RESEARCH ARTICLE

Formulation and evaluation of levothyroxine sodium tablets (low dose high potent drug substance) using rapid mixer technology to achieve content uniformity

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ABSTRACT:

The objective of this study is to prepare an immediate release tablet formulation of levothyroxine sodium, with which is a narrow therapeutic index drug having low dose, using rapid mixing technique to enhance content uniformity and attain formulation robustness. Blend operation was optimised and compared using an octagonal blender and a rapid mixing granulator with blending duration of 10, 20, and 30 minutes as the process variable. The 30th minute mix of Rapid Mixing Granulator was used to manufacture an tablet by direct compression method. The formulation was tested for various post and precompression parameter evaluations. It demonstrated that the formulation powder mix has good flow properties. The disintegration of all the formulated tablets were also determined and the average disintegration time is obtained which is 5 minutes and 18 seconds, proved to be better release profile of levothyroxine sodium.It was determined that the formulation of tablet of thyroid hormone (T4) improved and ensured content uniformity.

KEYWORDS: Levothyroxine sodium, Blend uniformity, Octagonal blender, Rapid Mixing Granulator, Process optimization.

INTRODUCTION :

Orally administered drugs are considered optimal if they have a long biological half-life, high bioavailability, low clearance, and short elimination half-life because the drug delivery system without the rate controlling properties provided by the above, such as coatings, etc., are generic and is adapted to, eg, dissolve quickly and release the drug. The goal of oral delivery strategies, including those for our synthetically-derived drug candidate, is to obtain rapid onset of pharmacological effect. Although its low-dose, high-strength drug product candidate is not yet approved by the FDA, it could be used for the treatment of hypothyroidism, which is the most common endocrine disease and can produce varying rates and degree of response that includes weight gain, fatigue, sensitivity to cold, depression, and in some instances, myxedema and the most extreme cases can result in death[1].

The dose of active ingredient present in the dosage unit of a low-doses drug product can be in the range of a few micrograms. The amount of excipients (carrier) divided by the amount of drug can be from 1000-10000 which is in sharp difference with the standard drug mixture. The composition of the formulation can have a distinct effect on drug product quality including uniformity, stability, potency, disintegration, apart from above all also is in within limit. When formulated at low-dose, common blend errors may result in marked potency variability (high RSD), outliers (stray values) in blend samples or final product assay. It says that large within-location variation in blend data will indicate poor mixing, sampling error, segregation and lumps, large particle size of the drug, and analytical error. Extreme variations in data between locations in the blend can indicate inadequate mixing[2].

A low-dosed medication has a large level of excipients in comparison to the drug per weight unit. But there is a lack of an in-depth characterisation and control of excipient quality. In the past, not much effort has been made to establish consensus methods of characterizing pharmaceutical excipients, and accurate databases and prediction links for excipient properties commonly used are still scant. Certain material properties will affect dosage form, amount of excipient, and method of manufacture. generally, the impact of excipient decreases significantly, when present at a lower level except for a few exceptions like lubricant and glidant[3].

After developing a blending/sampling method, verify and correlate the uniformity results of the powder blend with in-process stratified dosage unit data taken during filling of capsules or compressing tablets. Next is a comparison of the theoretical normal distribution and RSD of graded in-processing dosage unit samples. Grab a further seven dosing/dose units at key process points e.g. when the hopper is switched, filled or the machine is turned down and at the point in which the compression or fill operation begins and ends[4].

