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Review Article

Review on Process Validation of Pyrazinamide Tablets

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ABSTRACT

Validation is best viewed as an impartment and integral part of cGMP. Validation is therefore one element of quality assurance programs associated with a particular process. Then word validation simply means "assessment of validity" or action of proving effectiveness. This process involves addition of granulating agent to the dry mixed material and converting into granules. The goal of quality system is to consistently produce products that are suitable for their intended use. Process validation is a key element in assuring that these principles and goals are met. In this study concurrent process validation was carried out for pyrazinamide tablets IP 750 mg. In tablet dosage form, critical parameters like dry mixing, granulation, drying, sifting and milling, lubrication and compression were taken up for validation studies. In-process quality monitoring of all critical processing steps was done for three production batches. LOD of the dried, milled and lubricated granules were checked and found within the limit. Assay after lubrication was within the specified limit, indicating blend uniformity. Physical parameters, dissolution and assay were checked and results found within the acceptance criteria. During packing operation, blisters were checked and found satisfactory. Thus process validation of pyrazinamide tablets IP 750 mg was successfully completed and found within the specifications.

Keywords: Process validation, Pyrazinamide, Maize starch, Gelatine, Sodium starch glycolate.

INTRODUCTION[1-12]

USFDA Defines validation as

Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

WHO guidelines Defines validation as

Validation is documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results. Validation act of proving, in accordance of GMPs that any process actually leads to expected results. Documented evidence that the process, operated with in established parameters, can perform effectively reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

WHY VALIDATION?

- If would not be feasible to use equipment not knowing if it will produce the product we want, not to employ the people with no assurance that they can do or fail to implement process checks or examination to assure that product meet specifications.
- The pharmaceutical industry uses expensive material sophisticated facilities and equipments and highly qualified personals.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failure, rejects, reworks, recalls, complaints are the sufficient part of total production cost.
- Detailed study and controlled of the manufacturing process batch validation is necessary if failure cost is to be reduced and productivity is improved. There are three reasons by pharmaceutical industry are concerned that their processes perform consistently expected that is, that are validated.
- Assurance of quality, cost reduction.

Government regulations

Validation is considered to be integral part of GMPs essentially world wide, compliances with

validation requirements is necessary for obtaining approval to manufacture and to introduce new products. The FDA's cGMP refer to the concepts of the validation in both sections. They state that such control procedure shall be established to monitor out put and to validate the performance of those manufacturing process that may be responsible for causing variability in the characteristics of in process materials and drug materials. The Accuracy, sensitivity, specificity and reproducibility of test methods employed by the firm shall be established and documented. A generally stated requirement for process validation is contained in the medicinal device GMP regulations. Where deviations from device specification could occur as result of manufacturing process itself. There shall be written procedures describing any process controls necessary to assure conformance to specifications.

How validation is done?

The principle is characterized by harmony between the results obtained and requirements. This supposes specific requirements and objectives

- Available means
- Choices, which are justified in relation to objectives
- Each stage should begin when the previous stage is over

Certain depositions should be defined

How norms should be dealt with

- How modifications should be dealt with controlling evaluation will involve
- Set data for decision making
- Evaluation before decision making
- Justifying the decision
- Follow-up

TYPES OF VALIDATION

- **Prospective validation**

Prospective validation is defined as the Establishment of documented evidence that a system does what it purports to do based on a pre planned protocol. This validation is usually carried out prior to the introduction of new drugs and their manufacturing process. This approach to validation is normally under taken when ever new formula, process or facility must be validated before routine pharmaceutical formulation commences. In fact validation of process by this approach often leads to transfer of the manufacturing process from the development function to product. The objective of prospective validation is to prove or demonstrate that the process will work in accordance with a validation master plan or protocol prepared for pilot product trails.

- **Retrospective validation**

Retrospective validation is defined as the establishment of documented evidence that a system does what it purports to do on review and analysis of historical information. The sources of such data are production, QA and QC records. The issues to be addressed here are changes to equipment, process, specification and other relevant changes in the past.

- **Concurrent validation**

It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of 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.

PROCESS VALIDATION

"Process Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics."

Objectives of process validation

1) The manufacturing process, in addition to the individual equipment, must be validated.
2) The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.
3) A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.
4) Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.
5) In the end, process validation will ensure a robust product that is highly reproducible over time.

