methyl cellulose 5 cps, Hydroxypropyl methyl cellulose 15 cps, Polyethylene glycol 4000. Samples were collected at the end of coating stage.

Sampling plan

Table 5: Sampling plan

Stage	Sample location	Sample size	Test
Drying	After drying(composite sample)	5 g for LOD	% LOD
Blend (with lubricant)	From octagonal blender, after completion of blending, draw 10 point samples in triplicate (refer sampling location).	(X – 3 X) 625 – 1875 mg	1. Blend Uniformity (10 sample shall be tested)
Blend (with lubricant)	One pooled sample of top, middle and bottom location in duplicate.	100 x 2 sample	1. Appearance 2.Bulk density 3.Tapped density 4.Assay 5.Sieve test 6.LOD
Compression	Optimum speed One pooled sample from both the sides of the machine, at start, one pooled sample from both the sides of the machine at middle and one pooled sample from both the sides of the machine at the end of compression.	50 x 2 caplets for each compression run (for analytical test).	1. Description 2.Dimensions 3.Average weight 4.Uniformity of weight 5.Hardness 6.Thickness 7.Friability 8.Disintegration 9.Assay
	Minimum speed Draw one pooled sample from both the sides of the machine. Maximum speed Draw one pooled sample from both the sides of the machine	Physical test : 50 tablets	1. Description 2.Dimensions 3.Average weight 4.Uniformity of weight 5.Hardness 6.Thickness 7.Friability 8.Disintegration 9. Weight of 20 caplets.

	Low hardness – One pooled sample from both the sides of the machine. High hardness – Draw one pooled sample from both the sides of the machine.	Physical test: 50 tablets. For dissolution-18 tablets. (6+6+6 tablets)	1. Description 2.Dimensions 3.Average weight 4.Uniformity of weight 5.Hardness 6.Thickness 7.Friability 8.Disintegration 9. Dissolution /for high hardness tester.
Coating	One pooled sample drawn from 5 locations in coating pan from each lot.	50 x 2 caplets (for analytical test) 5 g for % LOD	1. Description 2. Uniformity of weight
	One pooled sample from different storage container.	100 x 2 caplets (for analytical test) 20 gm x 2 for microbial quality testing.	

Note: Samples were collected in duplicate and one set was retained with proper labeling and at proper storage conditions till the completion of validation report.

RESULTS AND DISCUSSION

Sampling was done as per the protocol and was subjected to QC testing and the results were used to prepare a validation report as under.

Analytical data of sampling test

Lubricated blend

Blending was carried out in octagonal blender (WT-137) for 10 minutes at 12 RPM as per BMR. Then transfer the lubrication in octagonal blender and blend the all granules for 5 minutes at 12 RPM. Samplings was done for blend uniformity, assay, bulk/tap density and particle size distribution as per protocol and results for all were found satisfactory for all three batches.

After blending of granules with specified lubricant for 5 minutes samples were collected from different location (10 point) to test blend uniformity. The result is as follows

Table 6: Blend uniformity of Paracetamol

Sr. no.	Location	Acceptance	Blend uniformity (% PCM)		
			Batch A	Batch B	Batch C
1	Sample 1	Individual value should be between 90 % to 110 % of the labeled amount of PCM with RSD not more than 5.0 %	90.94	93.48	103.01
2	Sample 2		96.97	94.57	100.59
3	Sample 3		96.34	97.64	98.12
4	Sample 4		93.23	95.61	97.21
5	Sample 5		95.26	98.44	97.60
6	Sample 6		93.67	95.80	97.81
7	Sample 7		91.63	94.12	96.09
8	Sample 8		94.34	95.34	97.06
9	Sample 9		95.44	98.53	100.88
10	Sample 10		95.58	95.20	97.82
11	Minimum		90.94	93.48	96.09
12	Maximum		96.97	98.53	103.01
13	Mean		94.34	95.87	98.70
14	% RSD		2.151	2.066	1.985
15	Process Capability Ratio (C_p)		2.093	1.842	2.124
16	Process Capability Index (C_{pK})		0.73	1.11	1.38

