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Process Validation of Solid Oral Dosage Form of Ethambutol.HCl and Isoniazid Combination Tablet

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ABSTRACT: The current study was designed to meet the current regulatory requirements and prove with assurance that, the product meets the predetermined specifications and quality attributes. The objective of the study was to systematically conduct the validation studies pertaining to the manufacturing activities of solid oral dosage form of tablet and to confirm that the product manufactured with the present method consistently meets the predetermined specifications and quality attributes. Concurrent process validation of manufacturing process of Ethambutol.HCl 800 mg and Isoniazid 300 mg combination tablet was being undertaken due to the addition of "Wet Milling" step for wet granulation. The purpose is to develop a proper design and a robust process along with tests for appropriate quality control checks which will lead to high quality product. Hence, the present work was carried out on the process validation of solid oral dosage form of the tablets. Present work was carried out on the process validation of solid oral dosage form of the tablets confirms that the observed sets of conditions are better suited for manufacturing.

Key Words: Validation, ethambutol, isoniazid, oral dosage form, tablet, manufacturing

1 INTRODUCTION

1.1 Validation

Validation is a documented program that provides high degree of assurance that a specific process, equipment, method or system consistently produces a result meeting pre-determined acceptance criteria. Validation provides documented evidence that a process, equipment, method or system produces consistent results (in other words, it ensures that uniforms batches are produced) [1-4]. Validation refers to the GMP which ensures that the method or process is valid and would be able to produce the expected results as per the specifications provided [2-6].

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1.2 Process Validation

Process validation can be defined as the collection and evaluation of data, from the process design part via commercial production, which produces scientific evidence that a process is capable of constantly delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. The process validation is defined in three stages such as process design, process qualification, and continued process verification [3-7].

Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, personnel), but it also includes the control on the entire process for repeated batches or runs" [6-12]. In the present research validation studied related to manufacturing process of solid oral dosage form for two different drug in combination was performed. First was EthambutolHCl is $C_{10}H_{24}N_2O_2.2HCl$ (Mol.Wt: 277.2) Chemical Name: (S, S)-N, N'-ethylenebis(2-aminobutan-1-ol) dihydrochloride. It is a White crystalline powder almostodourless. Ethambutol is a bacteriostatic agent. It acts by inhibiting the Arabinosyl Transferase enzyme. It is used as First line drug in the management of tuberculosis. The second component was Isoniazid $C_6H_7N_3O$ (Mol. Wt: 137.1)Isonicotinic acid hydrazide. It is aColorless crystals, or white crystalline powder, odourless. The most important mechanism of action of Isoniazid is inhibition of Mycolic Acid. Sythesis. It is mainly Bactericidal for the rapidly multipying mycobacteria, but is Bacteriostatic in case of the slow- growing ones. Used as a First Line drug in Anti-T.B [5-12].

2 MATERIALS AND METHODS

Concurrent Process Validation was performed on the three consecutive batches of Ethambutol.HCl and Isoniazid combination tablets. The three batches were labeled as, Batch I, Batch II, and Batch III. The experimental study followed the validation protocol for execution of actual validation studies.

The execution includes each and every step and procedure studied or reviewed right from the beginning of the process validation, i.e. Review of documents, followed by monitoring of the critical process parameters, and collection of the data from the In-process and validation sample analysis for the final compilation of the validation report. While the final product was tested in accordance with the product release specifications [7-14].

The explanation part of the experimental work has been explained with the help of the various tabular form representations for the better understanding of the actual work that was performed, and all these tabular representations have been

mentioned in this section of experimental work, according to the procedure followed for the execution of the process validation studies [7-15]. The list of equipment with their manufacturer are provided as per table 1 with details of input materials their grade as well as quantity as per table 2 and table 3.

Table 1. List of Equipments Used.

S.N.	Equipment	Make	Stages Involved
1	Vibratory Sifter	Gansons – Mumbai	Sifting
2	Rapid Mixer Granulator	Sai Industries – Mumbai	Granulation
3	Multi Mill	General Pharmaceuticals	Wet Granulation
4	Fluid Bed Drier	Alliance – Mumbai	Drying
5	Turbo Sifter-Cum-Miller	R.P. Products – Mumbai	Sizing
6	Ganscommunitor	Gansons – Mumbai	Sizing
7	Octagonal Blender	R.P. Products – Mumbai	Blending and Lubrication
8	Tablet Compression Machine	Cadmech – Ahmedabad	Compression
9	Combodeduster Metal Detector	Technofour	For Metal Contamination
10	Weighing Balance	Jaypan – Mumbai Mettler	All applicable stages

Table 2. Details of Input Raw Materials.