Advantages of process validation

1) Expanded real time monitoring and adjustment of process.
2) Enhanced ability to statistically evaluate process performance and product variables. e.g.,

individuals; mean; range; control limits

3) Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
4) Improved ability to set target parameters and control limits for routine production, correlating with validation results.
5) Enhanced reporting capability.

PROCESS VALIDATION PROTOCOL

"A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment and design points on what constitutes acceptable test results."

The validation protocol should be numbered, signed and dated, and should contain Protocol Approval sheet, Validation Team, Batches under validation, Introduction, Product profile, Objective, Scope, Validation criteria, Reference documents, General check points, Responsibilities, Manufacturing formula, Details of the equipment/facilities to be used (including measuring/ monitoring/ recording) with its calibration status, Process flow chart, Manufacturing procedure, Rationale for selection of critical steps and its parameters for validation, Process steps, control variables and response to be measured, Sampling plan (The samples to be taken- where, when, how, how many and the allowable range of variability), Sampling procedure, Specifications, Raw materials – Rationale, Wet granulation – Rationale, Compression – Rationale and Procedure, Calibration, Acceptance criteria, Validation report preparation, Deviation, Approach for handling out of specification results, Revalidation criteria, Summary and Conclusion.

MATERIALS AND METHODS[13-19]

All the materials are listed in Table 1 – 3.

EVALUATION OF TABLET[20-23]

The critical parameters considered during the process validation of pyrazinamide tablets IP 750 mg were Dry Mixing, Drying, Milling, Blending/Lubrication, Compression and Blister Packing.

Dry mixing

The dry-mixing step involves mixing of active ingredients with other additives using Rapid Mixer Granulator (RMG). Mixing speed and mixing time are the critical variables. Mixing speed is kept constant, mixing time shall be studied to validate dry mixing step. In dry mixing stage 3 batches like I, II and III are considered for validation. Dry mixing results of all the batches are well within the acceptance criteria.

Parameters:

Time of mixing : 7 minutes
Agitator speed : Slow

Drying

The drying step involves drying of wet mass. The level of moisture in the granules is important factor. If level of moisture is more in granules then blend will have poor flow & distribution characteristics. If level of moisture in blend is less it will produce tablet with capping, high friability and chipping problems. During drying the desired LOD will be maintained in the granules which will influence the quality parameters like tablet hardness, flow properties, physical properties during compression. Drying of granules in FBD controls the level of moisture. Inlet temperature of FBD is most critical variable for the same. LOD is checked at regular interval to establish the correlation with outlet temperature. Drying results of the batches are well with in the acceptance criteria. Results of Loss on drying are shown in

Table 4

Analysis	: Loss on drying (by IR moisture balance analyzer)
Acceptance criteria	: NMT 2.5% w/w at 105°C

Milling

Sizing of granules is to be obtained by sifting of granules from specified sieve and retention of granules on sieves is to be milled by using multimill, Speed of the multimill and Forward direction of knives is to be monitored and sample to be withdrawn at the end of the sizing operation for the monitoring of particle size distribution, bulk density and LOD as a part of validation. Results of milled granules are shown in Table 5 and 6.

Analysis : Particle size distribution, Untapped bulk density, tapped bulk density and LOD.

Acceptance criteria : LOD : NMT 2.5% w/w at 105°C

Blending/Lubrication

This step involves mixing of magnesium stearate with drug granules & other blending material. Sifted lubricants shall transfer to octagonal blender containing dried granules of pyrazinamide and mix for 10 minutes at slow speed. Sifted magnesium stearate shall transfer to octagonal blender and Mix for 3 minutes at slow speed. The purpose of blending is to get a uniform distribution of API. This is followed by mixing of the un lubricated blend with lubricant to get good flow and anti-adhesion property of the blend. Mixing speed and time are critical variables in this process. Mixing speed is kept constant. Mixing time is critical since under mixing will result in non-uniform distribution of drug and poor flow where as over mixing will result in de- mixing leads to

non-uniform distribution of drug. Checking content uniformity of API at fixed time shall validate blending time. In blending stage three batches i.e. Batch I, II and III shall be considered for validation. Blending results of all the batches are well with in the acceptance criteria. Results of content uniformity during blending were shown in Table 7. Results of particle size distribution, bulk density, LOD and assay of composite sample at the end of lubrication are shown in Table 8 and 9.

