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CONCURRENT PROCESS VALIDATION OF THYROXINE SODIUM TABLETS 100 MCG

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ABSTRACT

This research project's main goal is to concurrently validate the Thyroxine Sodium Tablets IP process. Process validation investigations were carried out for the three successive batches of Thyroxine Sodium Tablets in the current investigation. At each stage, from the dispensing of raw ingredients, sifting, and mixing, to the last processes, which include packing, samples were taken, and various parameters were assessed and validated. These samples were then assessed using the HPLC technique in compliance with the protocol. After the findings were compiled, it was found that they satisfied the requirements while remaining inside the bounds.. From this validation study, it was concluded that no changes to the current manufacturing process were necessary. Only in the event that the procedures, instruments, or raw materials were changed would further validation be required.

KEYWORDS: Thyroxine Sodium, Concurrent process validation, HPLC.

1. INTRODUCTION

1.1 TABLET

Tablets are a type of solid pharmaceutical preparation made up of one or more active substances and a variety of excipients such as diluents, binder, disintegrating agents, organoleptic agents, and other acceptable excipients. They are typically made by molding or compression methods and come in a variety of sizes and forms depending on the necessity and application.[1]

1.2 VALIDATION

A process, procedure, or approach is validated by demonstrating and documenting that it consistently produces the desired outcomes.[3]

In order to determine if systems, facilities, and processes carry out their intended functions sufficiently and consistently as defined, validation is a crucial component of quality assurance. Although validation by itself does not make a process better, it confirms that it has been developed effectively and is under control.

1.2.1 TYPES OF VALIDATION

1. Analytical Method Validation
2. Cleaning Validation
3. Equipment Validation
4. Process Validation

1.3 PROCESS VALIDATION

Process validation is the demonstrated evidence that a process can generate a drug component or intermediate that satisfies its predetermined specifications and quality attributes when run within the established limits.[5] Effective process validation makes a substantial contribution to ensuring drug quality. A medicinal product should be developed that is suitable for its intended purpose, according to the basic concept of quality assurance.

1.3.1 STAGES OF PROCESS VALIDATION

There are three stages of Process Validation.

1. Stage 1: Process Design

At this step, the commercial process is established using the knowledge acquired from the scaling-up and development processes.[4]

2. Stage 2: Process Qualification

At this stage, the process design is assessed to see if it can be used for effective commercialmanufacturing.

3. Stage 3: Continued process verification

Continual assurance that the process is under control is obtained during routine manufacturing.

1.3.2 TYPES OF PROCESS VALIDATION

The four types of process validation are

1. Prospective Validation
2. Concurrent Validation
3. Retrospective Validation
4. Revalidation

1. Prospective Validation

A risk assessment of the production procedure, which is subsequently divided into particular processes, is used for validation at the development stage. These steps are then assessed based on prior experience to see if they might potentially result in adverse conditions.[3]

2. Concurrent Validation

This method includes checking on key processing steps and assessing the finished product of current production to show that the manufacturing process is under control. Concurrent validation is used to establish recorded evidence that a facility and processes carry out what they promise to, using data generated during the process' actual operation.

3. Retrospective Validation

Retrospective validation is used to certify facilities, processes, and process controls that are currently in operation but have not undergone a proper validation procedure by using historical data.

4. Revalidation

Periodic assessment of a prior validated system (or a section thereof) to guarantee ongoing adherence to specifications. Revalidation is often performed for a periodic assessment to ensure original validation.

2. DRUG PROFILE AND EXCIPIENTS

2.1.DRUG PROFILE OF THYROXINE SODIUM

Thyroxine, a key endogenous hormone secreted by the thyroid gland, is available in thyroxine sodium, a synthetic form. It is generally used to treat hypothyroidism, a condition in which the thyroid gland is unable to generate enough T4 (tetraiodothyronine, or thyroxine), and T3 (triiodothyronine, or liothyronine), which reduces the hormones' downstream effects.[11]

2.1.1. PHYSIOCHEMICAL PROPERTIES OF THYROXINE SODIUM

Table 1: Physiochemical Properties of Thyroxine Sodium.[12]

IUPAC Name	(*S*)-2-Amino-3-[4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl]propanoic acid
Molecular Formula	$C_{15}H_{11}I_4NO_4$
Molecular Weight	776.874 $g \cdot mol^{-1}$
Color	A white yellow or slightly brownish yellow powder
Water Solubility	Slightly soluble (0.105 $mg \cdot mL^{-1}$ at 25 °C)

2.1.2. MECHANISM OF ACTION

Although the exact methods by which thyroid hormones exert their physiological effects are not fully known, it is believed that their main impacts come from controlling DNA transcription and protein synthesis. The thyroid hormones T3 and T4 diffuse into the cell nucleus where they interact to thyroid receptor proteins embedded in DNA. This hormone's nuclear receptor complex promotes cytoplasmic protein synthesis and messenger RNA as well as gene transcription.

2.2.EXCIPIENTS

2.2.1. MANNITOL

Mannitol is largely employed in pharmaceutical preparations as a diluent (10–90% w/w) in tablet formulations, where it is particularly useful because it is not hygroscopic and may therefore be used with active pharmaceutical ingredients that are moisture snesitive.

