Formulation and Process Validation of Oral Solid Dosage Form of Prothionamide Tablet

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***Abstract*—The World Health Organization (WHO) TB remains a major public health problem worldwide declared TB and is the second leading cause of death due to an infectious disease, second only to HIV/AIDS.Process validation is a requirement of the current GMP regulations for finished pharmaceuticals 21 CRF parts 210 and 211 and of the GMP regulations for medical devices 21 CRF parts 820 and therefore, is applicable to the manufacture of pharmaceuticals and medical devices. Prothionamide may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. Three consecutive validation batches of Prothionamide Tablet were manufactured as per approved batch manufacturing record. The raw materials required for these validation batches were procured from approved sources and were taken up for manufacturing after testing and release by quality control. The raw materials were dispensed as per standard operating procedure. The process validation was carried out for the three batches.**

***Index Terms*—TB, WHO, Validation, Quality control, Bacteriostatic, Bactericidal, Prothionamide**

I. INTRODUCTION

Tuberculosis (TB) is an infectious disease usually caused by the bacterium Mycobacterium tuberculosis. Tuberculosis generally affects the lungs, but can also affect other parts of the body. Most infections do not have symptoms, in which case it is known as latent tuberculosis. About 10% of latent infections progress to active disease which if left untreated, kills about half of those infected. The classic symptoms of active TB are a chronic cough with blood- containing sputum, fever, night sweats and weight loss. It was historically called consumption due to the weight loss. Infe.ction of other organs can cause a wide range of symptoms. (1) Mycobacterium tuberculosis (TB) is as old as the human species.

The World Health Organization (WHO) TB remains a major public health problem worldwide declared TB and is the second leading cause of death due to an infectious disease, second only to HIV/AIDS. While much progress has been made over the past 20 years since TB was declared a public health emergency, there is still much funding needed and work to do to control the disease. Since 1995, more than 56 million patients have been treated for TB resulting in an estimated 22 million lives saved. In addition, the global TB mortality rate has It most commonly affects the lungs, producing pulmonary TB. However, transported by the blood or lymphatic system, the TB bacilli can infect almost any part of the body, including lymph glands, joints, kidneys, and bone - extra pulmonary TB. It is critical to understand the disease, its etiology and its epidemiology to develop a strong TB control programmer.

"Process validation is defined as the collection & evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that process is capable of consistently delivering quality product".
Following are the various concepts of process validation that are regulated by FDA and current

GMP guidelines.

Purpose: This guideline outlines general principles that FDA considers to be acceptable elements of process validation for the preparation of human and animal drug products and medical devices.

Scope**:** This guidelines is issued under section 10.90 (21 CFR 10.90) and is applicable to the manufacture of pharmaceuticals and medical devices.it states principle and practice of general applicability that are not legal requirements but acceptable to the FDA.

Regulatory requirement**:** Process validation is a requirement of the current GMP regulations for finished pharmaceuticals 21 CRF parts 210 and 211 and of the GMP regulations for medical devices 21 CRF parts 820 and therefore, is applicable to the manufacture of pharmaceuticals and medical devices.

DRUG PROFILE

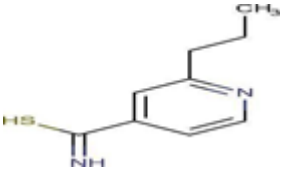
Properties of powder drug used in manufacturing process are given below:

PROTIONAMIDE

Chemical name: 2-propylpyridine-4-carboimidothioic acid

Molecular formula: $C_9H_{12}N_2S$

Molecular wt.: 180.27



Mechanism of action: Prothionamide may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. Prothionamide like Ethionamide and pyrazinamide is a nicotinic acid derivative related to isoniazid. It is thought that prothionamide undergoes intracellular modification and acts in a similar fashion to isoniazid. Isoniazid inhibits the synthesis of myoclonic acids, an essential component of the bacterial cell wall. Specifically isoniazid inhibits InhA, the enoyl reductase from *Mycobacterium tuberculosis*, by forming a covalent adduct with the NAD cofactor. It is the INH-NAD adduct that acts as a slow, tight- binding competitive inhibitor of INHA