Sr. No.	Ingredients	Grade	Unit
1	Ethambutol.HCl	IP (Indian Pharmacopoeia)	Kg (Kilo gram)
2	Isoniazid	IP	Kg
3	Diluent	IP	Kg
4	Disintegrant	IP	Kg
5	Binder	IP	Kg
6	Colorant	IP	Kg
7	Solvent	IP	L (Litre)

Table 3. Details of Lubrication Part.

Sr. No.	Ingrediants	Grade	Unit
1	Glidant	IP	Kg
2	Disintegrant	IP	Kg
3	Lubricant	IP	Kg

2.1 Manufacturing Procedure

The steps in the manufacturing process were followed as per the approved batch manufacturing record. Process parameters during each unit operation were monitored, to demonstrate that the protocol was followed [10-18].

The various stages involved in the manufacturing of Ethambutol.HCl and Isoniazid tablets are as given below:

2.1.1 Dispensing – The raw material was dispensed as per the Standard Operating Procedure.

2.1.2 Sifting – Ethambutol.HCl and Isoniazid along with the diluents were sifted through 20 Mesh of S.S. (Standard Size) sieve fitted to Turbo sifter and collected in R.M.G. (Rapid Mixer Granulator).

2.1.3 Dry Mixing – The materials were mixed by adding them to the R.M.G for 8 minutes, running the impeller at 'Slow' speed and the chopper 'Off'.

2.1.4 Preparation of Binder – Purified water was measured in a clean S.S. container and suspended in maize starch with S.S. spatula to form a uniform suspension. Purified water was measured in S.S. container and dispersed under mechanical stirrer along with "Lake of Sunset Yellow", and stirred till uniform dispersion was formed. Measure purified water in steam jacketed vessel and heat to boiling point, takes the hot purified water in S.S. container to uniform suspension. Remaining water was heated to boiling, and Gelatin was added to form a suspension in it, after Gelatin gets dissolved, color dispersion was added to the Starch suspension with stirring; till a thick uniform colored paste was formed.

2.1.5 Granulation –Mixer was started and binder added into R.M.G at "Slow" speed for impeller and chopper, and mixed for 2min.The Rapid Mixer Granulator (R.M.G) was stopped and the contents scraped from the side walls of the bowl, blades and chopper with S.S. scrapper. Again mixer was started for 10 min by running impeller and chopper at "Fast" speed. When the current drawn by the impeller was found in the range of 36-46 amperes, then the R.M.G was stopped and the mass unloaded in F.B.D (Fluidized Bed Dryer) bowel.

2.1.6 Wet Milling – The Multi-mill was started at knives forward, (High, Low, and Medium) speed, and the wet granules were milled through 9.5 mm S.S. Screen in to F.B.D bowl.

2.1.7 Drying – Initially the wet mass was air dried for 10 min in the fluid bed drier. Then further drying was done at the given inlet air temperature, by setting Fluidization control, damper value at 50-60%. Intermittent raking was done as required, and drying continued to get L.O.D between the desired ranges by Moisture Analyzer with intermittent checking of L.O.D. After completion of drying the L.O.D was checked and the results recorded, final L.O.D (Loss on Drying) reading was in between the ranges mentioned in the procedure, on Moisture Analyzer.

2.1.8 Sizing – The Granules were sized with Turbo sifter cum Miller fitted with 2.5 mm sifter and 2.5 mm Miler S.S. Screen or with Ganscomminutor.

2.1.9 Blending& Lubrication –

2.1.10 Sifting of Extra granular Material: The Talc and Maize Starch were sifted through the 40 mesh S.S. sieves using Vibratory sifter and separated in Polyethylene bag lined container.

2.1.11 Sifting of Lubricant: Magnesium Stearate was sifted through 40 mesh S.S. sieves using Vibratory sifter and collected separately in Polyethylene bag lined container.

2.1.12 Blending: Sifted material, along with Talc and Maize starch was transferred into the bin and loaded into Octagonal Blender and mixed for 10 min.