2.2.2. MICROCRYSTALLINE CELLULOSE PH 102

MCCP is a frequently employed as fillers, flow aids, disintegration agents, anti-sticking agents, adsorbents, and capsule diluents in pharmaceutical products.

2.2.3. CROSSCARMELLOSE SODIUM

In oral pharmaceutical formulations, croscarmellose sodium is used as a disintegrant for capsules, tablets, and granules. Both direct compression and wet granulation techniques can be used to make croscarmellose sodium for tablet formulations.

2.2.4. MAGNESIUM STEARATE

The most common application for the addition magnesium stearate is as a lubricant.

2.2.5. Brilliant Blue Lake

As colorants and UV absorbers, brilliant blue lake are widely employed in pharmaceutical,

food, and cosmetic applications. Due to the restrictions on some synthetic organic dyestuffs, they are becoming more and more significant as inorganic colorants.

3. MATERIAL AND METHODOLOGY

3.1. PROCESS VALIDATION PROTOCOL OF THYROXINE SODIUM TABLETS 100MCG IP

3.1.1. OBJECTIVE

The objective of this concurrent process validation of manufacturing process is to generate documented evidence that the method of manufacturing THYROXINE SOIDIM TABLETS 100 produces acceptable quality product in three consecutive batches.

3.1.2. SCOPE

✓ This process validation is prepared with an aim of providing factual information on concurrent process validation during manufacturing of Thyroxine Sodium Tablets 100 MCG.

3.1.3. RESPONSIBILITY

✓ To execute validation study of manufacturing procedure and to record the data obtained.

✓ To design the study, inscribe the protocol, control the performance, and confirm the accomplishment of the records.

✓ To review and accept protocol prior to the validation study and review, to approve the data invalidation report.

3.1.4. PROCESS VALIDATION OVERVIEW

3.1.4.1. PRODUCT DESCRIPTION

Generic Name: Thyroxine Sodium Tablets IPLabel Claim.

Each uncoated tablet contains.

Thyroxine Sodium IP equ. to Anhydrous Thyroxine Sodium 100 mcgColor: Brilliant Blue Lake.

3.1.4.2. TYPE OF VALIDATIONConcurrent Process Validation

3.1.4.3. EQUIPMENTS AND MACHINES USED FOR PROCESS VALIDATION

Table 2: List of Equipment and its code.

Equipment Name	Code
Vibro Sifter	EPDB-006
Octagonal Blender	EPDB-007
Rotary Compression Machine	EPDB-008

Semi-Automatic Tablet Counting and Filling Machine	EPDB-010
Cap Sealing Machine	EPDB-011
Disintegration Tester	EPDB-012
Automated Tablet Friabilator	EPDB-013
Vernier Caliper	EPDB-014
Hardness Tester	EPDB-015
Moisture Balance	EPDB-016
Leak Test apparatus	EPDB-017
Electronic Balance	EPDB-021

3.1.5. VALIDATION APPROACH AND OVERVIEW

3.1.5.1. PROCESS

- ✓ Critical processes and their variables are identified in the whole process and the corresponding test points are correlated.
- ✓ The processing parameters and values of the evaluation parameter are generated from actual processing and analysis of the materials, intermediate and bulk as well as finished products atdifferent stages as listed under critical parameter identification and acceptance criteria.
- ✓ All required critical parameters and values of validation test points shall be recorded in individual data record form.

3.1.5.2. ANALYTICAL TEST

- ✓ Samples shall be analyzed as listed in the test points in the protocol according to standardanalytical procedure.
- ✓ Additional confirmatory tests if desired by the validation team can be done.
- ✓ Physical analysis shall also be carried out in the IPQC in the production under the supervision of a validation team member.

3.1.5.3. EVALUATION

- ✓ All the reports and data shall be attached.
- ✓ Perform all necessary calculations and statistical analysis (pre-determined).
- ✓ All data are correlated with respect to acceptance criteria and a conclusion will be drawn if the processes described with their allowed variation are suitable for achieving the product quality with consistency.

3.1.6. PRODUCT/BATCH INFORMATION

3.1.6.1. GENERAL

Generic Name: Thyroxine Sodium Tablets IP

Label claim

Each uncoated tablet contains

Thyroxine Sodium IP equ. to Anhydrous Thyroxine Sodium 100 mcg Color: Brilliant Blue Lake

Batch Size: 2.0 Lakh Tablets (18.00 kg)

Product Dosage Form: Tablet (uncoated)

3.1.6.2. QUANTITATIVE COMPOSITION

The following table lists the ingredients' batch requirements as well as the product composition.

Table 3: Batch composition and formula.