II. MATERIALS

The sample of Prothionamide powder drug was arranged from Pen TSAO Chemical, dibasic calcium phosphate $2H_2O$ from Hindustan Phosphates PVT.LTD, Povidone K-90 from International Specificity Product, sodium starch glycolate from DMV, cornstarch from Universal, propylene glycol from DOW Chemicals, sodium benzonate from MERCK, microcrystalline cellulose from FMC Corporation, Talc from Vijai Minera, colloidal silicon dioxide from Evonic IND, magnesium stearate from Merck, purified water.

UTILITIES AND EQUIPMENT DESCRIPTION:

The list of utility and equipment used in manufacturing process are given in table 1

Manufacturing stage	Equipment	Manufactured By
Dispensing	Weighing Balance	Jay Pan / Mettler Toledo
Drying	Fluid bed dryer (200 kg)	Alliance
Dry Mixing/ Wet Granulation	Rapid mixer Granulator (700 L)	Sainath
Binder Preparation	Stirrer, Steam Jackated Vessel	Ashtami
Mixing	Rapid mixer Granulator (700 L)	Alliance
Sifting	Vibratory sifter	Gansons / Sweco
Dispensing	Weighing Balance	Jay Pan / Mettler Toledo

Milling	Turbo-sifter cum-miller	RP product
Lubrication	Pillar blender (Bin 750 /1350 L)	RP Product
Tablet Inspection	Tablet Inspection Machine	Accura
Film Coating	Ganscoater Coating Pan	Gansons Ltd.
Compression	Rotary compression machine	Sejong

III. EXPERIMENTAL WORK

1. Preformulation Studies

The preformulation study like characterization of drug sample which includes physical characterization and analytical methodologies, and evaluation of tablet blend including determination of bulk density, tapped density, compressibility index, Hausner ratio and LOD were performed for formulation Blend.

2. Physical Characterization of Drug Sample:

The sample of Prothionamide powder drug was arranged from Pen TSAO Chemical and was characterized for its identification and authenticity. The drug was physically characterized according to following methods.

1. Nature of Drug Sample
2. colour
3. Mp
4. Confirmation of Drug
5. Evaluation of Blend

3. Pre-compression Parameter

1. Bulk Density
2. Tapped Density
3. Carr's Index
4. Hausner Rule

Table No. 02: Hausner's ratio as an Indicator of Powder Flow Properties

Sr. No.	Hausner's Ratio	Type of flow
1.	< 1.18	Excellent
2.	1.19-1.25	Good
3.	1.3-1.5	Passable
4.	>1.5	Very poor

5. For dried granules:

1. Residual Solvent (Methanol): By Gas Chromatography

Blank Preparation: Pipette out 1 ml of dimethylsulfoxide in to a vial. Seal with a septum and crimp cap. Standard Solution: Weigh accurately about 240 mg of Methanol in a 50 mL volumetric flask containing about 20 mL of dimethylsulfoxide. Dissolve and dilute to the volume with the same solvent. Pipette out 5.0 ml of this
solution in a 50 mL volumetric flask, dilute to the volume with dimethysulfoxide. Pipette out 1 mL of the solution in to a vial and seal with a Septum and crimp cap.

Test Preparation: Weigh and transfer about 2.0 g of blend to a 50 ml volumetric flask, add about 20 ml of dimethylsulfoxide and sonicate it to disperse. Then dilute to volume with dimethylsulfoxide. Centrifuge the solution for 5 minutes at 3000 rpm in stopper test tube and transfer 1.0 ml of the supernatant solution to headspace vial. Crimp it and keep for injection.

Chromatographic system:

Instrument : Perkin Elmer Auto system Gas Chromatograph.