MATERIALS AND METHODS:

Materials

Table 1. Instruments used

S. No.	Name of the Instrument	Model
1	Weighing Balance Sartorius	Sartorius
2	Analytical Balance	Essae
3	Rapid Mixer Granulator	Anchor Mark
4	Blender	Anchor Mark
5	Tapped Density Apparatus	Electrolab
6	Compression Machine	Cadmach
7	Hardness tester	Electrolab
8	Friabilator	Electrolab
9	Vernier Callipers	Mitutoyo
10	Disintegration apparatus	Electrolab
11	High Pressure Liquid Chromatography	Waters

Table 2. Chemicals used

S.No.	Chemicals and reagents	Grade	Manufacturer
1	Levo Thyroxine Sodium	AR	Iscochem Laboratories
2	Microcrystalline cellulose	AR	Nice Chemicals
3	Starch	AR	Nice Chemicals
4	Acacia	AR	Iscochem Laboratories
5	Sodium citrate	AR	Nice Chemicals
6	Magnesium stearate	AR	Iscochem Laboratories
7	Hydrochloric acid	AR	Nutan Chemicals
8	Acetonitrile	AR	Antares ChemPvt.Ltd.
9	Sodium Hydroxide	AR	Hirdaan Pharma Chem.
10	Orthophosphoric acid	AR	Vinipul Inorganics Pvt.Ltd.
11	Sulphamic acid	AR	Pure Chemicals Co.
12	Methanol	AR	N/A

Pre-Formulation study :

Physical Description / Organoleptic properties:
a) Description: Determine the drug under magnifying lens for the determination of its physical form.
b) Organoleptic properties: Examine a small amoount of sample in well lighted place[5].

Flow Characteristics
In order to formulate dosage form, it was necessary to determine the following precompression parameters such as Hausner's ratio, bulk density, tapped density, compressibility index, and angle of repose[6].

Method of formulation of Levothyroxine Sodium tablet:

The processing of drug products was mostly achieved through by direct compression method, this method can be defined as basically mixing and processing of formulation ingredient then compressed into tablets.

Table 3. Formulation of Levo Thyroxine Sodium tablet

S. No.	Ingredients	mg/tab	% Comp.
Blending			
1	Levothyroxine Sodium	0.10	0.10
2	Microcrystalline cellulose 102	59.50	59.50
3	Starch	34.40	34.40
4	Acacia	1.00	1.0
5	Sodium citrate	4.00	4.0
Lubrication			
6	Magnesium stearate	1.00	1.00
Total weight of Tablet		100.00	100.00

Formulation 1- method of preparation

1. Co-Sift API and Microcrystalline cellulose pass through sieve No.40 and collect in container separately.
2. Co-sift Maize starch, Sodium citrate and Acacia through No.40 sieve and collect separately.
3. Sift Magnesium Stearate passed through sieve No.60 and collect in separate container.
4. Pre-mixing: Transfer co-sifted drug substance and microcrystalline cellulose (step 1) into the blender.
5. Add co-sifted Maize starch, Acacia, and Sodium citrate (step 2) to the blender (step 4).
6. Mix the blend for 30 min at 20 RPM (Collect the pre-mix samples at intervals of 10 min, 20 min and 30 min).
7. Put the sifted Magnesium stearate to the prepared blend mix and start the mixing operation for 3 min at 20 RPM.

Formulation 2- method of preparation

1. Microcrystalline cellulose and API were co-sifted after passing through sieve No. 40 and gather in appropriate container.
2. Co-sift Maize starch, Sodium citrate and Acacia through No.40 sieve and collect in container separately.
3. Sift Magnesium Stearate passed through sieve No.60 and collect in separate container.
4. Transfer step 1 collected into the Rapid mixer granulator (RMG).
5. Add step 2 collected to the Rapid Mixer Granulator (RMG) (step 4).
6. Mix the blend for 30 min with the settings in table, (Collect the pre-mix samples at intervals of 10 min, 20 min and 30 min)
7. Lubrication: Add Magnesium stearate to the above mix (step 9) and continue mixing for 3 min with the settings (Table).