2.1.13 Lubrication: Sifted material, Magnesium Stearate, were transferred into empty bin and loaded into Octagonal Blender and mixed for **7** min.

2.1.14 Compression –Compression was performed on Double Rotary compression machine as per Specification, compressed tablets were passed through metal detector to remove tablets with any metallic impurities.

2.1.15 Inspection – Core tablets were inspected through tablet inspection machine to remove defected tablets.

2.2 Dry Mixing

The dry mixing was performed using RMG. The dry mixing involves mixing of sifted raw material to ensure homogeneous mixing. All ingredients were mixed into two parts viz. ETB part and INH part separately. All the sifted raw material was collected according to BMR and the mixer was started and material mixed in RMG for 7 min. running impeller at “slow” speed and chopper “off”. The critical parameters for this step were mixing time, agitator speed and blend uniformity assay, which were performed to estimate uniform mixing [8-19].

2.3 Granulation

The granulation was performed using RMG**.** The granulation step involved converting the powder into wet rough mass. The granule strength, bulk density of blend, dissolution, hardness of tablets etc. are influenced by mixing time. Paste of Pre-gelatinized starch with water as binder solvent is being used for granulation. The granulation end point is critical process and the end point of granulation which were checked against the amperage readings of impeller & chopper of the RMG, giving the correlation to the granulation end point [15-19].

2.4 Drying

Drying of wet granules was performed in FBD. The inlet temperature of the FBD was controlled and outlet temperature monitored, both of which were later correlated with the corresponding LOD of the granules. Samples were drawn from different positions of the FBD bowl and to check the LOD. Same procedure was repeated at different outlet temperatures [12-19].

2.5 Lubrication

Sifted Isoniazid part was loaded& half Quantity magnesium stearate in to the pillar blender and mixed for 3 minutes, extra

granular material was mixed for 5 minutes and to it EthambutolHCl part was mixed blended for 15 minutes and samples were collected from 10 point locations in duplicate. One set was taken for analysis other set kept as reserved sample. And also a pooled sample was taken after blend unloading. Blend uniformity assay tests were performed on the samples withdrawn from IPC container to ensure uniform mixing and blending.

- Sieve analysis
- Bulk density
- Tapped density
- Blend uniformity
- Assay

2.6 Compression

Compression of the material was performed with the help of compression machine, Type of machine: 62 station double rotary compression machine. Type of tooling: 'D' Compression which was carried out as per batch manufacturing record using circular shape punches with break line on upper punches & lower punches are plain. The machine was run at the speed of 12-40 RPM of the turret and the sample was collected at maximum and minimum speed, maximum and minimum hardness, for Batch I and at initial, Middle, and End stage of compression stage for all the three consecutive batches [12-18].

2.7 Sampling Location Diagram

2.7.1 Sampling plan diagrams of RMG (Rapid Mixer Granulator)

Six samples were collected from different parts of the RMG as shown in figure 1. One set was taken for analysis other set kept as reserved sample. And also one pooled sample was taken after blend unloading.

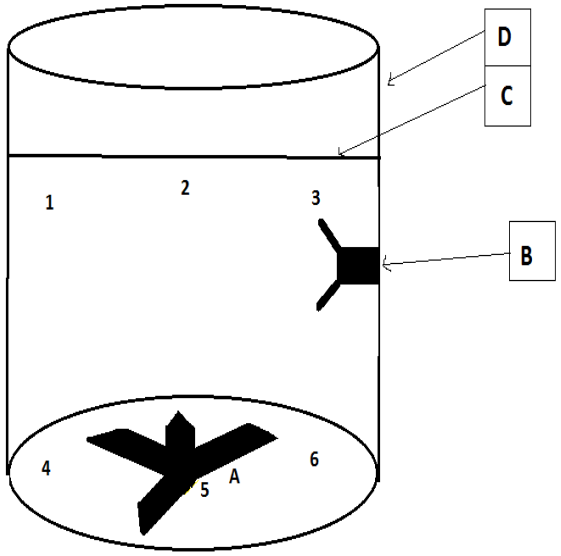

Figure 1. Sampling Plan Diagram for RMG (1 to 6=Sampling locations; A: Impeller, B: Chopper, C: Powder Bed, D: Bowl of RMG).

