

**DEVELOPMENT AND IN VITRO EVALUATION OF THYROXINE SODIUM SUSTAINED
RELEASE TABLETS BY USING DIRECT COMPRESSION METHOD**

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ABSTRACT

The present study aimed to develop sustained release (SR) matrix tablets of Thyroxine sodium to maintain prolonged therapeutic levels and improve patient compliance in the treatment of hypothyroidism. The tablets were prepared by direct compression technique using different concentrations of HPMC and Ethyl cellulose as matrix-forming polymers. The pre-compression parameters indicated satisfactory flow and compressibility. The formulated tablets were evaluated for hardness, friability, drug content, thickness, disintegration time, and in-vitro drug release. Among all formulations (F1–F8), formulation F6, containing Ethyl cellulose, exhibited the best performance with 98.89% drug release within 8 hours, following zero-order kinetics and fitting well with the Higuchi diffusion model. FTIR studies confirmed no significant interaction between the drug and excipients. Stability studies conducted at room temperature, 30°C/75% RH, and 40°C/75% RH for 90 days revealed no significant change in physical or chemical properties. The study concludes that sustained release matrix tablets of Thyroxine sodium using Ethyl cellulose can effectively control drug release, offering a promising approach for long-term management of hypothyroidism.

Keywords: Thyroxine sodium, Sustained release, Matrix tablets, Ethyl cellulose, HPMC, Direct compression, In-vitro drug release.

INTRODUCTION

Oral drug delivery remains the most preferred and convenient route of administration due to its simplicity, patient compliance, and cost-effectiveness. However, conventional dosage forms often require multiple daily administrations to maintain therapeutic plasma concentrations, which can lead to fluctuations in drug levels, poor compliance, and reduced therapeutic efficacy.¹ To overcome these limitations, sustained release (SR) matrix tablet systems have been developed to deliver the drug at a controlled rate, maintaining uniform plasma concentration for a prolonged period while minimizing side effects.² Thyroxine sodium, a synthetic form of the thyroid hormone thyroxine (T₄), is widely prescribed for the treatment of hypothyroidism, a chronic endocrine disorder characterized by decreased production of thyroid hormones.³ Conventional immediate-release formulations of thyroxine sodium often necessitate strict dosing schedules due to its short half-life and variable absorption profile. Consequently, the development of a sustained release dosage form can offer improved pharmacokinetic control, enhanced bioavailability, and greater patient adherence.⁴ The present study was designed to formulate and evaluate sustained release matrix tablets of Thyroxine sodium using HPMC and Ethyl cellulose as release-retarding polymers.⁵ The objectives included assessing pre- and post-compression parameters, in-vitro drug release profiles, kinetic modeling of release data, and stability studies of the optimized formulation. The ultimate goal was to develop a stable, effective, and patient-friendly sustained release oral dosage form of Thyroxine sodium capable of maintaining consistent therapeutic levels for extended periods.

MATERIALS

Thyroxine sodium was procured from Hetero Labs, HYD. HPMC and Ethyl cellulose was obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY

FTIR Spectroscopy

The range of FTIR is basic proof giving satisfactory details of the compound. FTIR technique gives a range containing a significant figure of the absorption band as of which information can be deduced

about the design of an organic compound. The pellets were produced using 10 mg drug and 100 mg dry potassium bromide powder blend, compacted by using the pressure of 10 tons with a hydraulic press to yield a transparent pellet. The thin pellet was positioned in a pellet disk to obtain IR spectra (Shimadzu 84005).⁶

Formulation Development

Table-1: Formulation of SR Tablets

S.NO.	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
1	Thyroxine sodium	25	25	25	25	25	25	25	25
2	HPMC	25	50	75	100	-	-	-	-
3	Ethyl cellulose	-	-	-	-	25	50	75	100
4	MCC	20	20	20	20	20	20	20	20
5	Lactose	125	100	75	50	125	100	75	50
6	Magnesium stearate	3	3	3	3	3	3	3	3
7	Talc	2	2	2	2	2	2	2	2
8	Total Wt.	200	200	200	200	200	200	200	200