S.N.	Material	Std.	mg/ tab	% Composition	kg/ batch
1	Thyroxine Sodium	IP	0.100	0.11	0.02
2	Mannitol	IP	35.25	39.17	7.05
3	Microcrystalline Cellulose PH 102	IP	50.000	55.56	10.00
4	Croscarmellose Sodium	IP	3.600	4.00	0.72
5	Magnesium Stearate	IP	0.900	1.00	0.18
6.	Brilliant Blue Lake	IHS	0.15	0.17	0.03
	Total uncoated tablet		90.000	100.00	18.00

3.1.6.3. QUALITY CONTROL SPECIFICATION OF THE PRODUCT/INTERMEDIATES

Table 4: Product Specification.

S. No.	TESTS	SPECIFICATION
1.	Description	Product: Light blue colored, round, biconvex uncoated tabletwith smooth surface on both sides.
		Primary Packing: PET bottle containing 120 tablets
2.	Identification	In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference/working standard solution.
3.	Average Weight	90mg ± (7.5%)
4.	Weight variation	Max: +7.5% of Average Weight
		Min: - 7.5% of Average Weight
5.	Thickness	2.5mm – 2.9 mm
6.	Hardness	Not Less Than 20N
7.	Friability	Not More Than 1%
8.	Disintegration	Not More Than 15 minutes
9.	Uniformity of Content	Not Less Than 85% and Not More Than 115% of the stated amount of *Thyroxine Sodium.*
10.	Dissolution	Not Less Than 70%(D) of the stated amount of *Thyroxine Sodium.*

11.	Assay	Not Less Than 90.0% & Not More Than 110.0% (90 mcg–110 mcg) of stated amount of *Thyroxine Sodium*.

3.1.6.4. PROCESS FLOW CHART

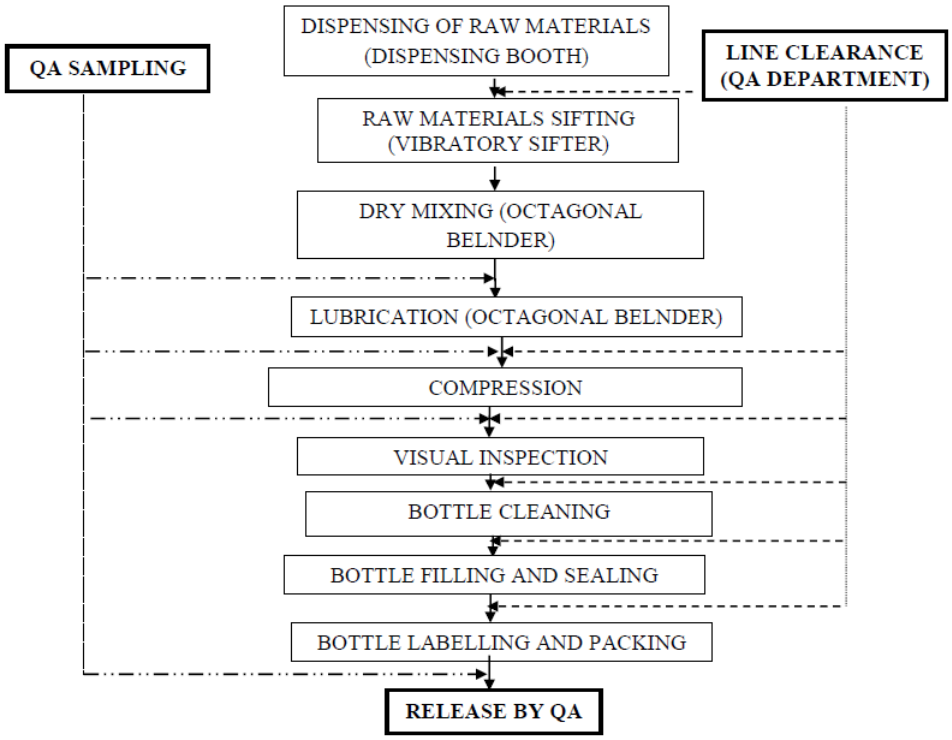

Fig 1: Process flow chart.

3.1.6.5. PROCESS DESCRIPTION, IDENTIFICATION OF CRITICAL PARAMETERSAND TESTING POINTS

The manufacturing processes as identified in the flow chart are detailed below along with theingredients and equipments involved.

Table 5: Process Description and Identification of critical parameter.

Steps	Process and Starting materials	Equipment	Critical Parameters	Testing Points
A. Geometrical Mixing	Thyroxine sodium 0.02 KgSieved through 100 mesh. Mixed geometricallywith Mannitol	-Manual Operation -Sieves	-Sieves used - Particle size and Bulk Densityof Mannitol -Pre-mixing time	- Bulk density
B. Mixing	The following materials are charged in Octagonal Blender and allow mixing for15 min at 15 RPM	Octagonal Blender 50 Liters	-Blender speed -Mixing time -Order and	-Assay of Thyroxine sodium after running the mixer for 5,10