Table 4. Blender Settings

S. No.	Stage	Mixing Time	Blender RPM
1	Pre-mixing	30 Sec	20 ± 1
2	Mixing	20 min	20 ± 1
3	Lubrication	03 min	20 ± 1

Table 5. RMG Settings

S. No.	Stage	Mixing Time	Impeller RPM
1	Pre-mixing	30 Sec	64 ± 1
2	Mixing	20 min	64 ± 1
3	Lubrication	03 min	64 ± 1

8. Compression: Compress the prepared blend with the machine settings mentioned in Table 6[7].

Table 6. Machine Settings

S. No.	Details	Parameters
1	Average weight	100 mg
2	Punch size	6.5 mm, round shaped, SC Punches

Post Compression Study / Physicochemical Evaluation :

I) Physical Evaluation

a) Description

Place about 20 tablets of sample aliquots on clean dry petridish. Record colour, size and nature of medicine.

b) Average weight

Calculate the average weight of 20 tablets that were chosen at random. Note the weights and report them.

c) Uniformity of weight

This test is used to check that the weight of each medicine is uniform and remains between the specified limits. It is done by selecting and weighing 20 tablets and calculating the Mean weight. The Mean and standard deviation were calculated and no more than two individual weights deviated from the average weight by more than the percentage.

d) Thickness

Calibrate the Vernier calliper and ensure the value is "0.00 mm", when the moveable and immovable jaws of Vernier calliper are in contact. Place the tablet vertically between jaws and note the value as measured.

e) Hardness

Insert the tablet horizontally in the jaws of a calibrated hardness tester.Allow the tablet to be crushed and note the crushing strength in "Newton."

f) Friability

Weigh 20 tablets randomly for the test. For 4 minutes, place the tablets in Friabilator and allow the apparatus to rotate at 25 rpm speed. Take out the tablets and dust after four minutes. The percentage of friability (limit: not more than 1 percent) was then calculated by weighing the tablets.

g) Disintegration test

Firstly, six dose units should be placed, one in each of the tubes of the basket containing disc. The equipment should then be adjusted to 37 ± 0.5C, using water as the immersion fluid. Take the basket from the immersion medium and evaluate the dose units: each has dissolved entirely. If one or two of the tablets do not fully dissolve, then perform the test with 12 more tablets. The criteria is satisfied when at least 16 of the 18 tablets tested are disintegrated[8].

II) Chemical Evaluation

a) Assay

To find the assay percentage, take the mean of 10 tablets from the test for uniformity of the tablets.

b) Uniformity of Dosage unit

Preparation of Diluent (0.05M NaOH): Dissolve 2 g of Sodium hydroxide Pellets into 1000mL water.

Preparation of Mobile phase:

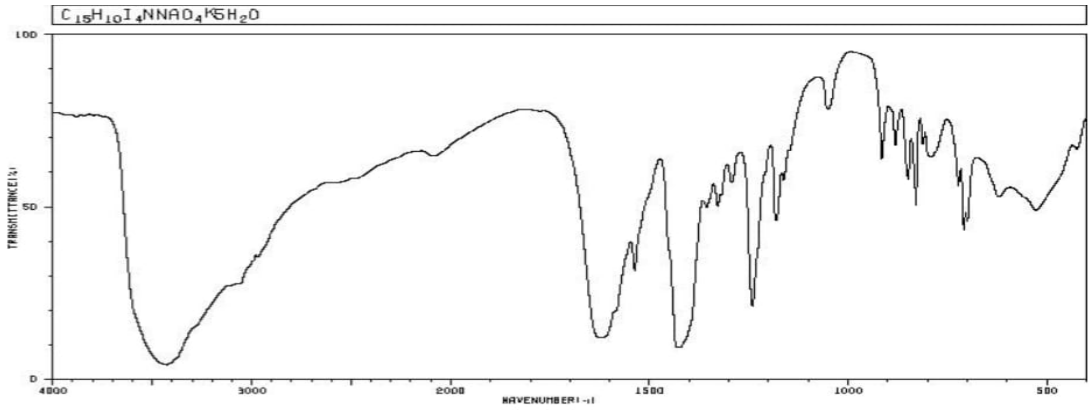
Mix 5 volumes of orthophosphoric acid, 300 volumes of acetonitrile, and 700 volumes of water thoroughly, then degas.