Preparation method

Thyroxine sodium sustained release tablets were prepared by direct compression method as per the formulae given in Table. All the materials required as per the formulae were blended in a closed polyethylene bag. The blends were compressed into tablets on a tablet punching machine to a hardness of 6 kg/cm² using 8 mm concave punches.⁷



Fig-1: Tablet punching machine

EVALUATION PARAMETERS

Hardness

Hardness of all eight preliminary batches determined by Monsanto tester. From the six determinations, the average is considered as “hardness factor”⁸



Fig-2: Pfizer hardness tester

Thickness

Thickness and diameter of tablets were accurately measured by using digital Vernier caliper for desired uniformity in size and shape.⁹

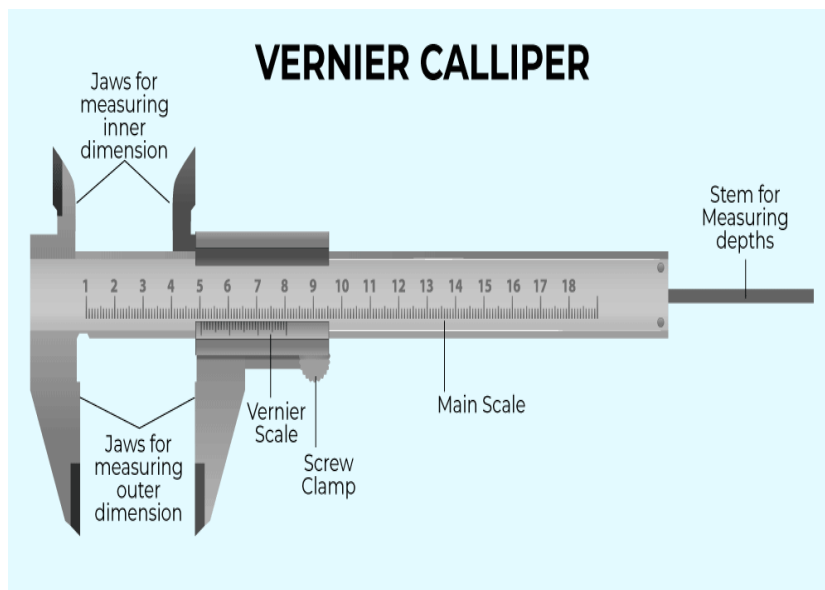


Fig-3: Vernier calliper

Uniformity of weight

All preliminary batches were evaluated for the weight variation test by individually weighing all the final twenty batches selected for the study. Weight obtained from the resolved tablet. Finally, individual and average weights were compared with each other. Differences in the case of percentage variation in weight ought to be between 7.5% of the acceptable limit. Finally determined the % deviation using the below formulae¹⁰

$$\text{Deviation (\%)} = \frac{\text{Weight (individual)} - \text{Weight (average)}}{\text{Weight (average)}} \times 100$$

Friability test

Friability of batches (preliminary) was performed with Roche Friabilator (Kumar Mfg. Ltd.). Combine weighed 10 tablets and placed inside the friability. Turned on the stabilator with the rate of 25 rpm.

Tablets permitted rolling inside the friabilator, and coming about since free tablet falling inside the chamber. Following 100 revolutions per 4 minutes, samples were taken it out, and tablets intact were weighed again collectively.¹¹ Allowed friability limit is 1.0 %. The friability in percent was resolved to utilize the below formulae.