Column : DB-624, Dia.0.53mm, 60mtr, 3.0 □m. Fused silica capillary,

Detector : Flame ionization Detector (FID)
Carrier gas : Nitrogen / Helium

Gas Chromatograph parameters: Carrier gas Pressure: 5.0 psig. Detector temperature :

250 □C Injectortemperature : 200 □C Detectorrange 1

Attenuation 64

2. For lubricated granules:
1. Water Content:

Determine the test on 0.5 g of the sample using Karl Fischer apparatus.
Reporting: Report the results as % w/w.

2. Blend uniformity by HPLC Instrumental Conditions:

Column : Inertsil ODS 3V (150 X 4.6)mm, 5µ or equivalent

Flow Rate : 1.2 ml/min.

Wavelength : 257 nm
Injection Volume : 20 µl

Column Temperature:30°C

Run time : 8.0 min. Auto sampler temperature : 10°C

IV. RESULTS AND DISCUSSION

As per the procedure followed and discussed in the experimental section for different stage, here the list of results explained individually for concerned three consecutive batches.
LOSS ON DRYING OF DRIED GRANULES

Table 03: Loss on Drying of Dried Granules

Sr. No	Batch No.	Sampling Location					
		Upper Layer		Middle Layer		Lower Layer	
		Lot-1	Lot-2	Lot-1	Lot-2	Lot-1	Lot-2
1.	A801888	2.31	2.55	2.49	2.38	2.44	2.29
2.	A801889	2.35	2.25	2.32	2.37	2.19	2.30
3.	A801927	2.25	2.20	2.28	2.28	2.17	2.40

Acceptance criteria:
NMT 2.0% - 3.0% w/w at 105°C
Evaluation : % LOD of dried granules comprising of upper, middle, lower layers of FBD bowl for three process performance qualification batches were found in the range of 2.31 – 2.55 % w/w.

7.2 BLEND UNIFORMITY AT LUBRICATION STAGE

Table 04: blend uniformity for Batch No. A801888, A801889, A801927

Sr. No. a	mpling Layer and Location	Blend uniformity (%)		
	Batch No.	A801888	A801889	A801927
1	Upper Left	99.9	99.1	100.1
2	Upper Center	100.3	99.5	100.0
3	Upper Right	100.3	100.2	100.3
4	Middle Left	100.0	99.2	100.3
5	Middle Center	99.4	98.9	99.9
6	Middle Right	99.1	98.7	100.3
7	Lower Left	99.9	100.6	100.6
8	Lower Center	99.5	99.1	99.7
9	Lower right	99.3	100.0	100.1
10	Bottom center	99.8	100.3	98.9
11	Min	99.1	98.7	98.9
12	Max	100.3	100.6	100.6
13	Avg	99.8	99.5	100.0
14	RSD (%)	0.4	0.7	0.5

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Acceptance criteria

1) Individual samples: test results within ± 10% of mean
2) Individual Samples results found: 95 % to 110 % of label claim
3) RSD: NMT 5.0%

PHYSICAL PARAMETERS OF LUBRICATED BLEND

Table 05: physical parameters:

	PARAMETERS	BATCH NO.		
Sr. No				
		Yellow granular	Yellow granular	ow granular powder
2	Bulk density (gm/ml)	0.64	0.63	0.65
3	Tapped density (10 taps)	0.69	0.69	0.68
4	Tapped density (500 taps)	0.79	0.79	0.77
5	Tapped density (1250 taps)	0.80	0.81	0.79
	Compressibility index (%)(10			
	Compressibility index (%)(500			
	Compressibility index			
9	Hausner ratio (10 taps)	1.09	1.09	1.05
10	Hausner ratio (500 taps)	1.24	1.26	1.19
11	Hausner ratio (1250 taps)	1.26	1.28	1.22
Particle	Size	% cumulative retention		
	Over 20 #	4.12	4.26	4.26
	Over 40 #	26.45	26.55	26.60
	Over 60 #	43.27	43.25	43.24
	Over 80 #	54.97	54.95	54.81

	Over 100 #	59.04	59.02	59.13
	Below 100 #	40.96	40.98	40.87

Evaluation: Flow of the blend throughout the compression activity for three process performance qualification batches were found satisfactory.