2.7.2 Sampling Plan Diagrams of FBD Bowl

Three samples were collected from Upper, Middle and lower layer of Fluidized Bed Dryer as per figure 2. One set was taken for analysis other set kept as reserved sample. And also one pooled sample was taken after blend unloading [19-28].

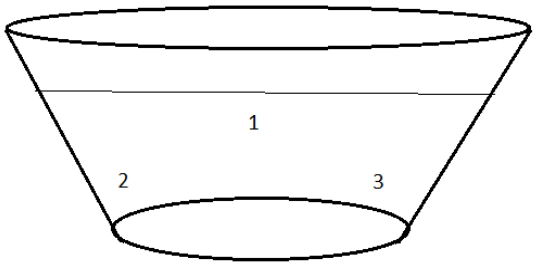

Figure 2. Sampling plan diagram of FBD Bowl (Sample No. 1, 2 & 3; sampling location (Upper, Middle & Lower)).

2.7.3 Sampling Plan Diagrams of Pillar Blender Bin

Ten samples were collected from ten different parts of the Pillar Blender Bin as shown in figure 3. One set was taken for analysis other set kept as reserved sample. And also one pooled sample was taken after blend unloading.

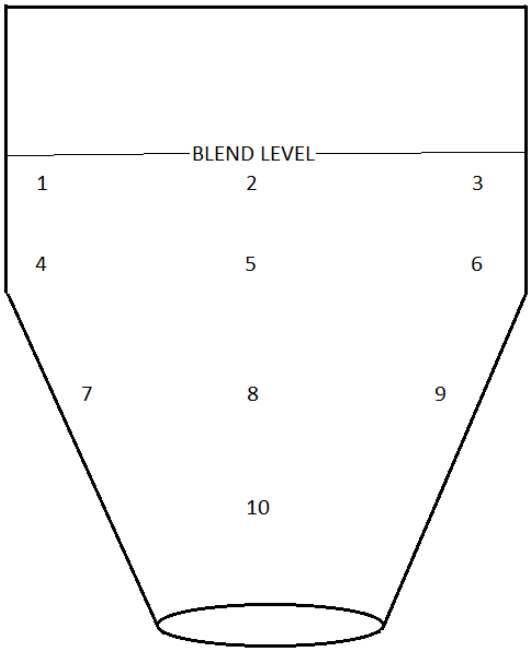

Figure 3. Sampling plan diagrams of Pillar Blender Bin **(**Sampling Location 1, 2, 3, 4, 5, 6, 7, 8, 9, 10).

3 RESULT AND DISCUSSION

3.1 Overview

This report describes results obtained during the different processing steps to evaluate and qualify the acceptability of the manufacturing process of Ethambutol.HCl 800 mg and Isoniazid 300 mg combination tablets due to change in the manufacturing procedure by addition of the "Wet Milling" for granulation, and inclusion of new equipment Octagonal blender (2300 L) in place of Conta-Blender (750 L) which was used earlier.

3.2 Product Details

Product Name: Ethambutol.HCl 800 and Isoniazid 300 Combination Tablet.

Label Claim: Each film of uncoated tablet contains Ethambutol.HCl -800 mg and Isoniazid-300 mg.

Description of Tablet: Light orange colored, capsule shaped tablet with break line on one-side.

3.3 Analytical DataforBlend

3.3.1 Blend Uniformity of Dry Mix

Blend uniformity of dry mix as provided in table 4 represents that blend uniformity for all the batches was in the range of acceptance criteria which clearly indicates that the process is properly validated.

Table 4. Blend Uniformity of Dry Mix.

S. N.	Sampling layer & Location	Acceptance Criteria	Blend Uniformity (%)					
			Batch I		Batch II		Batch III	
			ETB (Ethambutol)	INH (Isoniazid)	ETB	INH	ETB	INH
1	Upper right:1	Not less than 90.0% and not more than 110.0% of the labeled amount of Ethambutol.HCl and Isoniazid with RSD NMT 5.0%.	99.8	100.8	101.0	103.7	98.8	101.6
2	Upper centre:2		98.7	101.0	100.3	99.7	99.1	99.9
3	Upper left:3		97.2	99.1	98.7	100.6	99.5	99.3
5	Lower right:4		100.1	98.0	102.8	100.1	98.7	100.7
6	Lower centre:5		97.8	97.3	98.7	100.9	100.0	97.4
7	Lower left:6		100.70	98.3	99.8	101.0	99.0	97.9
Minimum			**97.2**	**97.3**	**98.7**	**99.7**	**98.7**	**97.4**
Maximum			**100.7**	**101.0**	**102.8**	**103.7**	**100.0**	**101.6**
Mean			**99.1**	**99.1**	**100.2**	**101.0**	**99.2**	**99.5**
RSD (%)			**1.4**	**1.5**	**1.6**	**1.4**	**0.5**	**1.6**