Table 7: Blend uniformity of Caffeine

Sr. no.	Location	Acceptance	Blend uniformity (% Caffeine)		
			Batch A	Batch B	Batch C
1	Sample 1	Individual value should be between 90 % to 110 % of the labeled amount of Caffeine with RSD not more than 5.0 %	92.28	94.52	102.65
2	Sample 2		98.08	95.41	100.10
3	Sample 3		98.65	97.38	97.53
4	Sample 4		95.82	94.77	98.57
5	Sample 5		97.62	99.06	97.26
6	Sample 6		96.67	95.58	97.90
7	Sample 7		93.16	94.28	95.46
8	Sample 8		96.55	96.44	99.34
9	Sample 9		97.44	99.42	100.08
10	Sample 10		96.99	93.73	98.37
11	Minimum		92.28	93.73	95.46
12	Maximum		98.65	99.42	102.65
13	Mean		96.32	96.05	98.72
14	% RSD		2.151	2.066	1.985
15	Process Capability Ratio (C_p)		1.61	1.68	1.7
16	Process Capability Index (C_{pK})		1.02	1.02	1.48

Table 8: Blend uniformity of Aspirin

Sr. no.	Location	Acceptance	Blend uniformity(% Aspirin)		
			Batch A	Batch B	Batch C
1	Sample 1	Individual value should be between 90 % to 110 % of the labeled amount of Aspirin with RSD not more than 5.0 %	101.01	101.90	97.12
2	Sample 2		95.47	99.54	98.21
3	Sample 3		97.98	98.23	102.21
4	Sample 4		102.40	101.19	100.67
5	Sample 5		96.60	96.64	99.90
6	Sample 6		99.07	98.44	99.64
7	Sample 7		101.53	100.88	99.45
8	Sample 8		98.42	97.99	98.28
9	Sample 9		96.47	99.24	95.25
10	Sample 10		97.66	96.49	98.14
11	Minimum		95.47	96.49	95.25
12	Maximum		102.40	101.90	102.21
13	Mean		98.66	99.05	98.88
14	% RSD		2.356	1.869	1.961
15	Process Capability Ratio (C_p)		1.43	1.80	1.72
16	Process Capability Index (C_{pK})		1.24	1.63	1.53

Lubricated blend: Pooled sample results

Table 9: Lubricated blend

Test	Acceptance	Batch A	Batch B	Batch C
Description	White free flowing powder	White free flowing powder	White free flowing powder	White free flowing powder
Assay	Not less than 95.0 % and not more than 105 % of the labeled amount of PCM, Caffeine, Aspirin.	PCM - 98.4 % Caffeine - 98.5 % Aspirin- 95.9 %	PCM - 98.6 % Caffeine - 97.7 % Aspirin - 97.0 %	PCM – 96.5% Caffeine – 97.9 % Aspirin – 103.1 %
Bulk density (gm/ml)	For information only	0.698	0.715	0.649
Tap density (gm/ml)	For information only	0.858	0.835	0.833
Sieve test (% retained)	For information only			
	20#	7.11	4.50	7.10
	40 #	36.38	27.25	36.89
	60 #	51.27	44.39	51.36
	80 #	56.95	52.44	57.39
	100 #	63.71	61.45	61.89

Compression result

During compression samples were withdrawn at initial, middle and end of compression at optimum

speed and minimum and maximum speed of compression cycle.

The compression of three validation batches was performed using table compression machine. The samples were collected during the compression at optimum (20 RPM) at initial, middle, end of compression cycle. The sample was collected for minimum speed at (15 RPM), maximum speed at (30 RPM), low hardness and high hardness.

All the samples were found complying as per the acceptance criteria with respect to the parameters evaluated. Based on data obtained, all compression parameter are satisfactory with compression speed of 15 RPM to 30 RPM using tablet compression machine CPV IV (WT-179).

During compression it was observed that the disintegration time of the tablets increases rapidly above 140 N hardness. Though the dissolution study carried out on high hardness tablets indicates that the increases in disintegration time of the tablet does not have impact on dissolution, it is recommended to keep the higher limit for hardness as 140 N. It was also observed that the hardness of the tablet below 140 N is achieved only when it is compressed above 5.4 mn. Considering this, the batches were compressed at thickness range between 5.45-5.55 mm.