Analysis : Blend uniformity, particle size distribution, Bulk density, LOD and Assay
Acceptance criteria : LOD: NMT 2.5 % w/w
Assay: 95.0 -105.0 %

Compression
This step involves consistent flow of an adequately lubricated, uniform blend, into dies where the granules are being compressed into tablets. Compression is to be carried out as per batch manufacturing record. Collect the samples at various stages i.e. at Minimum Hardness, Maximum Hardness, Minimum Speed, Maximum Speed and At Optimum speed Initial stage, Middle stage and End stage of compression and carry out the testing of physical parameters such as Appearance, Group wt., Diameter, Hardness, Thickness, Friability, Disintegration time and Average wt., Dissolution at max hardness only and Assay. In compression stage three batches i.e. Batch No A, B and C shall be considered for validation. Compression results of all the batches are well with in the acceptance criteria. Various physical parameters, approximate sample size, acceptance criteria during compression and results of various physical parameters are shown in Table 10- 1 8 .

Thickness, Length and Width
30 tablets were randomly selected from each batch and their thickness, length and width were measured by using digital Vernier caliper.

Hardness
The crushing strength Kg/cm^2 of prepared tablets was determined for 6 tablets of each batch by using Erweka tablet hardness tester. The mean of hardness was determined.

Friability
9 tablets (Approximate 6.5 g) were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were deducted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(W_t/W)\} \times 100$$

Where,
% F = friability in percentage
W = Initial weight of tablet
W_t = weight of tablets after revolution

Disintegration time
6 tablets were placed in the tablet disintegration test apparatus and on it. Disintegration time of the tablets was noted.

Weight variation
30 tablets were randomly selected from each batch and individually weighed. The average weight of 30 tablets was calculated. The batch passes the test for weight variation test if the tablet weight are within the acceptance criteria shown in Table 10.

Capability Index
The capability indices to be calculated for weight sample using following formula:
Cp = (USL – LSL)/6s
CpU = (USL - X)/3s
CpL = (X – LSL)/3s
CpK = min (CpU, CpL)
(smallest of the values for CpU and CpL i.e. Capability Index)

Where
USL = upper specification limit for weight
LSL = lower specification limit for weight
X = mean for weight
S = standard deviation

Dissolution
Medium: water; 900 mL
Apparatus 2: 50 rpm
Time: 45 minutes
Procedure : Determine the amount of $C_5H_5N_3O$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 268 nm on filtered portions of the solution under test, suitably diluted with dissolution medium, if necessary, in comparison with a standard solution having a known concentration of pyrazinamide RS in the same medium.
Tolerance: Not less than75 % of the labeled amount of $C_5H_5N_3O$ is dissolved in 45 minutes.
Uniformity of dosage units meet the requirements.
The results are shown in Table 19.

Assay
Weigh and powder 20 tablets. Weigh accurately a quantity of the powder containing about 0.1 g of Pyrazinamide, add 200 ml of water, allow to stand for 10 minutes, swirling occasionally, mix with the aid of ultrasound for 10 minutes and dilute to 500.0 ml with water. Filter and discard the first 20 ml of

the filtrate. Dilute 5.0 ml of the filtrate to 100.0 ml with water and measure the absorbance of the resulting solution at the maximum at about 268 nm. Calculate the content of $C_5H_5N_3O$ taking 650 as the specific absorbance at 268 nm. The results are shown in Table 20.

Finished product analysis report is shown in Table 21.

Packing

Blister packing is to be done as per batch packing record and involves packing of tablets in Clear thermoformable rigid PVC film and Printed Aluminium foil. In packing stage three batches i.e. Batch I, II and III shall be considered for validation. Packing results of all the batches are well with in the acceptance criteria. Results of blister packing were shown in Table 22 and 23.

Validated parameters:

Sealing Roller : 200 ± 10˚C
Forming Temperature : 160 ± 10˚C
Machine Speed : 60± 20 cuts/minute

RESULTS AND DISCUSSION

All the results are tabulated in Table 4 - 23.

The quality system regulation defines process validation by establishing objective evidence that a process consistently produces a result or product meeting its predetermined specifications. The goal of quality system is to consistently produce products that are suitable for their intended use. Process validation is a key element in assuring that these principles and goals are met.

In this study concurrent process validation was carried out for one product. In tablet dosage form, critical parameters were taken up for validation studies.