3.3.2 Blend Uniformity of Lubricated Blend

From the results obtained of blend uniformity it was found that the results of assay was within the limits (90-110%) as provided in table 5 which showed the process was properly validated for all the samples.

Table 5. Blend Uniformity of Lubricated Blend.

Sr. No.	Sampling Layer & Location	% Assay					
		Batch I		Batch II		Batch III	
		ETB	INH	ETB	INH	ETB	INH
1	1 Pt.	104.4	100.3	101.1	97.7	98.6	100.0
2	2 Pt.	101.7	100.2	99.9	99.0	94.8	99.9
3	3 Pt.	100.7	100.9	99.0	100.0	96.8	98.1
4	4 Pt.	104.1	101.5	100.6	98.5	100.9	97.9
5	5 Pt.	102.4	102.1	99.3	99.2	94.9	104.1
6	6 Pt.	103.9	100.8	99.6	97.7	97.8	99.0
7	7 Pt.	101.6	100.8	105.3	105.3	98.7	99.2
8	8 Pt.	100.6	100.7	102.2	103.0	98.1	98.6
9	9 Pt.	102.5	100.1	100.7	99.3	94.3	99.3
10	10 Pt.	102.2	100.1	101.1	100.8	97.0	99.3
Minimum		**100.6**	**100.1**	**99.0**	**97.7**	**94.3**	**97.9**
Maximum		**104.4**	**102.1**	**105.3**	**105.3**	**100.9**	**104.1**
Mean %		**102.4**	**100.9**	**100.9**	**100.1**	**97.2**	**99.5**
R.S.D. %		**1.3**	**0.6**	**1.8**	**2.4**	**2.1**	**1.8**

The physical character of lubricated blend as provided in table 6 indicates that the blend has excellent flowing properties in terms of compressibility, hausner ratio, bulk density, and tapped density.

Table 6. Physical Characters of the Lubricated Blend.

Sr. No.	Parameters	Batch No.		
		Batch I	Batch II	Batch III
1	Description	Light Orange color, Granular powder	Light Orange color, Granular powder	Light Orange color, Granular powder
2	Bulk Density (g/ml)	0.71	0.72	0.73
3	Tapped Density (g/ml) (500 Taps)	0.78	0.80	0.81
4	Tapped Density (g/ml) (1250 Taps)	0.81	0.82	0.83
5	Compressibility Index (%) (Considering, Tap Density- 500 Taps)	9.52	10.77	10.60
6	Hausner Ratio (Considering, Tap Density- 500 Taps)	1.10	1.12	1.11

The value representing the label claim as assay was found to be within the limits as provided individual monograph as per table 7.

Table 7. Assay of Lubricated Blend.

	Drug	Limit	Batch I	Batch II	Batch III
% Assay	Ethambutol.HCl	92.5 -107.5%	99.1	99.3	99.2
	Isoniazid	92.5 -107.5%	102.2	100.1	101.4

3.4 Analytical Data of Compressed Tablets

The in-process checks during table compression as described in table 8 confirms that all the in-process quality control tests were found within the limits for all the batches which ensures that the method is valid.

Table 8. In-Process Checks during Tablet Compression.

Sr. No.	Parameters	Limit	Batch No.	Observations		
				Initial	Middle	End
1	Description	Light Orange colored, capsule shaped tablet with Break Line on 1-Side	I II III	Same Same Same	Same Same Same	Same Same Same
2	Average Weight (mg)	1270 -1300 mg	I II III	1288.23 1297.18 1286.65	1292.45 1291.87 1287.33	1292.12 1289.27 1287.11
3	Uniformity of Wt. of tab.	±5.0% of Avg. Wt.	I II III	Complies Complies Complies	Complies Complies Complies	Complies Complies Complies
4	Hardness (N)	NLT 60	I II III	136 117 110	119 117 107	122 116 111

Table 8. In-Process Checks during Tablet Compression (continued).