The analytical data is as follows:

Table 10: Compression result of Batch A

Test	**Specification**	**Results (Batch A) optimum speed (20 RPM)**		
		Initial	**Middle**	**End**
Description	White to off white, capsule shaped caplets	White capsule shaped caplets	White capsule shaped caplets	White capsule shaped caplets
Dimension	17.5 ± 0.1 mm x 7.0 ± 0.1 mm	17.6 mm x 7.0 mm	17.6 mm x 7.0 mm	17.6 mm x 7.0 mm
Average weight	609.0 – 641.0 mg (625 mg)	624.8 mg	624.6 mg	625.1 mg
Uniformity of weight	Not more than 2 caplets deviate by ± 5% of the average and none deviate by ± 10 % from the average weight.	Max: + 0.8 Min: - 0.9	Max: + 0.7 Min: - 0.8	Max: + 1.1 Min: - 0.9
Hardness	Not less than 40 N	132	126	125
Thickness	5.3 mm to 5.6 mm	5.5	5.5	5.5
Friability	Max 1.0 % w/w	0.1	0.1	0.2
Disintegration	Max 15 minutes in purified water at 37°C ± 2° C with disc	0.4 min 25 sec	0.4 min 45 sec	0.4 min 37 sec
Aspirin	285.0 to 315.0 mg per caplet (Between 95% to 105 %)	303.9 (101.3 %)	302.2 (100.7)	305.4 (101.8)
Paracetamol	190.0 to 210.0 mg per caplet (Between 95% to 105 %)	198.0 (99.0)	194.9 (97.4)	197.6 (98.8)
Caffeine	42.75 to 47.25 mg per caplet (Between 95% to 105 %)	44.80 (99.6)	44.09 (98.0)	44.51 (98.9)

The analytical results found are satisfactory.

Table 11: Compression result of Batch B

Test	Specification	Results (Batch B) optimum speed (20 RPM)		
		Initial	Middle	End
Description	White to off white, capsule shaped caplets	White capsule shaped caplets	White capsule shaped caplets	White capsule shaped caplets
Dimension	17.5 ± 0.1 mm x 7.0 ± 0.1 mm	17.5 mm x 7.0 mm	17.5 mm x 7.0 mm	17.6 mm x 7.0 mm
Average weight	609.0 – 641.0 mg (625 mg)	623.4 mg	621.1 mg	622.7 mg
Uniformity of weight	Not more than 2 caplets deviate by ± 5% of the average and none deviate by ± 10 % from the average weight.	Max: + 0.8 Min: - 0.8	Max: + 1.3 Min: - 1.0	Max: + 1.2 Min: - 1.4
Hardness	Not less than 40 N	128	119	116
Thickness	5.3 mm to 5.6 mm	5.5	5.5	5.5
Friability	Max 1.0 % w/w	0.2	0.1	0.1
Disintegration	Max 15 minutes in purified water at 37°C ± 2° C with disc	0.4 min 17 sec	0.4 min 40 sec	0.4 min 11 sec
Aspirin	285.0 to 315.0 mg per caplet (Between 95% to 105 %)	310.0 (103.3 %)	306.1 (102.0)	305.2 (101.7)
Paracetamol	190.0 to 210.0 mg per caplet (Between 95% to 105 %)	197.5 (98.8)	193.47 (96.7)	198.6 (99.3)
Caffeine	42.75 to 47.25 mg per caplet (Between 95% to 105 %)	49.37 (98.7)	48.79 (97.6)	49.74 (99.5)

Conclusion: The analytical results found are satisfactory.

Table 12: Compression result of Batch C

Test	Specification	Results (Batch C) optimum speed (20 RPM)		
		Initial	Middle	End
Description	White to off white, capsule shaped caplets	White capsule shaped caplets	White capsule shaped caplets	White capsule shaped caplets
Dimension	17.5 ± 0.1 mm x 7.0 ± 0.1 mm	17.6 mm x 7.0 mm	17.6 mm x 7.0 mm	17.6 mm x 7.0 mm
Average weight	609.0 – 641.0 mg (625 mg)	624.8 mg	624.8 mg	625.8 mg
Uniformity of weight	Not more than 2 caplets deviate by ± 5% of the average and none deviate by ± 10 % from the average weight.	Max: + 1.4 Min: - 0.7	Max: + 1.0 Min: - 0.8	Max: + 1.5 Min: - 1.3
Hardness	Not less than 40 N	136	123	133
Thickness	5.3 mm to 5.6 mm	5.5	5.5	5.4
Friability	Max 1.0 % w/w	0.2	0.1	0.1

Disintegration	Max 15 minutes in purified water at 37°C ± 2° C with disc	0.4 min 03 sec	0.4 min 34 sec	0.4 min 49 sec
Aspirin	285.0 to 315.0 mg per caplet (Between 95% to 105 %)	311.1 (103.7 %)	310.1 (103.4)	308.8 (102.9)
Paracetamol	190.0 to 210.0 mg per caplet (Between 95% to 105 %)	194.3 (97.1)	194.5 (97.2)	195.6 (97.8)
Caffeine	42.75 to 47.25 mg per caplet (Between 95% to 105 %)	44.24 (98.3)	44.23 (98.30)	44.08 (98.00)

Conclusion: The analytical results found are satisfactory.