In tablet dosage form, the critical parameters are:

- Dry Mixing
- Drying
- Milling
- Blending/Lubrication
- Compression
- Blister Packing

Dry mixing

The dry-mixing step involves mixing of pyrazinamide with other additives using Rapid mixer granulator. The mixing of the active ingredient depends on the mixing time.

Drying

The drying step involves drying of wet mass. Moisture in granules is important factor. If moisture is more in granules it will lead to poor flow and sticking problem. If moisture is less it will lead to capping, high friability and chipping. During drying the LOD of granules should be taken in to consideration. The inlet temperature of the FBD is controlled during the drying process and the outlet temperature is monitored and correlated with the corresponding LOD of the granules under drying.

Milling

Dried granules were than sifted and milled on multimill. At the end of milling, composite sample was withdrawn and tested for particle size distribution, bulk density and LOD. Results obtained were found well within the limit and recorded.

Blending/Lubrication

The blending of three batches was performed and the samples at the designated locations were drawn after 3 minutes of blending after transferring magnesium stearate to octagonal blender for determining the blend uniformity and RSD values of pyrazinamide. The RSD values meet the acceptance criteria. From the analytical results it is clear that the drug distribution pattern in the blend is almost homogeneous. Hence the blending time of 3 minutes after addition of magnesium stearate as mentioned in the BMR stands was validated.

Compression

The compression for all the three batches has been validated for minimum and maximum hardness, minimum and maximum speed and at optimum speed; initial stage, middle stage and end stage of compression. The results of physical parameters like appearance, thickness, length, width, hardness, friability, disintegration time, group weight, average weight, uniformity of weight and capability index, dissolution and assay of the tablets were well within the acceptable limits. The results are comparable among all the three batches.

Blister packing

This process involves packing of tablets in clear thermoformable rigid PVC film and printed aluminium foil. Temperature of blister sealing rollers, forming rollers and speed of machine are critical variables. Adequate sealing roller temperature is essential to get proper sealing, less temperature will lead to improper sealing which cause leakage and higher temperature will result in burning or spoilage of PVC film or aluminum foil. Leak test and blister appearance are carried out to establish the above variables during blister packing operation.

CONCLUSION

Process validation study on three consecutive batches, Batch I, II and III of pyrazinamide IP 750 mg tablets having batch size of 120000 tablets was successfully completed and the manufacturing

critical process parameters were validated of this transferred product to show that the process was under control. The study includes the validation of critical steps of manufacturing such as blending, compression and blister packing. It shall also establish the suitability of equipments and area used for the production. The all process validation batches had been manufactured and validated in full compliance with cGMP requirement.

Based on the results of the validation data, it shall be concluded that the manufacturing process consistently produces the product of pre-determined quality parameters. The Process validation showed that there was no significant batch-to-batch variation and all the process variables were studied and it showed consistent and reproducible results. Therefore it can be concluded that the process stands validated and the data can be used in regulatory submission.

Table 1: List of Raw materials and their Functions

S. No.	Ingredients	Function
1	Pyrazinamide	API (Antituberculous)
2	Maize Starch	Diluent / Binder
3	Gelatine	Binder
4	Purified water	Vehicle
5	Colloidal silicon dioxide (Aerosil 200)	Rheology Modifier / Thickener
6	Sodium starch glycolate	Disintegrant, Dissolution aid, Suspending agent
7	Purified talc	Lubricant, Glidant
8	Magnesium stearate	Diluent / Lubricant

Table 2: List of Equipments and their Uses

S. No.	Equipment name	Used for
1	Vibro sifter (20 #, 40 #, 60 #, 80 #,100 # sieves)	Sifting of raw materials
2	Multimill	Milling
3	Rapid mixer granulator (High shear granulator)	Dry mixing and granulation
4	Paste kettle	Preparation of paste
5	Mechanical stirrer	Stirring
6	Fluid bed dryer	Drying
7	Octagonal blender	Blending
8	Unit dose Sampler	Sampling of granules
9	Rotary Tablet Press	Compression
10	Metal detector	Detecting metal, if any
11	Tablet inspection belt	Inspection of tablets
12	Blister pack machine	Packing of tablets

Table 3: List of Instruments and their Uses

S. No.	Instrument name	Used for
1	Analytical balance	Weighing
2	IR (Electronic) moisture balance analyzer	LOD
3	Roche friabilator	Friability
4	Tablet disintegration test apparatus	Disintegration Time
5	Hardness Tester (Erweka)	Hardness
6	Vernier calipers	Thickness, length and width
7	Leak test apparatus	leak test
8	Infra-red	Identification
9	UV-visible spectrometer	Identification, Dissolution, Assay
10	High performance liquid chromatography	Related substances
11	Thin layer chromatography	Related substances