Preparation of Standard solution:
Weigh accurately and transfer about 20 mg of API working standard into a 200 mL volumetric flask add 150 mL of diluent and sonicate for 10 minutes to dissolve the content, then make up to the volume with diluent and mix well. Pipette out 2 mL of the above solution into 50 mL volumetric flask and make up to the volume with diluent and mix well. **(Conc. :**4 µg/mL of API)
Preparation of Sample solution:
Add one tablet into 25 mL volumetric flask add about 16 mL of diluent, mix with the aid of ultrasound until the tablet is fully dispersed, cool and shake for 2 minutes. Makeup volume with diluent and mix well. Filter through glass microfiber filter (Whatman GF/C is suitable) and use the filtrate. (**Conc.:** 4 µg/mL of API).**Note:** Repeat the procedure for tablets.
Procedure:
Inject 20 µL of diluent as Blank, Standard solution and Sample solution using below chromatographic conditions and record the area of Levothyroxine sodium peak.
Column : Waters Spherisorb (or) Discovery CN (250x4.6) mm - 5µm
Flow rate : 1 mL/minute
Detection wavelength : 225 nm
Run time : 20 minutes

c) Packing Details
Ensure that the tablets are packed in blister pack containing PVC/PVDC as base foil and Aluminium as lidding foil in 1 x 10's configuration. Confirm the blister pockets are in line with the filled tablets with minimum gap to avoid moisture pickup during storage[9].

RESULTS AND DISCUSSIONS:
Materials
Drug substance
The findings from the FT-IR spectroscopy indicated that the FT-IR spectrum of levothyroxine was similar to the spectrum of Sumatriptan. Compatibility studies were conducted by FT-IR spectroscopy, found to be significant because the study of the FT-IR spectrum of pure drug and physical mixture of drug and polymer showed character is absorption peaks for Sumatriptan at 4000 - 500cm^{-1} . So it appears that there are no chemical interactions between Sumatriptan and polymer's used. It was observed that peaks which were obtained in spectra drugs and polymers.

Figure 7. FT- IR spectrum of pure drug



Excipients
Excipients for the manufacturing of proposed low dose potent tablets was selected based on the excipients used in the reference product. Below table indicates the specific functions of selected excipients.

Table 7. Selection of Excipients

Ingredients	Function
Levo Thyroxine sodium	Active
Microcrystalline cellulose	Diluent
Maize Starch	Disintegrant
Acacia	Binder
Sodium citrate	Alkalizer
Magnesium stearate	Lubricant

Chemicals and Reagents

All chemicals and reagents used for evaluation of the drug substance and excipients were of analytical grades only. Distilled water were used for the dilution of buffer and other solutions present in the formuation.

Equipment

All equipment used for the processing of proposed low dose potent tablets were well calibrated. In-process accessories like scoops and containers were made delicately to avoid dusting of powders in the inner walls. Additionally, dispensing of API were done using an air tight black poly bag to avoid exposure during the transport process.

Pre-Formulation Study :

The organoleptic characteristics and solubility of the medication were used to characterise the API. It was essential to determine the identify of the drugs obtained before to beginning the research study. The first step in the study is to characterize these properties, which aids in both identifying the drug substance and estimating the likelihood of patient compliance.

Physical description / Organoleptic properties

The initial step in identifying a drug substance involves assessing its physical characteristics, such as organoleptic properties. Alterations in the color or smell of a raw material within a formulation can offer rapid insights into the formulation's stability. Investigation of colour, odour and nature were assessed and tabulated below,

Table 8. Investigation of colour, odour and nature

Colour	A nearly white or slightly brownish-yellow colour.
Nature	Crystalline powder with a mild hygroscopicity
Odour	Odourless

Precompression study:

Flow characteristics

In many pharmaceutical operations such as blending, compression, filling, flow properties of powders have an utmost importance and the data obtained for flow and consolidation properties of a proposed placebo blend was evaluated and summarized in Table 9.