COMPRESSION

As per the procedure during compression it was observed that all parameters complies with specification (Initial, Middle, End).

Here is the list of results obtained during compression in table

Table 6: Physical parameter of three batches

Sample ID and Description	Tests	Acceptance criteria		Results		
				Batch No's.		
				A801888	A801889	A801927
Compression	Description	Yellow coloured circular, biconvex tablets plain on both Sides.		Complies	Complies	Complies
	Weight of 20 Tablets (g)	7.000g ± 0.20	Min	6.969	6.973	6.985
			Max	7.052	7.034	7.028
			Avg.	7.014	7.005	7.002
	Uniformity of weight (mg)	350 mg	Min	338	341	340
			Max	358	362	359
		(332.500 mg to	Avg.	351	351	349
	Thickness (mm)	4.75 ± 0.35 mm (4.40 to	Min	4.63	4.59	4.58
			Max	4.83	4.70	4.74
			Avg	4.69	4.65	4.65
	Hardness (N)	NLT 40	Min	56	59	51
			Max	81	91	97
			Avg	66.63	71.75	67.63
	Disintegration Time(Minutes: Seconds)	NMT 15 minutes	Min	02:11	02:11	03:07
			Max	03:01	02:52	03:31
	Friability (% w/w)	NMT 1.0 %w/w	Min	0.121	0.135	0.120
			Max	0.255	0.239	0.196

Table 7: Thickness & Hardness of each batch

Sr. No	Thickness (4.80 - 5.60 mm)			**Hardness (70-140 N)**		
	Batch No.			**Batch No.**		
	A801888	A801889	A801927	**A801888**	**A801889**	**A801927**
1	4.63	4.57	4.58	**57**	**68**	**74**
2	4.62	4.60	4.67	**64**	**68**	**74**
3	4.58	4.64	4.54	**87**	**97**	**91**
4	4.58	4.59	4.68	**74**	**73**	**79**
5	4.58	4.64	4.64	**74**	**69**	**70**

Table 8: Dissolution of compression tablets

Dissolution %									
Batch No.	A801888			A801889			A801927		
	Initial	Middle	End	Initial	Middle	End	Initial	Middle	End
Min	98	101	102	100	101	101	101	104	102
Max	100	104	104	102	104	105	106	106	105
Avg.	99	102	103	102	102	102	104	105	104

Acceptance criteria: Not less than 75% of the labeled amount of Prothionamide is dissolved in

45 minutes Evaluation

As per table % dissolution of Prothionamide at initial, middle, end stage of compression of three batches was found in the range 95%-102%, 96%-103%, 94%-100% respectively

COATING

As per the procedure followed for coating section, here the list of results obtained for the coating process was validated by measuring parameters and specification, coating pan rpm, inlet temp and atomizing air pressure, peristaltic pump speed given in table

Table 9: Coating process parameter and specification

Parameters	Limit	Observation					
		A801888		A801889		A801927	
		LOT-1	LOT- 2	LOT-1	LOT-2	LOT-1	LOT- 2
Pan speed (rpm)	2.0 – 8.0	3.0 –7.9	3.1 –7.8	3.0 – 7.9	3.0 –7.9	3.0-7.8	3.0-7.9
Inlet temperature (°C)	50 - 70	48.8 –51.3	50.1 – 50.7	49.3 –50.1	49.3 –50.5	48.1-51.3	49.0-52.6
Outlet temperature (°C)	28-54	3–40.9	35.6 – 38.0	35.3–39.3	35.3-40.1	35.2-41.6	35.6-42.2
total spray rate (g/minutes)	434.0 –755.0	572.29	572.67	572.23	572.36	570.38	572.53