Friability = $100 \times \frac{\text{tablet weight (before weight)} - \text{tablet weight (after test)}}{\text{Tablet weight (before the test)}}$



Fig-4: Friability apparatus

Drug content

Drug content of every single primer group is resolved to choose arbitrarily twenty tablets though effectively determined normal of loads. Tablets crushed utilizing a mortar and exactly ordinary checked proportion of tablets, chose triturate for examination. Tests moved into different flagons though adequately weakened using pH 6.8 phosphate buffer. The substance was shaken well and put something aside for 30 minutes for dissolving the prescription completely. Mixes were isolated and weakenings were appropriately done. In each tablet, the substance of medication was assessed to 283 nm λ_{max} close by looking at reference as a reference.¹²

In Vitro Disintegration Test

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.¹³



Fig-5: Disintegration Apparatus

In- Vitro Release study

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for remaining period of time. Temperature maintained at 37⁰ C. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The solution was filtered through Whattmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (Labindia). The drug release was plotted against time to determine the release profile of various batches.¹⁴



Fig-6: Dissolution apparatus

Drug release kinetics¹⁵

To examine the release pattern from the tablets the release statistics were investigated using accompanying models of mathematics:

A. Kinetic (0 order)

$$Q_0 = Q_t + k_0t$$

Whereas, the release of drug at the time (t) - Q_t Constant for zero-order release - k_0 Amount of drug present at $t = 0$ - Q_0

B. Kinetics (1st order)

$$\ln(100 - Q) = \ln Q_0 - k_1t$$

Whereas, the release of drug at time t - Q Initially drug present - Q_0 Constant of 1st order release - K_1

C. Equation of Higuchi

$$Q = k_H t^{1/2}$$

Whereas, drug release amount at t - Q, Dissolution constant of Higuchi - K_H

D. Model of Korsmeyer - Peppas

$$Q = kP^n$$

Whereas,

KP is steady including geometric and structural attributes of the device of release. Mechanism of demonstrative release exponent 'n'.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared sustained release Matrix tablets of Thyroxine sodium were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, $40 \pm 2^\circ\text{C}$ and refrigerator $2-8^\circ\text{C}$ for a period of 90 days.¹⁶