Table 4: Drying - Loss on Drying

Sample	Weight Required (g)	Batch I		Batch II		Batch III	
		Weight taken (g)	LOD % w/w	Weight taken (g)	LOD % w/w	Weight taken (g)	LOD % w/w
T1	2 – 5	2.501	1.84	2.527	1.88	2.023	2.13
T2	2 – 5	2.230	1.71	2.290	1.90	2.015	2.34
M1	2 – 5	2.059	1.80	2.239	1.67	2.164	1.90
M2	2 – 5	2.530	1.74	2.420	1.68	2.045	2.05
M3	2 – 5	2.063	1.79	2.367	1.62	2.156	1.95
B1	2 – 5	2.116	1.89	2.425	1.75	2.026	2.02
B2	2 – 5	2.671	1.69	2.066	1.80	2.130	2.20

Table 5: Milling - Particle size distribution

Sieve Size	Acceptance Criteria	% w/w Retention		
		Batch I	Batch II	Batch III
20 # ↑	To record	7.69	14.81	28.35
40 # ↑		22.56	27.32	20.01
60 # ↑		22.69	19.28	10.58
80 # ↑		12.36	11.49	5.69
100 # ↑		6.33	5.71	3.92
% w/w Passed Through				
100 # ↓		26.51	20.94	29.97

Table 6: Milling - Bulk density and LOD

Batch	Untapped bulk density (g/mL)	Tapped bulk density (g/mL)	LOD (% w/w)
I	0.63	0.76	1.54
II	0.58	0.76	1.70
III	0.63	0.82	2.15
Acceptance Criteria	To Record	To Record	NMT 2.5 % w/w

Table 7: Lubrication - Content uniformity

Sample	Batch I		Batch II		Batch III	
	3 min		3 min		3 min	
	Weight taken (g)	% Assay	Weight taken (g)	% Assay	Weight taken (g)	% Assay
T1	1.655	101.2	1.665	100.4	1.723	98.0
T2	1.708	97.0	1.679	98.9	1.736	98.8
T3	1.716	101.6	1.642	101.3	1.727	99.6
T4	1.681	99.9	1.659	100.4	1.733	100.2
M1	1.731	99.1	1.659	101.1	1.723	100.6
M2	1.741	99.6	1.639	102.1	1.722	101.6
M3	1.735	101.6	1.652	101.1	1.726	101.3
B1	1.701	101.3	1698	97.7	1.737	100.7
B2	1.691	100.4	1.667	100.9	1.722	101.3
B3	1.717	98.9	1.670	100.8	1.740	100.6
Mean		100.1		100.5		100.3
RSD		1.48		1.26		1.16

Table 8: Lubrication - particle size distribution

Sieve Size	Acceptance Criteria	% w/w Retention		
		Batch I	Batch II	Batch III
20 # ↑	To Record	13.95	13.97	18.88
40 # ↑		30.46	30.48	30.73
60 # ↑		15.92	15.89	15.98
80 # ↑		6.26	6.26	6.47
100 # ↑		3.62	3.60	3.80
% w/w Passed Through				
100 # ↓		29.37	29.40	22.59

Table 9: Lubrication - Bulk density, LOD and Assay

Batch	Sample	Untapped bulk density (g/ml)	Tapped bulk density (g/ml)	LOD (% w/w)	Assay (%)
I	Composite	0.67	0.79	1.99	100.0
II		0.65	0.79	1.59	100.4
III		0.68	0.83	1.81	98.7
Acceptance Criteria		To record	To record	NMT 2.5	95.0 -105.0

Table 10: Various Physical parameters, Approximate sample size and Acceptance criteria during compression