5	Thickness (mm)	6.70 -7.20 mm	I II III	6.87 6.81 6.93	6.82 6.89 6.90	6.82 6.98 6.92
6	Friability (%)	NMT 2.0%	I II III	0.21 0.29 0.25	0.20 0.33 0.23	0.21 0.23 0.29
7	Disintegration Time (Min)	NMT 15 min	I II III	8 min 47 sec 8 min 42 sec 8 min 28 sec	8 min 50 sec 8 min 40 sec 8 min 34 sec	8 min 54 sec 8 min 32 sec 8 min 32 sec

3.5 Content Uniformity of Compressed Tablets

Table 9, 10, and 11 provides the content uniformity for both the drugs formulations as per data obtained it was found thatthe content uniformity was within the limit as specified in individual monograph. All the batches were having the limit above 90% which is a good sign from the pharmacopeial prospective.

Table 9. Content Uniformity Results of Batch I.

Sr. No.	Content Uniformity at Optimum Speed (%)					
	Initial		Middle		End	
	ETB	INH	ETB	INH	ETB	INH
1	97.4	98.4	95.6	99.4	96.8	94.9
2	96.8	98.5	98.3	98.5	96.7	95.8
3	98.4	96.7	97.8	97.8	97.1	97.4
4	96.0	99.9	95.9	96.7	94.5	96.6
5	99.6	96.7	97.9	98.4	97.1	97.9
6	96.9	99.6	98.4	99.2	98.9	97.3
7	99.9	102.3	96.9	101.4	98.1	99.7
8	96.0	98.0	97.0	98.4	98.7	96.4
9	96.6	96.5	99.6	100.3	94.6	96.0
10	95.5	98.6	99.6	95.5	99.0	99.4
Minimum	95.5	95.6	95.6	95.5	94.5	94.9
Maximum	99.9	102.3	99.6	101.4	99.0	99.7
Average	97.3	98.5	97.7	98.5	97.1	97.1
% R.S.D.	1.5	1.8	1.4	1.7	1.6	1.5

Table 10. Content Uniformity Results of Batch II.

Sr. No.	Content Uniformity at Optimum Speed (%)					
	Initial		Middle		End	
	ETB	INH	ETB	INH	ETB	INH
1	101.7	99.3	106.3	102.1	101.1	103.7
2	101.2	100.4	102.8	98.7	100.8	103.1
3	101.7	99.5	101.2	99.8	98.4	103.7
4	101.5	100.1	105.9	100.4	102.8	104.5
5	106.5	102.5	102.9	98.2	100.5	103.9
6	101.4	96.1	106.1	99.8	100.8	102.8
7	102.8	98.9	106.2	101.8	102.7	104.5

Table 10. Content Uniformity Results of Batch II (continued).

8	103.0	99.1	101.3	99.9	101.0	102.6
9	101.3	100.0	106.4	102.3	101.1	103.7
10	103.0	98.6	106.8	102.4	100.5	103.1
Minimum	101.2	96.1	101.2	98.2	98.4	102.6
Maximum	106.5	102.5	106.8	102.4	102.8	104.5
Average	102.4	99.5	104.8	100.5	101.0	103.6
% R.S.D.	1.6	1.6	2.2	1.5	1.2	0.6

Table 11. Content Uniformity Results of Batch III.

Sr. No.	Content Uniformity at Optimum Speed (%)					
	Initial		Middle		End	
	ETB	INH	ETB	INH	ETB	INH
1	100.1	103.3	102.0	101.8	100.9	101.6
2	102.5	103.2	100.8	102.4	101.2	102.3
3	101.1	103.1	100.9	102.1	98.9	101.5
4	102.1	103.0	102.0	102.3	99.8	101.6
5	102.1	102.5	101.5	101.5	102.0	101.3
6	100.3	103.2	100.2	101.7	100.4	101.3
7	101.0	103.0	101.1	102.3	101.5	101.6
8	100.8	102.8	98.6	101.6	99.7	101.7
9	99.7	103.1	98.5	101.3	101.5	101.6
10	102.0	102.6	102.0	101.8	101.9	101.8
Minimum	99.7	102.5	98.5	101.3	98.9	101.3
Maximum	102.5	103.3	102.0	102.4	102.0	102.3
Average	101.2	103.0	100.7	101.9	100.8	101.6
% R.S.D.	1.0	0.3	1.3	0.4	1.0	0.3

3.6 Dissolution Of compressed Tablets

From dissolution study data as provided in table 12, and 13 it was confirmed that both the drugs formulation were passing the dissolution criteria as specified in individual monographs for respective drugs. Both the formulations were able to release more than 90% of drug within the time limit prescribed.