Table 9. Flow and consolidation properties

S.No.	Parameters	Mean (±SD)	Flow
1	Bulk density	0.406 g/Ml	N/A
2	Tapped Density	0.540 g/Ml	N/A
3	Compressibility Index	24.814	Passable
4	Hausner’s ratio	1.330	Passable

From the flow consolidation study, which indicates that the placebo blend has acceptable (passable) flow behaviour. The observed BD (0.406 g/mL) and TD (0.540 g/mL) of the placebo blend indicates that the tablet weight and proposed 6.5 mm punch are feasible to proceed. Compressibility index and Hausner's ratio was passable as the observed values were within the passable range 21-25 and 1.26 - 1.34 respectively. However, by considering the passable values and the degradable nature of API in heat, light and moisture, formulation process was chosen to be in direct compression method in order to maintain the existing flow property.

Formulation & Development :

Process Optimization (blender):

The blend was mixed for 10 minutes at 20 rpm in the octagonal blender. Samples were taken from five locations for the purpose of assessing the consistency of the mixture.The blend was allowed to continue blending for another 10 minutes at 20 rpm and samples at 20 min were collected from 5 locations to evaluate the uniformity of blend. The blend was allowed to continue blending for another 10 minutes at 20 rpm and samples at 30 min were collected from 5 locations to evaluate the uniformity of blend.

Table 10. Blending (blender)

Formulation (F1)	**Limits**	**Time (min)**		
Blending/Mixing	N/A	**10**	**20**	**30**
Results	N/A	**Observation**		
Location 1	90-105%	90.9	99.4	97.8
Location 2		93.6	99.4	99.5
Location 3		104.6	88.9	96.4
Location 4		89.7	90.7	92.9
Location 5		102.9	93.6	100.7
Blend Assay		96.34	94.40	97.46
Blend uniformity	%RSD (±5%)	7.20	5.15	3.10

From the above study(F1), 10 and 20 minutes of blending time at 20 RPM was found to be not meeting the limit of blend assay (90-105%) and blend uniformity (%RSD ±5%) respectively. Hence, it is evident that the blending time of 30 minutes is essential to achieve the limits of blend assay and blend uniformity.

Process Optimization (RMG):

Samples (10 min) were taken from five locations to assess the blend's homogeneity after the prepared blend was loaded into the RMG and mixed for 10 minutes at an impeller RPM of 64± 1. The blend was allowed to continue mixing for another 10 minutes at impeller RPM 64± 1and samples (20 min) were collected from 5 locations to evaluate the uniformity of blend.The blend was allowed to continue mixing for another 10 minutes at impeller RPM 64± 1 and samples (30 min) were collected from 5 locations to evaluate the uniformity of blend.

Table 11. Mixing (RMG)

Formulation (F2)	**Limits**	**Time (min)**		
Blending/Mixing	N/A	**10**	**20**	**30**
Results	N/A	**Observations**		
Location 1	90-105%	99.1	99.5	99.1
Location 2		99.6	96.9	100.2
Location 3		99.2	98.9	99.7
Location 4		96.9	99.2	99.2
Location 5		99.7	98.5	98.9
Blend Assay		98.90	98.60	99.42
Blend uniformity	% RSD (±5%)	1.16	1.03	0.53

From the above study (F2), 10, 20 and 30 minutes of mixing time at 64 RPM was found to be meeting the limit of blend assay (90-105%) and blend uniformity (%RSD ±5%) respectively. However, mixing time of 30 minutes was optimised since there is no significant variation observed between the samples taken at different location.