	-Blend of mannitol and Thyroxine sodium -MCCP PH 102 -CroscarmelloseSodium -Brilliant BlueLake		placement of the ingredients -Bulk density of the ingredients -Particle size of the ingredients	and 15 min Moisture content Bulk Density of Excipients Bulk density of mixed powder
C. Lubrication	Magnesium stearate pre-sieved from mesh #80 is charged inOctagonal Blender Along with the blendfrom Step B and mixed for 5 minutes at20 RPM	Blender	- Compositionof lubricant - Mixing time	- Moisture Content -Sieve analysis from mesh #60 andmesh #100 -Bulk Density andCarr's Index - Assay of Thyroxine sodium after running the mixer for 2 and 5 minutes
D.Compression (Tableting)	The lubricated granules are compressed into tablets at 90 mg per tablet using Die (RDI 001B), Upper Punch (RUP 001B), and Lower Punch (RLP 001B) Set of 6 mm in rotary tablet press.	27 station Rotary Punching machine	-Machinemakes -Machinespeed -Tabletingtools -Compression force	-Friability -Hardness -Disintegration time -Thickness -Individual wt.variation -% Yield -Capping and sticking -Dissolution -UoC -Assay
E. Packing	The compressed tablets from the compression stage	-Tablet Counting and filling machine	- tablet count	-Filled bottle wt. variation -Tablet count -Leak test -Assay

3.1.7. ACCEPTANCE CRITERIA

The criteria for the acceptance of the test values identified above are tabulated below.

Table 6: Acceptance Criteria.

A	Assay of mixed powder for the content of Thyroxine sodium	90% - 110 % of theoretical Statistical Acceptance Criteria for Assay: CpK>1
B	Moisture Content of dried granules	1.5 % – 2.5 %
C	Sieve analysis of lubricated granules from mesh # 60 and # 100	60 fines: 75 – 90 % 100 fines: 55 – 75 %
D	Assay of lubricated powder for the Thyroxine sodium	90% - 110 % of theoretical RSD NMT 5% All individuals are within ±10% of the mean
E	Moisture Content of lubricated granules	Not more than 3.5 %
F	Granules flow from the hopper and intothe turret	Smooth flow of granules almost like fluid, with no noise and squeaking should be observed in the rotary tablet press during compression
G	Individual Weight Variation (% deviation from average)	± 7.5%
H	Hardness (N)	Not less than 20
I	Friability (%)	Not more than 1.0%
K	Assay of Thyroxine Sodium % (Bulk)	90% - 110 % of theoretical Statistical Acceptance Criteria for Assay: CpK>1
L	Uniformity of Content (Thyroxine sodium)	85% - 115% of theoretical
M	Disintegration Time (min)	Not more than 15 minutes
N	Sticking on the die/punch	No sticking
O	Average Thickness (mm)	2.5 mm – 2.9 mm
P	The tendency of common tableting problems like Capping, picking, and sticking	No capping and sticking
Q	Leak	Nil
R	Assay of Thyroxine Sodium % (Finished)	90% - 110 % of theoretical Statistical Acceptance Criteria for Assay: CpK>1
S	Bottle Pack	Good appearance and integrity

3.1.8. SAMPLING PLAN

Table 7: Sampling Plan.

Sample	Sample description	Quantity	Remarks
A	Powder from premixing	1g	Assay
B	Powder from mixing (in blender)	1gm x 9 x 3 5gm x 3	Thyroxine Sodium Assay following 5, 10, and 15 minutes of blender operation 1. from the bottom (Threesamples) 2. from mid-depth (Three samples) 3. from the top (Three samples) -Moisture analysis of top, Mid, andBottom
C	Lubricated granules	5gm x3 50 gm	Moisture analysis top, Mid, and Bottom For sieve analysis (sample not to be discarded)

		2g x 3 x 2	Assay of Thyroxine sodium after running the blender for 2 and 5 min 1. from bottom 2. from mid-depth 3. from top
D	Compressed tablets	Qs	As per IPQC practice and /or usual practice during product sampling at 10 RPM, 15 RPM, and 20 RPM. (Samples must be drawn from a running condition after all adjustments have been done).
E	Packed tablets	Qs	As per IPQC practice and /or usual practice during product sampling.

3.1.9. DATA ANALYSIS AND REPORTING

All the generated data are analyzed and evaluated in the light of product quality and applicable specifications, references. Correlation of the processing parameters and variables with the product parameters will be done to estimate the best possible processing parameters to produce the required product quality consistently with minimum of deviation and difficulties in the processing. Statistical approach (RSD, CpK) should be used as far as possible to the interpretation of the data.

3.1.9.1. INTERPRETATION OF THE RESULTS AS VALIDATION OUTCOME

On the basis of generated data and its analysis, conclusion will be drawn to establish the suitability of the material or processes. Some part of the result may be in the form of suggestion for modification or may be recommendation for repeating certain part of the validation activity.

3.1.10. REVALIDATION CRITERIA

In the following situations, the validation will no longer be valid and must be repeated (in wholeor in part).

- ✓ If the equipment used in the manufacture of Thyroxine Sodium Tablets 100 MCG has beenchanged.
- ✓ If there is change in the formulation or packing of the product and manufacturing procedure.

4. RESULT AND DISCUSSION

4.1.BLENDING

Table 1: Observed physical parameters in blending stage.