Compression challenge test

Compression challenge test: At minimum speed and maximum speed

The samples were collected from compression machine at minimum speed (15 RPM) and maximum speed (30 RPM) and carried out the physical test as per BMR. The physical test results are recorded in the respective BMR. The result found satisfactory.

Compression challenge test: At low hardness and high hardness

The samples were collected from compression machine at low hardness (86.3) and high hardness (148.4) is carried out the physical test as per BMR. The physical test results are recorded in the respective BMR. The result found satisfactory.

Dissolution test was carried out for high hardness sample only to evaluate the impact of high hardness. The dissolution test was found satisfactory.

Table 13: Dissolution test results

Test	**Specification**	**Result**		
Dissolution		**Batch A**	**Batch B**	**Batch C**
Aspirin		Minimum: 99 % Maximum: 104 % Mean: 101 %	Minimum: 99.4 % Maximum: 104.3 % Mean: 102 %	Minimum: 98 % Maximum: 104 % Mean: 99 %
Paracetamol	Not less than 70 % in 45 min	Minimum: 99 % Maximum: 107 % Mean:101 %	Minimum: 97.8 % Maximum: 102.2 % Mean: 100 %	Minimum: 99% Maximum: 103 % Mean: 101 %
Caffeine		Minimum: 100 % Maximum: 108 % Mean: 102 %	Minimum: 100.7 % Maximum: 103.1% Mean:102 %	Minimum:99 % Maximum: 105 % Mean:102 %
Disintegration test (High hardness)	NMT 15 min Max to be recorded	15 min	14 min 16 sec	10 min 2 sec

Hardness	NLT 40 N Max to be recorded	148.4	152.6	142.2

Conclusion: The result found satisfactory.

Coating results

Coating of three validation batches were carried out using auto coater (WT-21). All coating parameters were found to comply as per BMR specification and which were recorded in three validation batches, rolling of tablets found satisfactory and no coating defects observed whereas in validation batches.

During coating samples were withdrawn from coating pan after completion of each lot for each batch. The analytical data are as follows:

Table 14: Coating results for Batch A

Test	**Specification**	**Results (Batch A)**			
		Lot I	**Lot II**	**Lot II**	**Lot IV**
Description	White to off white, film coated capsule shaped caplets	White film coated capsule shaped caplets.	White film coated capsule shaped caplets	White film coated capsule shaped caplets	White film coated capsule shaped caplets
Uniformity of weight	Not more than 2 caplets deviate by more than +5% of the average and non deviate by +10% from the average weight.	Minimum:- 1.0 % Maximum: +1.0 %	Minimum: - 1.1 % Maximum: +0.8 %	Minimum: - 0.9 % Maximum: + 1.2 %	Minimum: - 1.2 % Maximum: 0.7 %
LOD	For information only	4.38	4.10	4.28	4.20

Table 15: Coating results for Batch B

Test	**Specification**	**Results (Batch B)**			
		Lot I	**Lot II**	**Lot II**	**Lot IV**
Description	White to off white, film coated capsule shaped caplets	White film coated capsule shaped caplets.	White film coated capsule shaped caplets	White film coated capsule shaped caplets	White film coated capsule shaped caplets
Uniformity of weight	Not more than 2 caplets deviate by more than +5% of the average and non deviate by +10% from the average weight.	Minimum:- 0.9 % Maximum: +1.3 %	Minimum: - 1.0 % Maximum: +1.1 %	Minimum: - 1.4 % Maximum: + 1.6 %	Minimum: - 1.2 % Maximum: 1.0 %
LOD	For information only	3.46	3.26	3.39	4.23

Table 16: Coating results for Batch C

Test	Specification	Results (Batch C)			
		Lot I	Lot II	Lot II	Lot IV
Description	White to off white, film coated capsule shaped caplets	White film coated capsule shaped caplets.	White film coated capsule shaped caplets	White film coated capsule shaped caplets	White film coated capsule shaped caplets
Uniformity of weight	Not more than 2 caplets deviate by more than +5% of the average and non deviate by +10% from the average weight.	Minimum:- 0.9% Maximum: + 0.8 %	Minimum: - 1.1 % Maximum: + 1.2 %	Minimum: - 1.7 % Maximum: + 0.8 %	Minimum: - 1.5 % Maximum: + 1.5 %
LOD	For information only	4.08	3.65	3.88	3.37

Conclusion: The results found satisfactory.