Table 12. For Ethambutol.HCl.

Parameters		Batch I			Batch II			Batch III		
		Ini	Mid	End	Ini	Mid	End	Ini	Mid	End
% Dissolution	Min.	101	101	104	99	99	99	96	95	93
	Max.	108	107	109	107	101	101	97	98	96
	Avg.	104	104	105	101	100	101	97	97	95

Acceptance Criteria

NLT 75% (D) of the labeled amount of Ethambutol.HCl is dissolved in 45 minutes.

3.7 Analytical Data for Finished Product

One pooled sample from each batch of Ethambutol.HCl 800mg and Isoniazid 300mg combination Tablets was collected and analyzed as per Finished Product Specifications and results obtained in table 14 and 15 confirm that all the formulation batches passes the acceptance criteria.

Table 14. Batch Details of Finished Product.

Sr. No.	Test	Acceptance Criteria	Batch		
			I	II	III
1	Description	Light Orange colored, capsule shaped tablet with Break Line on One side	Complies	Complies	Complies
2	Identification of actives	The retention times of the Ethambutol.HCl and Isonoazid in the chromatogram of the assay preparation correspond to those in the chromatogram of standard preparation, as obtained in the assay for Ethambutol.HCl and Isoniazid	Complies	Complies	Complies
3	Average weight (mg)	Between 1270 - 1300 mg	1286.46 mg	1284.71 mg	1287.33 mg
4	Uniformity of weight of tablet (mg)	± 5.0% of average weight	Complies	Complies	Complies
5	Thickness (mm)	Between 6.7-7.2 mm	6.87	6.89	6.83
6	Disintegration (minutes)	NMT 15 min at 15-25 ^{0}C	08 min 10 sec	07 min 15 sec	08 min 30 sec

Table 15. Batch Details of Finished Product: (Dissolution & Assay).

S. N.	Test		Observations			Specifications	
	Batch		I	II	III		
1	Dissolution %	Min	99	97	104	Ethambutol .HCl IP	NLT 75% (D) of Ethambutol .HCl is dissolved in 45 minutes
		Max	100	101	106		
		Avg.	100	99	105		
		Min	100	95	97	Isoniazid IP	NLT 75% (D) of Isoniazid is dissolved in 45 minutes
		Max	104	101	99		
		Avg.	102	99	98		
2	Assay % (HPLC)	Label Claim	800 mg	800 mg	800 mg	Ethambutol .HCl IP	(92.5-107.5%)
		Mg/tab	798.37 mg	809.70 mg	803.08 mg		
		%	99.8	101.2	100.4		
		Label Claim	300 mg	300 mg	300 mg	Isoniazid IP	(92.5-107.5%)
		Mg/tab	298.67	297.77	302.79		
		%	99.6	99.3	100.9		

4 CONCLUSION

From the results obtained it can be concluded that all the validation parameters for both the drug formulations were found within the limits of acceptance criteria which clearly indicated the steps of mixing, lubrication, drying, wet granulation, and compression are properly validated with respect to random sampling and conditions of mixing and speed. Based on the manufacturing details during processing, data generated by carrying out the In-process checks during tablet compression and as per the results of finished product analysis, it is evident that the product Ethambutol.HCl 800 and Isoniazid 300 tablets are successfully manufactured with the given set of equipments, environmental conditions, and the manufacturing instructions as given in Batch Manufacturing Record (B.M.R), of Ethambutol.HCl and Isoniazid Combination Tablets. The current method of formulation suggest that how one can produce the formulation of mentioned drugs as per standard protocol of regulatory bodies and it is being applied for industrial manufacturing to be complied with regulatory requirements.

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6 AUTHOR CONTRIBUTIONS

Hypotesis: SMS and KR.; Design: SMS., AH; Literaturereview: B.A., İ.A. K.A.; Data Collection: SMS, KS; Analysis and/or interpretation: SMS., KS.; Manuscript writing: SMS., AH., KR.

7 CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

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