BATCH NO.	022.010	022.011	022.012
Date	02.08.2022	03.08.2022	04.08.2022
Sieve size	#60, #80 and #100	#60, #80 and #100	#60, #80and #100
Total Mixing Time (min:sec)	15:00	15:00	15:00
RPM	15	15	15
Load size (kg)	17.82	17.82	17.82
Bulk Density (g/ml)	0.422	0.4483	0.4354

Table 2: Observed assay parameter in blending stage.

Blending Time	Sampling Point	Limit : 90%-110% of Label Claim Content (%) of Thyroxine in				Cpk (NLT 1)
		022.010	022.011	022.012	Average	
5 minutes	Top right	99.81	100.7	101.2	101.436	2.24026
	Top left	100.32	101	102.99		
	Top centre	102.4	100.9	103.6		
	Middle Right	102.82	100.96	100.15	101.824	1.19291
	Middle Left	105.36	101.49	98.33		
	Middle Centre	105.06	101.81	100.44		
	Bottom Right	100.79	101.09	101.76	101.508	2.89493
	Bottom Left	103.31	101.77	100.82		
	Bottom Centre	100.55	100.72	102.76		
10 minutes	Top right	99.03	101.45	100.06	100.501	2.48464
	Top left	98.08	101.1	100.29		
	Top Centre	101.45	101.04	102.07		
	Middle Right	98.71	101.17	99.77	100.401	3.03964
	Middle Left	101.4	101.72	99.6		
	Middle Centre	100.8	101.06	99.38		
	Bottom Right	99.85	101.18	103.58	100.849	2.19735
	Bottom Left	99.23	101.12	101.04		
	Bottom Centre	98.94	101.33	101.29		
15 minutes	Top right	100.02	101.22	100.07	100.432	4.93617
	Top left	99.65	101.07	100.07		
	Top Centre	99.84	101.38	100.57		
	Middle Right	99.09	101.28	99.85	100.744	3.0303
	Middle Left	101.34	101.33	100.01		
	Middle Centre	100.09	101.48	102.26		
	Bottom Right	99.85	101.26	101.03	100.964	3.58903
	Bottom Left	102.78	101.28	100.47		
	Bottom Centre	100.2	101.09	100.72		

OBSERVATION

Bulk density of the blended powder was uniform among three batches indicates that the blending process has proved to be consistent among the batches. The Process Capability

Index (Cpk) calculated for all the three consecutive batches during every 5 minutes interval for total time of 15 minutes dry mixing stage are within the specification limits (i.e Cpk is more than 1). Hence optimum dry mixed powder can be achieved if the same dry mixing process parameters are maintained for routine production batches.

4.2.LUBRICATION

Table 3: Observed physical parameters in lubrication stage.

BATCH NO.	022.010		022.011		022.012	
Date	02.08.2022		03.08.2022		04.08.2022	
Sieve size	#60, #80 and #100		#60, #80 and #100		#60, #80 and #100	
Total Mixing Time (min:sec)	5.00		5.00		5.00	
RPM	20		20		20	
Load size (kg)	18:00		18:00		18:00	
Bulk Density (g/ml)	0.457		0.49		0.439	
Tapped density (g/ml)	0.529		0.583		0.520	
Carr's Index %	13.63%		16.00%		15.625%	
Retention %	#60:	11.603%	#60:	10.747%	#60:	10.907%
	#100:	29.988%	#100:	29.005%	#100:	29.464%
Passing %	#60:	88.396%	#60:	89.525%	#60:	89.092%
	#100:	70.011%	#100:	70.994%	#100:	70.535%

Table 4: Observed assay parameter in lubrication stage.

Lubrication Time	**Sampling Point**	**Limit : 90% - 110% of the Label Claim Content (%) of Thyroxine in**		
		022.010	022.011	022.012
2 minutes	Top	104.11%	101.38%	100.79%
	Middle	107.18%	101.86%	102.17%
	Bottom	106.90%	103.02%	102.93%
Average		106.09%	102.09%	101.96%
RSD (NMT 5%)		1.62%	0.83%	1.06%
5 minutes	Top	105.39%	103.75%	102.17%
	Middle	104.72%	105.65%	103.38%
	Bottom	103.86%	105.62%	100.33%
Average		104.66%	105.01%	101.96%
RSD (NMT 5%)		0.73%	1.04%	1.51%

OBSERVATION

The Carr's Index calculated for all the three consecutive batches during lubrication stage are within the specification limits. The Relative Standard deviation (RSD) calculated for all the threeconsecutive batches during lubrication stage are within the specification limits (i.e RSD is less than 5%). Hence optimum lubricated granules can be achieved if the same lubrication process parameters are maintained for routine production batches.

4.3.COMPRESSION

Table 5: Observed physical parameters in compression stage.