S. No.	Individual In-process Test Parameter	Approximate sample size	Acceptance criteria
1	Appearance	30 tablets	White, capsule shaped uncoated tablets having plain surface on both the sides of each tablet
2	Thickness	30 tablets	6.0 ± 0.2 mm (5.8 - 6.2 mm)
3	Length	30 tablets	21.5 mm ± 0.2 % (21.3 – 21.7 mm)
	Width	30 tablets	7.5 mm ± 0.2 % (7.3 – 7.7 mm)
4	Hardness	6 tablets	4.0 to 8.0 Kg/cm^2
5	Friability	9 tablets (Approx. 6.5 g)	NMT 1.0 % w/w
6	Disintegration time	6 tablets	NMT 15 minutes
7	Weight of 30 tablets (Group weight)	30 tablets	30.30 g ± 2.5 % (29.54 g to 31.06 g)
8	Average weight	30 tablets	1010 mg ± 2.5 % (984.75 – 1035.25 mg)
9	Uniformity of weight	30 tablets	1010 mg ± 5 % (959.50 – 1060.50 mg)
10	Capability index	30 tablets	Not less than 1.33

Table 11: Thickness

Thickness (mm)							
Stage of Sampling		Batch I		Batch II		Batch III	
		Min	Max	Min	Max	Min	Max
Minimum Hardness		6.12	6.17	6.12	6.18	6.17	6.19
Maximum Hardness		5.86	5.90	5.84	5.90	5.82	5.88
Minimum Speed		5.98	6.04	5.97	6.04	5.97	6.01
Maximum Speed		5.99	6.02	5.99	6.04	5.99	6.03
Initial stage	At Optimum speed	6.02	6.07	5.96	6.04	5.97	6.05
Middle stage		5.94	6.04	5.98	6.04	5.97	6.06
End stage		5.98	6.04	5.98	6.09	5.97	6.04

Table 12: Length and Width

Stage of Sampling		Parameter	Batch I		Batch II		Batch III	
			Min	Max	Min	Max	Min	Max
Minimum Hardness		Length	21.51	21.54	21.50	21.53	21.49	21.56
		Width	7.50	7.53	7.49	7.52	7.48	7.54
Maximum Hardness		Length	21.49	21.51	21.48	21.55	21.50	21.53
		Width	7.50	7.55	7.51	7.53	7.49	7.52
Minimum Speed		Length	21.51	21.53	21.50	21.54	21.51	21.53
		Width	7.49	7.52	7.51	7.54	7.50	7.54
Maximum Speed		Length	21.50	21.52	21.49	21.55	21.48	21.55
		Width	7.51	7.53	7.48	7.51	7.51	7.53
Initial stage	At Optimum speed	Length	21.48	21.52	21.51	21.54	21.51	21.54
		Width	7.49	7.51	7.50	7.53	7.50	7.53
Middle stage		Length	21.50	21.53	21.50	21.55	21.49	21.52
		Width	7.51	7.54	7.49	7.52	7.51	7.53
End stage		Length	21.51	21.55	21.50	21.54	21.50	21.53
		Width	7.50	7.52	7.51	7.53	7.51	7.54

Table 13: Hardness

Stage of Sampling		Hardness (Kg/cm^2)						Mean
Batch I								
Minimum Hardness		5.4	6.0	6.2	5.9	6.4	6.0	**6.0**
Maximum Hardness		7.4	7.5	7.8	7.6	7.6	6.9	**7.5**
Minimum Speed		6.6	6.8	7.1	6.7	7.0	7.0	**6.9**
Maximum Speed		6.9	6.8	6.4	6.6	7.2	6.2	**6.7**
Initial stage	At Optimum speed	7.2	6.9	6.6	7.0	6.8	6.9	**6.9**
Middle stage		7.4	7.2	7.0	7.0	6.9	7.1	**7.1**
End stage		7.1	6.9	7.2	6.8	7.0	7.0	**7.0**
Batch II								
Minimum Hardness		5.7	6.0	5.9	5.8	6.1	5.7	**5.9**
Maximum Hardness		7.6	7.7	7.5	7.8	7.8	7.7	**7.7**
Minimum Speed		7.4	7.0	7.1	7.2	6.9	7.2	**7.1**
Maximum Speed		7.0	7.3	6.8	7.2	6.9	6.9	**7.0**
Initial stage	At Optimum speed	7.0	6.8	6.9	7.1	6.7	6.5	**6.8**
Middle stage		7.0	6.8	7.2	6.9	6.8	6.7	**6.9**
End stage		7.0	7.4	6.7	6.9	6.8	6.9	**6.6**
Batch III								
Minimum Hardness		5.9	6.4	6.0	6.0	5.4	5.9	**5.9**
Maximum Hardness		7.6	7.8	7.5	6.9	7.5	7.4	**7.5**
Minimum Speed		6.6	6.8	7.1	7.0	6.7	7.1	**6.9**
Maximum Speed		6.8	6.9	6.2	7.2	6.2	6.4	**6.6**
Initial stage	At Optimum speed	7.2	6.9	6.8	6.6	6.6	6.9	**6.8**
Middle stage		7.0	6.9	7.1	7.0	7.4	7.0	**7.1**
End stage		6.9	7.1	7.0	7.2	7.2	6.8	**7.0**