LOD of coated tablets

After coating 5 gm of coated sample collected from coating pan and triturate the coated tablets. The triturate samples are subjected for LOD test at 105 ^{0}C on halogen moisture analyzer for 20 minutes. The results are as follows:

Table 17: LOD of coated tablets

Test	Procedure	Results		
		Batch A	Batch B	Batch C
LOD of coated tablets	At 105 ^{0}C for 20 min on halogen moisture analyzer	1.51 %	1.46 %	1.67 %

Conclusion: The results found satisfactory.

Finished Product Results

Pooled sample from each batch of EPPC tablets was collected after coating and analyzed as per finished product specification. The results are complying as per the drug product release specification. The results are tabulated below:

Table 18: Finished Product Results

Test	Specification	Results		
		Batch A	Batch B	Batch C
Appearance	White to off white, fine coated, capsule shell caplets	White film coated capsule shaped caplets	White film coated capsule shaped caplets	White film coated capsule shaped caplets
Identification • Aspirin • Paracetamol • Caffeine	 Positive Positive Positive	 Positive Positive Positive	 Positive Positive Positive	 Positive Positive Positive
Uniformity of	Not more than 2	Maximum: + 2.1	Maximum: + 1.2	Maximum: + 1.7

weight	caplets deviate by more than ±5% of the average and now deviate by more than±10% from average weight	Minimum: - 1.4	Minimum: - 1.7	Minimum: - 4.1
Dissolution Aspirin	Not less than 70% in 45 minutes	Minimum: 99.1 % Maximum: 106.7% Mean: 102	Minimum: 100 % Maximum: 104 % Mean: 102	Minimum: 100 % Maximum: 104 % Mean: 102
Paracetamol	Not less than 70% in 45 minutes	Minimum: 97.5 % Maximum: 104.2 % Mean: 99	Minimum: 96 % Maximum: 103 % Mean: 98	Minimum: 95 % Maximum: 100 % Mean: 97
Caffeine	Not less than 70% in 45 minutes	Minimum: 97.9 % Maximum: 103.9 % Mean: 100	Minimum: 96 % Maximum: 105 % Mean: 100	Minimum: 96 % Maximum: 102 % Mean: 99
Assay Aspirin	285.0 to 315.0 mg per caplet (between 95 to 105%)	302.6 (100.9 %)	307.6 (102.5 %)	299.6 (99.9 %)
Paracetamol	190.0 to 210.0 mg per caplet (between 95 to 105%)	201.7 (100.8 %)	193.8 (96.9 %)	199.3 (99.6 %)
Caffeine	42.75 to 47.25 mg per caplet (between 95 to 105%)	45.16 (100.4 %)	43.93 (97.6 %)	44.59 (99.1 %)
4-Aminophenol	Not more than 0.1%w/w	0.002	0.001	0.002
Free salicylic acid	Not more than 1.0%w/w	0.17	0.1	0.1
Impurities				
Single unknown impurities	Not more than 0.1%w/w	ND	0.002	0.002
Total unknown impurities	Not more than 0.3%w/w	ND	0.003	0.003
Microbial contamination				
Total viable aerobic count	Not more than 1000 CFU per g	< 10 CFU per g	< 10 CFU per g	< 10 CFU per g
Fungi	Not more than 100 CFU per g	< 10 CFU per g	< 10 CFU per g	< 10 CFU per g
Escherichia coli	Must be absent	Absent	Absent	Absent

Conclusion: All product quality parameter are meeting as per approved finished product specification.

CONCLUSION

It is very necessary for an industry before the launch of product to ensure that quality is built into

system at every step. Three batches of EPPC caplets were taken for revalidation. All the critical process parameter, analytical test results for blending, compression and coating were well within the approved standard parameters and limit. The results of all stages were found within the standard specification and acceptance criteria mentioned in the process validation protocol and finished product specification. Thus, the process of manufacturing EPPC caplets can be considered validated.

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