Batch no.	RPM	HopperLevel	Tests					
			Avg. Weight (90 mg)	Wt Variation (±5%)	Hardness (NLT 20N)	Thickness (2.5 mm – 2.9 mm)	Disintegration Time (NMT 15 Minutes)	Friability (NMT 1%)
022.010	10	Full	89.95	Complies	54.5	2.81	1 minute 51 seconds	0.08%
		Half	89.95	Complies				
		Low	88.2	Complies				
	15	Full	90.35	Complies	51.78	2.80	1 minute 43 seconds	0.05%
		Half	89.4	Complies				
		Low	88.9	Complies				
	20	Full	89.95	Complies	54.21	2.82	1 minute 52 seconds	0.05%
		Half	90.05	Complies				
		Low	89.4	Complies				
022.011	10	Full	89.85	Complies	54.016	2.80	1 minute 32 seconds	0.05%
		Half	90.2	Complies				
		Low	89.85	Complies				
	15	Full	89.9	Complies	51.8	2.81	1 minute 28 seconds	0.00%
		Half	89.85	Complies				
		Low	90.2	Complies				
	20	Full	89.90	Complies	53.76	2.80	1 minute 27 seconds	0.03%
		Half	89.80	Complies				
		Low	89.70	Complies				
022.012	10	Full	89.95	Complies	55.1	2.80	59 seconds	0.13%
		Half	89.95	Complies				
		Low	89.3	Complies				
	15	Full	89.75	Complies	51.8	2.82	1 minute 35 seconds	0.05%
		Half	89.25	Complies				
		Low	89.55	Complies				
	20	Full	89.95	Complies	53.8	2.80	1 minute 22 seconds	0.02%
		Half	89.65	Complies				
		Low	90.25	Complies				

Table 6: Observed assay and Uniformity of content (UOC) parameters in compression stage.

Test			Assay	UOC	Statistical Acceptance Criteriafor Assay: CpK >1
Acceptance Criteria			NLT 90% and NMT 110 % of the label Claim	NLT 85% and NMT 115% of the stated amount ofThyroxine Sodium	
Batch No	022.010	10 RPM	101.18	106.29%-113.93%	21.113
		15 RPM	100.97	105.68%-114.61%	
		20 RPM	100.91	103.78%-113.86%	
	022.011	10 RPM	101.15%	101.28%-112.11%	7.586
		15 RPM	100.63%	101.98%-111.06%	
		20 RPM	101.4%	100.94%-109.16%	

	022.012	10 RPM	100.7%	101.71%-113.20%	10.068
		15 RPM	100.91%	102.61%-109.25%	
		20 RPM	101.29%	103.87%-112.76%	

OBSERVATION

The physical attributes of the compressed tablets for all three batches lies within the specified range when the tablets are compressed in the speed of 10 RPM, 15 RPM and 20 RPM. The Process Capability Index (Cpk) calculated for all the three consecutive batches compressed at 10 RPM, 15 RPM and 20 RPM lies within the specification limits (i.e Cpk is more than 1). Hence, optimum compressed tablet can be achieved if the RPM of Compression machine is maintained from 10 RPM to 20 RPM for routine production batches.

4.4.PACKING

Table 7: Observed physical parameters in packing stage.

S.N.	022.010		022.011		022.012	
	Wt. of filled bottles (gm)	No of tablets/bottle	Wt. of filled bottles (gm)	No of tablets/bottle	Wt. of filled bottles (gm)	No of tablets/bottles
1.	20.051	120	20.051	120	20.051	120
2.	20.050	120	20.053	120	20.052	120
3.	20.049	120	20.048	120	20.049	120
4.	20.048	120	20.054	120	20.046	120
5.	20.051	120	20.049	120	20.052	120
6.	20.050	120	20.054	120	20.058	120
7.	20.052	120	20.051	120	20.054	120
8.	20.048	120	20.055	120	20.053	120
9.	20.051	120	20.053	120	20.052	120
10.	20.052	120	20.049	120	20.053	120
11.	20.052	120	20.054	120	20.052	120
12.	20.047	120	20.054	120	20.054	120
13.	20.052	120	20.058	120	20.053	120
14.	20.044	120	20.049	120	20.051	120
15.	20.053	120	20.054	120	20.049	120
16.	20.054	120	20.051	120	20.054	120
17.	20.049	120	20.046	120	20.052	120
18.	20.052	120	20.051	120	20.055	120
19.	20.049	120	20.052	120	20.055	120
20.	20.052	120	20.050	120	20.049	120
21.	20.049	120	20.052	120	20.052	120
22.	20.053	120	20.051	120	20.056	120
23.	20.049	120	20.053	120	20.049	120
24.	20.051	120	20.049	120	20.055	120
25.	20.049	120	20.046	120	20.053	120
26.	20.052	120	20.051	120	20.055	120
27.	20.051	120	20.052	120	20.051	120

28.	20.050	120	20.053	120	20.047	120
29.	20.055	120	20.052	120	20.051	120
30.	20.051	120	20.049	120	20.052	120
31.	20.052	120	20.051	120	20.055	120
32.	20.053	120	20.052	120	20.053	120
33.	20.051	120	20.051	120	20.051	120

Table 8: Observed assay parameter in packing stage.

Test	Acceptance Criteria	010.004	010.005	010.006
Assay	NLT 90 % and NMT 110 % of the stated amount of Thyroxine Sodium.	104.381 %	104.954%	103.87%
Statistical Acceptance criteria for Assay of 3 batches RSD (NMT 5%) Cpk > 1		RSD = 0.549%Cpk = 3.266s		

Observation

The Relative Standard Deviation and Process Capability Index calculation for inter batch finished product lies within the specified range (i.e RSD is less than 5% and Cpk is more than 1) for three concurrent validation batches. Hence optimum finished tablets can be achieved if the same processsing parameters are maintained for routine production batches.