Post Compression Study / Physicochemical Evaluation

I) Physical Evaluation

Table 12. Physical Evaluation

Parameters	Specification	F1	F2
Description	Off white coloured, circular shaped uncoated tablets.		
Average weight (mg)	92.5 – 107.5	101.60	100.50
Thickness(mm)	3.3 – 3.7	3.36	3.38
Hardness(N)	40 – 100	60-90	55-95
Friability (%)	NMT 1.0	Nil	0.09
DT (min)	NMT 15	3'10" -4'30"	4'40" -5'18"

II) Chemical Evaluation

a) Assay

The assay of the drug in formulation F1 and F2 was found to be 89.80 % and 99.78% respectively and was within the limits recommended by official monograph (90 -105 %).

b) Uniformity of Dosage unit:

Compressed tablets of 30 minutes samples of F1 and F2 was evaluated for content uniformity and interpreted from the below data.

Table 13. Uniformity of Dosage unit

Tablet	Limit	Blender (F1)	RMG (F2)
1	Assay 90-105%	91.0	99.4
2		88.7	99.4
3		89.4	100.9
4		89.8	102.7
5		88.9	100.8
6		90.1	97.8
7		89.6	96.7
8		89.2	96.4
9		90.2	99.7
10		90.6	103
-	Avg.	89.8	99.7
-	AV NMT 15	10.5	5.4

From the above data, RMG mixing time (F2) of 30 minutes at 64 rpm was optimised since the Assay and Content uniformity of the proposed process was found to be 99.7 % and AV – 5.4 respectively. So, further chemical tests were performed only for the formula (F2).

c) Packing Details

Packing material: Aclar-Alu Blister

Pack size: 1 x 10's

d) Determination of Short-term Stability Study

The stability studies were performed for 1 month and evaluated the samples for the alteration in physical and chemical nature of the drug.

Table 14. Short term stability results

S. No.	Tests	Initial	1st Month(40±2°C/75±5%RH)
1	Description	Off white coloured, circular shaped uncoated tablets.	
2	Assay (%) – 90.0 to 105.0	99.78	97.8
3	Content uniformity AV (NMT15)	5.4	6.2

Results of the study reveal, the tested parameters were within the limits Even there is stability up to 1st Month. Therefore, it could be assumed that the formulated tablet would be stable throughout the stability period.

Comparison of physical characteristics

Table 15. Comparison of F1 and F2

Parameters	Test (F1)	Test (F2)
Description	Off white coloured, circular shaped uncoated tablets.	Off white coloured, circular shaped uncoated tablets.
Thickness (mm)	3.36	3.38
Diameter (mm)	6.5	6.5
Hardness (N)	60-90	55-95
Disintegration time (min)	3’10” -4’30”	4’40” -5’18”
Assay (%)	89.80	99.78
Content uniformity (AV)	10.5	5.4
Packing material	PVC/PVDC-alu Blister	PVC/PVDC-alu Blister
Packing configuration	Pack size: 1 x 10’s	Pack size: 1 x 10’s

SUMMARY AND CONCLUSION:

SUMMARY

The objective was to design a cost effective immediate release tablet equivalent to BP standards. Two primary goals were established to develop a stand-alone formulation of a highly potent molecule and to overcome poor distribution of low-dose drugs. The characterization of the drug product by organoleptic features, were the first studies that were performed and were they intended to evaluate the physico-chemical aspect of the drug, and if there are some sensory analyses that can change the form of patient administration. Poor flow of the powder was indicated from flow and consolidation tests. This was based on the fact that API was degradable in the presence of heat, light, and moisture and that it was possible to optimize the process using an RMG at defined mixing times. Tablet examination confirmed that the physical parameters, content uniformity at several time points, and assays were within specification. Short term stability studies were carried out at room temperature and 40°C/75% RH for one month, giving satisfactory results within the specified limits.

CONCLUSION :

Therefore, the Adopted and optimized process in adding of API and excipients may be considered as a promising method for the uniform mixing of low dose formulations, based on our research results. For processing, optimal room temperature and controlled humidity ensure prolonged product stability. In general, the developed formula for the conventional tablets of high potency low dose molecule was well evaluated and the process was shown to be quite flexible for the homogeneity of content improvement. Furthermore, a low cost and quality product may be provided to patients that is comparable to BP standard.

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