Atomizing air pressure (kg/cm^2)	2.0-3.5	2.5	2.5	2.5	2.5	2.5	2.5
Peristaltic pump	20.0-31.0	23.7 –25.5	23.4 – 24.9	23.7 –25.1	23.5 –25.1	23.1-25.3	23.8-25.6
Distance between spray gun and product bed (cm)	15 to 35	23	23	23	23	18	18

ANALYTICAL RESULTS OF FINISHED PRODUCT

Table 10: Analytical results of finished product: Batch No. A802071

Sr.	Test		Specifications	Results
1	Description		Yellow coloured circular , beveled edged , biconvex film coated tablets plain on both sides.	Complies
2	Identification (By IR)		The Infra-red absorption spectrum of the KBr dispersion of the residue is concordant with the spectrum of Prothionamide WS, prepared in the same way.	Complies
3	Water content (%w/w)		Not more than 3.0	1.41
4	Dissolution (%)	Min	Not less than 75% of the labeled amount of Prothionamide is dissolved in 45 minutes	98
		Max		101
		Avg.		100
5.	Uniformity of dosage units		Meets the requirement as per current BP	1.4
6	Related substance			
	2-Ethylpyridine4carbothioamide		Not more than 1.0 %	0.11
	4-Thioisonicotinicamide		Not more than 0.2 %	0.02
	Any other		Not more than 0.2 %	0.02
	Total impurities		Not more than 2.0 %	0.15
7	Assay (%)		95.0 to 105% of label claim	97.7

Table 11: Analytical results of finished product:

Sr. No.	Test	Specifications	Results
1	Description	Yellow coloured circular , beveled edged , biconvex film coated tablets plain on both sides.	Complies

			The Infra-red absorption spectrum of the KBr dispersion of the residue is concordant with the spectrum of Prothionamide WS, prepared in the same way	
3	Water content (%w/w)		Not more than 3.0	1.00
4	Dissolution (%)	Min	Not less than 75 % (Q) of the labeled amount of Prothionamide is dissolved in	96
		Max		100
		Avg.		98
5.	Uniformity of dosage units		Meets the requirement as per current BP	1.8
	Related substance			
	2-Ethylpyridine-4- carbothioamide		Not more than 1.0 %	0.11
	4-Thioisonicotinicamide		Not more than 0.2 %	0.02
	Any other		Not more than 0.2 %	0.01
	Total impurities		Not more than 2.0 %	0.14
6	Assay (%)		95.0 to 110.% of label claim	100.5

Table 12: Analytical results of finished product:

Sr. No.	Test		Specifications	Results
1	Description		Yellow coloured circular , beveled edged , biconvex film coated tablets plain on both sides.	Complies
2	Identification (By HPLC)		The Infra-red absorption spectrum of the KBr dispersion of the residue is concordant with the spectrum of Prothionamide WS, prepared in the same way	Complies
3	Water content (%w/w)		Not more than 3.0	1.18
	Dissolution (%)	Min	Not less than 75 % (Q) of the labeled amount of Prothionamide is dissolved in	97
		Max		99
		Avg.		98
5.	Uniformity of dosage units		Meets the requirement as per current BP	2.0
	Related substance			
	2-Ethylpyridine-4-carbothioamide		Not more than 1.0 %	0.11

6	4-Thioisonicotinicamide	Not more than 0.2 %	0.02
	Any other	Not more than 0.2 %	0.01
	Total impurities	Not more than 2.0 %	0.14
7	Assay (%)	95.0 to 110.% of label claim	98.7

As per table 10, table 11and table 12, the critical parameters considered during the process validation of tablets were weight variation, hardness test, thickness. The quality control data of three validation batches comply as per product release specification.

V. DISCUSSION

Three consecutive validation batches of Prothionamide Tablet were manufactured as per approved batch manufacturing record. The raw materials required for these validation batches were procured from approved sources and were taken up for manufacturing after testing and release by quality control. The raw materials were dispensed as per standard operating procedure. The process validation was carried out for the three batches. The critical steps of manufacturing such as dry mixing, wet granulation, drying, lubrication, compression and coating were studied

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