5. CONCLUSION

Process validation of Thyroxine Sodium Tablets was conducted for a batch size of 100000 tablets, which included the validation of critical steps of manufacturing such as blending, compression and packing. All the physical and analytical parameters observed were within the specified limits. The RSD and Cpk value calculated for assay and UOC parameters at various stages of manufacturing lies within the specification limits. Hence, desired tablets can be achieved if same processing parameters are maintained during routine batch production.

REFERENCES

1. Lieberman, H.A., Lachman, L., Schwartz, J.B., Pharmaceutical Dosage Forms: Tablets, Volume 1, 2nd Edition, Edition, Marcel Dekker Inc, Newyork, 195-229.
2. Aulton M. E., Pharmaceutics The Science of Dosage Form Design, 2nd Edition, Churchill Livingstone, 398: 365 – 374.
3. *trs1019-annex3-gmp-validation.pdf*. (2019). Annex 3 Good manufacturing practices: Guidelines on validation. Retrieved November 25, 2022, from https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf

4. Abraham, J. (2010). International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use. In *Brill | Nijhoff eBooks* (pp. 1041–1053). https://doi.org/10.1163/ej.9789004163300.i-1081.897
5. Analytical Procedures and Methods Validation for Drugs and Biologics. (2015). *FDA*.
6. *Process-Validation--General-Principles-and-Practices*. (2016, November 21). Guideline on Process Validation for Finished Products - Information and Data to Be Provided in Regulatory Submissions. Retrieved November 25, 2022, from https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-process-validation-finished-products-information-data-be-provided-regulatory-submissions_en.pdf.
7. Vaja, M. D., Patel, B. D., Patel, K. K., & Chaudhary, A. (2021). A Review on process validation of solid dosage form. *Journal of Drug Delivery and Therapeutics*, *11*(4): 157–160. https://doi.org/10.22270/jddt.v11i4.4880
8. The Four Types of Process Validation - Kneat. (n.d.). Kneat. Retrieved November 26, 2022, from https://kneat.com/article/the-four-types-of-process-validation/
9. *LEVOXYL® Clinical Pharmacology (levothyroxine sodium) | Pfizer Medical Information - US*. (n.d.). LEVOXYL® Clinical Pharmacology (Levothyroxine Sodium) | Pfizer Medical Information - US. Retrieved November 27, 2022, from https://www.pfizermedicalinformation.com/en-us/levoxyl/clinical-pharmacology
10. Levothyroxine: Uses, Interactions, Mechanism of Action | DrugBank Online. (2005, June 13). Levothyroxine: Uses, Interactions, Mechanism of Action | DrugBank Online. Retrieved November 26, 2022, from https://go.drugbank.com/drugs/DB00451
11. Levothyroxine - Wikipedia. (2020, February 22). Levothyroxine - Wikipedia. Retrieved November 26, 2022, from https://en.wikipedia.org/wiki/Levothyroxine
12. Umed A., Abhijit V., V. R., C. S. An Overview of Pharmaceutical Process Validation of Solid Dosage Form. Journal of Current Pharma Research, 2013 Feb 15; 3(2): 824–35. Available from: http://dx.doi.org/10.33786/jcpr.2013.v03i02.006
13. Curry SH, Gums JG, Williams LL, Curry RW, Wolfson BB. Levothyroxine Sodium Tablets: Chemical Equivalence and Bioequivalence. Drug Intelligence & Clinical Pharmacy, 1988 Jul; 22(7–8): 589–91. Available from: http://dx.doi.org/10.1177/106002808802200715
14. Obinna E, Martin M, Syed Ali 1, Remigius U A.Levothyroxine Sodium – An Overview of Challenges Related to Interchangeability and Stability of Different Formulations.

Journal of Endocrinology and Thyroid Research, 2021 May 17; 6(1). Available from: http://dx.doi.org/10.19080/jetr.