Table 14: Friability

Friability (% w/w)				
Stage of Sampling		**Batch I**	**Batch II**	**Batch III**
Minimum Hardness		0.09	0.14	0.31
Maximum Hardness		0.09	0.10	0.12
Minimum Speed		0.21	0.07	0.23
Maximum Speed		0.06	0.13	0.14
Initial stage	At Optimum speed	0.12	0.14	0.17
Middle stage		0.10	0.12	0.19
End stage		0.07	0.12	0.16

Table 15: Disintegration time

Disintegration time (minutes, determined at 37˚C ± 2˚C)				
Stage of Sampling		**Batch I**	**Batch II**	**Batch III**
Minimum Hardness		00 min 16 sec	00 min 16 sec	00 min 18 sec
Maximum Hardness		00 min 34 sec	00 min 36 sec	00 min 50 sec
Minimum Speed		00 min 22 sec	00 min 30 sec	00 min 24 sec
Maximum Speed		00 min 34 sec	00 min 29 sec	00 min 25 sec
Initial stage	At Optimum speed	00 min 22 sec	00 min 24 sec	00 min 27 sec
Middle stage		00 min 31 sec	00 min 28 sec	00 min 27 sec
End stage		00 min 30 sec	00 min 29 sec	00 min 26 sec

Table 16: Group weight

Group weight (g)				
Stage of Sampling		**Batch I**	**Batch II**	**Batch III**
Minimum Hardness		30.535	30.338	30.364
Maximum Hardness		30.531	30.348	30.326
Minimum Speed		30.470	30.317	30.319
Maximum Speed		30.494	30.327	30.318
Initial stage	At Optimum speed	30.559	30.357	30.361
Middle stage		30.566	30.369	30.349
End stage		30.576	30.379	30.348

Table 17: Average weight

Average weight (mg)				
Stage of Sampling		**Batch I**	**Batch II**	**Batch III**
Minimum Hardness		1017.8	1011.3	1012.1
Maximum Hardness		1017.7	1011.6	1010.9
Minimum Speed		1015.7	1010.6	1010.6
Maximum Speed		1016.5	1010.9	1010.6
Initial stage	At Optimum speed	1018.6	1011.9	1012.0
Middle stage		1018.9	1012.3	1011.6
End stage		1019.2	1012.6	1011.6

Table 18: Capability Index

Capability Index				
Stage of Sampling		**Batch I**	**Batch II**	**Batch III**
Minimum Hardness		2.73	1.75	2.28
Maximum Hardness		3.04	1.81	2.09
Minimum Speed		3.52	1.72	1.97
Maximum Speed		2.91	1.73	2.07
Initial stage	At Optimum speed	3.15	1.80	1.98
Middle stage		2.81	1.80	1.96
End stage		3.68	1.87	2.14

Table 19: Dissolution

Batch	**At Maximum Hardness - Dissolution %**						**Mean (%)**
I	95.6	93.5	96.3	97.2	95.5	96.4	**95.8**
II	98.5	96.7	97.6	95.2	96.1	97.5	**96.9**
III	96.6	97.3	96.9	95.5	97.3	94.6	**96.4**

Table 20: % Assay

% Assay				
Stage of Sampling		**Batch I**	**Batch II**	**Batch III**
Minimum Speed		99.9	99.4	102.3
Maximum Speed		99.6	99.5	101.4
Initial stage	At Optimum speed	99.5	99.8	102.4
Middle stage		99.7	100.1	100.4
End stage		99.7	100.1	101.6