15. Collier JW, Shah RC, Bryant A, Habib MJ, Khan MI, Faustino PJ. Development and application of a validated HPLC method for the analysis of dissolution samples of levothyroxine sodium drug products. Journal of Pharmaceutical and Biomedical Analysis, 2011 Feb 20; 54(3): 433–8. Available from: https://doi.org/10.1016/j.jpba.2010.08.025
16. Karthik S, Kumar PA, Kulkarni SV, Babitha S. Concurrent process validation of Ramipril tablets. 2011 Aug 1; Available from: https://www.researchgate.net/publication/292110989_Concurrent_process_validation_of_Ramipril_tablets
17. Patil PB, Chatap VK, More MP, Khan ZG. Prospective Process Validation Study of Glibenclamide 2.5 mg Tablets. Current Research in Pharmaceutical Sciences, 2018 Jul 8; 8(2): 224–33. Available from: http://dx.doi.org/10.24092/crps.2018.080201
18. Aleem HA, Zhao YB, Lord SD, McCarthy T, Sharratt PN. Pharmaceutical process validation: An overview. Proceedings of the Institution of Mechanical Engineers, Part E: Journal of Process Mechanical Engineering, 2003 May 1; 217(2): 141–51. Available from: https://doi.org/10.1243/095440803766612801
19. Bonthagarala B, Ch S, Sai PDL, Sivaiah KV. Process validation: An essential process in pharmaceutical industry. International Journal of Advances in Scientific Research, 2015 May 30; 1(4): 179. Available from: https://doi.org/10.7439/ijasr.v1i4.1781
20. Alam S, Pradesh H. Pharmaceutical Process Validation: An Overview. Journal of Advanced Pharmacy Education & Research, 2012 Jan 1; 2(4): 185–99. Available from: http://www.japer.in/doc/oct%20des%202012/74.pdf
21. Sai Kiran A. Dara, Ravi N. Tiwari. Pharmaceutical Process Validation: An Industrial Perspective.Research Journal of Pharmacy and Technology, July 2014; 7(7): 810-814.
22. Shahin.Mohammad, K.Ayeshabegum, P.Sandhya. Process Validation for Aceclofenac 100mg and Paracetamol 500mg Tablets. International Journal of Thesis Projects and Dissertations, 2018 Dec; 2(4): 43–56.
23. S LPandian, Tnk S, Ruckmani K, Thirumurugan R. Concepts of Process Validation in Solid Dosage Form [Tablet] – An Overview. Scholarena Journal of Pharmacy and Pharmacology [Internet], 2014 Aug 16; 1(1). Available from: https://doi.org/10.18875/2375-2262.1.103

24. P. Kiruba Rachel et al. Process Validation of Extended Release Bi-Layered Tablet Containing Metformin, Pioglitazone and Glimipiride. Journal of Pharmacy Research, 2017; 11(2): 146-155.
25. Rohokale BS, Jadhav VM, KadamVJ. Studies in Prospective Process Validation ofMetformin HCl Tablet Dosage Formulation. International Journal of PharmTech Research, 2018 Jul; 2(3): 1673–78.
26. Popatbhai PH, Shrivastava AK, Dinesh J. Process Validation of Benazepril HCl 5 mg Tablet. International Research Journal of Pharmaceutical and Applied Sciences [Internet], 2012 Aug 31; 2(4): 1–16. Available from: https://scienztech.org/index.php/irjpas/article/view/299.
27. Mishra G, Thakur A, Kaur S. Process Validation of Metformin Hydrochloride Tablet (500 mg) according to USFDA. Biological Sciences, 2022 Jan 1; 01(01): 27–37. Available from: https://doi.org/10.55006/biolsciences.2021.1102
28. Xun M, Guo H, Cui Q, Zhang G, Feng ZR, Gui L, et al. Process validation and in vitro-in vivo evaluation of rosuvastatin calcium tablets. Drug Development and Industrial Pharmacy, 2022 Apr 3; 48(4): 140–45. Available from: https://doi.org/10.1080/03639045.2022.2101061.
29. Pandey P, Anju G. Process Validation of Pharmaceutical Dosages Form: A Review. Biomedical Journal of Scientific and Technical Research, 2017 Oct 25; 1(5): 1467–75. Available from: https://doi.org/10.26717/bjstr.2017.01.000463.
30. Sharma C, Rana A, Bala R, Seth N. An overview of industrial process validation of tablets. Journal of Drug Delivery and Therapeutics [Internet], 2013 May 15; 175–83. Available from: https://doi.org/10.22270/jddt.v3i3.489.
31. Nidhi Aswal, Pallavi Joshi, Alka N. Prospective Validation of Paracetamol Tablet Dosage Form. International journal of pharmaceutical and chemical sciences, 2013 sep; 2(3): 1416-25
32. *Process-Validation--General-Principles-and-Practices*. (2013, May 2). Process Validation: General Principles and Practice. Retrieved November 25, 2022, from https://www.fda.gov/files/drugs/published/Process-Validation--General-Principles-and-Practices.pdf
33. *Draft Annex 15 - V12 200115 - for PICS and EC adoption*. (2015, March 30). EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Retrieved November 25, 2022, from https://health.ec.europa.eu/system/files/2016-11/2015-10_annex15_0.pdf

34. *GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEX 15* *. (2015, April 13). Pharmaceutical Inspection Convention. Retrieved November 26, 2022, from https://picscheme.org/users_uploads/news_news_documents/ps_inf_11_2015_pics_gmp_revised_annex_15.pdf
35. Process validation (Continuous process verification) for finished products - Pharmaceutical Guidance. (2021, December 2). Pharmaceutical Guidance. Retrieved November 26, 2022, from https://pharmaguidances.com/continuous-process-verification/
36. Eghtedari, B., & Correa, R. (2022, September 4). *Levothyroxine - StatPearls - NCBI Bookshelf*. Levothyroxine - StatPearls - NCBI Bookshelf. Retrieved, November 27, 2022; from https://www.ncbi.nlm.nih.gov/books/NBK539808/