Table 21: Finished product analysis report

S. No.	**Test**	**Specification**	**Results**		
			Batch		
			I	**II**	**III**
1.	**Description**	White, capsule shaped, uncoated tablet with plain surface on both the sides.	Complies	Complies	Complies
2.	**Identification**				
	A)By IR	The infrared absorption spectrum of the residue, in potassium bromide should be concordant with the reference spectrum of pyrazinamide working standard.	Complies	Complies	Complies
	B)By UV Absorption	The light absorbance of resulting solution in the range 290nm to 360nm should exhibits maximum at about 310nm. The diluted solution should exhibit a maximum at about 268nm; the absorbance at 268nm should be between 0.64 and 0.68.	Complies	Complies	Complies
	C)By odour of Ammonia	Ammonia recognizable by the odour should be evolved.	Complies	Complies	Complies
3.	**Average weight** (mg)	1010.0 ± 2.5 % (984.75-1035.25)	1014.58	1015.61	1011.93
4.	**Uniformity of**	Average weight ± 5.0 %	Min:-0.76	Min:-0.96	Min:-0.59

	weight (%)		Max:+1.00	Max:+0.81	Max:+0.54
5.	**Length** (mm)	21.5 ± 0.2 (21.3 – 21.7)	Min:21.59 Max:21.64	Min:21.60 Max:21.64	Min:21.64 Max:21.68
6.	**Width** (mm)	7.5 ± 0.2 (7.3 – 7.7)	Min:7.55 Max:7.61	Min:7.56 Max:7.60	Min:7.59 Max:7.62
7.	**Hardness** (Kg/cm^2)	4.0 to 8.0	Min:6.9 Max:7.5	Min:6.8 Max:7.4	Min:5.3 Max:6.5
8.	**Friability** (%w/w)	Not more than 1.0	0.06	0.08	0.09
9.	**Disintegration time** (minutes, determined at 37˚C ± 2˚C)	Not more than 15	02 min 10 sec	02 min 08 sec	02 min 56 sec
10.	**Related substances** (By TLC)	Any secondary spot in the chromatogram obtained with solution (1) should be not more intense than the spot in the chromatogram obtained with solution (2).	Complies	Complies	Complies
11.	**Dissolution** (%)	Not less than 75% of the labeled amount in 45 minutes	Mean:98.8	Mean:98.5	Min:99.3
12.	**Uniformity of dosage units** (By weight variation) (% of labeled amount)	85.0 to 115.0 RSD : Not more than 6.0%	Min:99.8 Max:101.3 RSD:0.50	Min:99.7 Max:100.8 RSD:0.35	Min:101.0 Max:102.0 RSD:0.33
13.	**Assay** Pyrazinamide IP mg/tablet % of label claim	712.50 to 787.50 (95.0 to 105.0 %)	754.78 100.6	752.99 100.4	761.75 101.6
	Additional Test				
1.	**Loss on drying** (% w/w)	Not more than 5.0	1.63	1.31	1.46
2.	**Related substances** (% w/w, by HPLC) Pyrazine-2-carboxylic acid Any other single impurity Total impurities	Not more than 0.20 Not more than 0.10 Not more than 0.50	0.012 Not detected 0.012	0.012 Not detected 0.012	0.009 Not detected 0.009
3.	**Microbiological purity**				
	Total viable aerobic bacterial count (cfu/gm)	Not more than 1000	07	07	03
	Fungi (cfu/gm)	Not more than 100	Nil	Nil	Nil
	Pathogens (Salmonella, S. aureus, E. coli, P. aeruginosa)	Should be absent	Absent	Absent	Absent

Table 22: Blister packing and Leak test

Batch	**Frequency**	**Blister sealing roller temperature** (˚C)	**Blister forming roller temperature** (˚C)	**Leak test**	**Appearance** (Sealing/Cutting/Coding)
I	Initial	203	162	Pass	Complies
	Middle	201	161	Pass	Complies
	End	201	160	Pass	Complies
II	Initial	203	163	Pass	Complies
	Middle	201	161	Pass	Complies
	End	201	161	Pass	Complies
III	Initial	202	157	Pass	Complies
	Middle	202	156	Pass	Complies
	End	201	155	Pass	Complies

Table 23: Camera challenge test

Test Parameters	Standard	Observation								
		Batch I			Batch II			Batch III		
		I	M	E	I	M	E	I	M	E
Blisters with good tablets	Should be passed by the camera	√	√	√	√	√	√	√	√	√
Blisters with broken tablets	Should be rejected by the camera	√	√	√	√	√	√	√	√	√
Blisters with empty pockets	Should be rejected by the camera	√	√	√	√	√	√	√	√	√
Blisters with discolored tablets	Should be rejected by the camera	√	√	√	√	√	√	√	√	√

√ Put for passing the challenge test.
× Put for rejection during the challenge test.
I – Initial
M – Middle
E – End

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