RESULTS AND DISCUSSION

FT-IR Spectrum of Thyroxine sodium

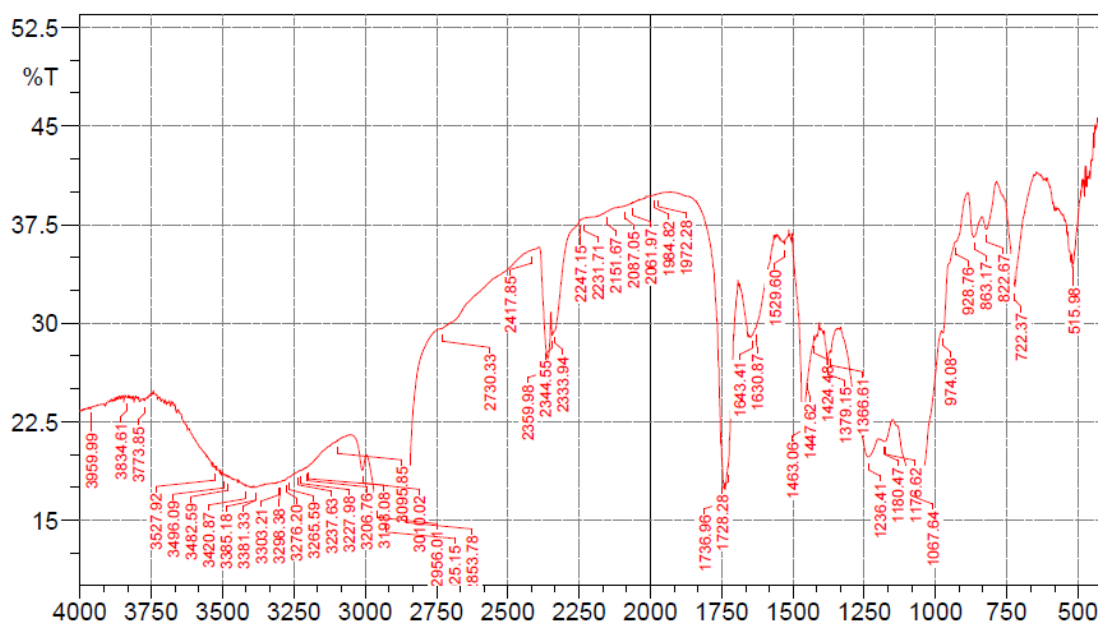


Fig-7: FTIR Spectra of Thyroxine sodium

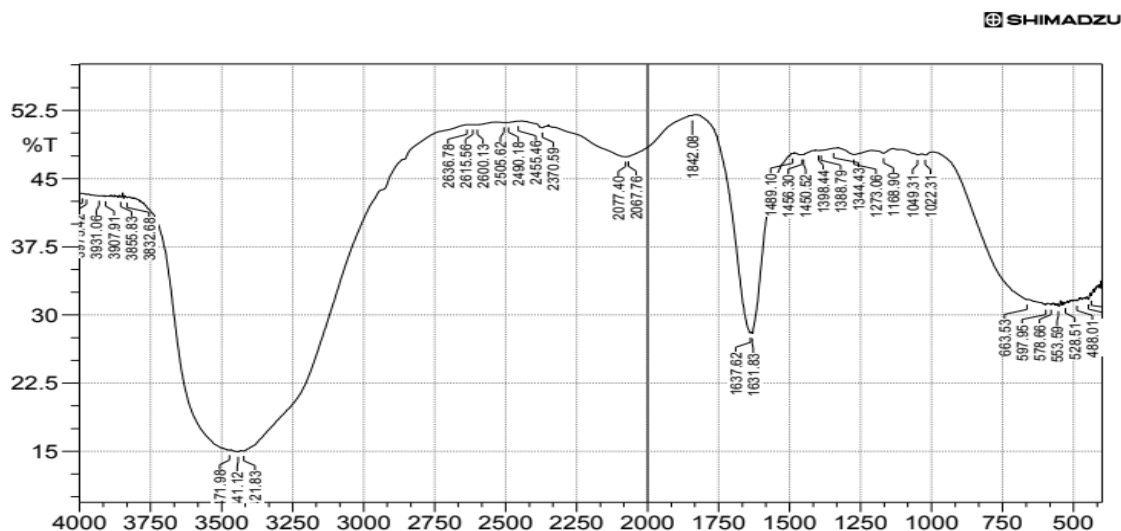


Fig-8 : FT-IR graph for optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks was obtained as above and as they were in official limits ($\pm 100 \text{ cm}^{-1}$) the drug is compatible with excipients.

EVALUATION PARAMETERS

Weight variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of $\pm 7.5\%$ of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 2.8 mm to 3.5 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 3.9 to 4.9 kg/cm^2 . This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F8 was found to be between 78.63 % to 84.23 % of Thyroxine sodium, it complies with official specifications.

Disintegration Time:

In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods.

Table-2: Evaluation parameters of Thyroxine sodium SR tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)	Disintegration time (min)
F1	200	3.2	4.2	0.29	78.63	14
F2	199	2.9	3.9	0.30	80.12	17
F3	200	3.4	4.5	0.27	79.63	13
F4	201	3.3	4.3	0.25	81.55	12
F5	200	3.1	4.7	0.22	82.25	10
F6	199	2.8	4.6	0.26	84.23	09
F7	200	2.6	4.9	0.27	79.85	13
F8	200	3.5	4.1	0.26	78.22	12

Dissolution studies

All the 8 formulation of Thyroxine sodium tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-3: Drug release studies of all formulations

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	16.38	17.36	18.12	19.65	17.56	19.77	17.55	18.11
2	24.59	25.12	24.97	25.32	28.10	29.68	26.30	27.46
3	36.32	35.49	34.50	35.69	36.93	37.82	38.10	35.55
4	55.10	54.28	55.82	57.83	58.42	59.66	55.49	56.33
5	64.37	65.37	66.93	67.98	68.42	69.55	65.55	62.25
6	71.21	70.13	72.36	73.65	74.56	75.86	76.30	75.84
7	84.56	82.34	83.69	84.53	85.82	86.12	82.69	83.55
8	94.25	93.64	95.82	96.82	97.55	98.89	96.22	95.82

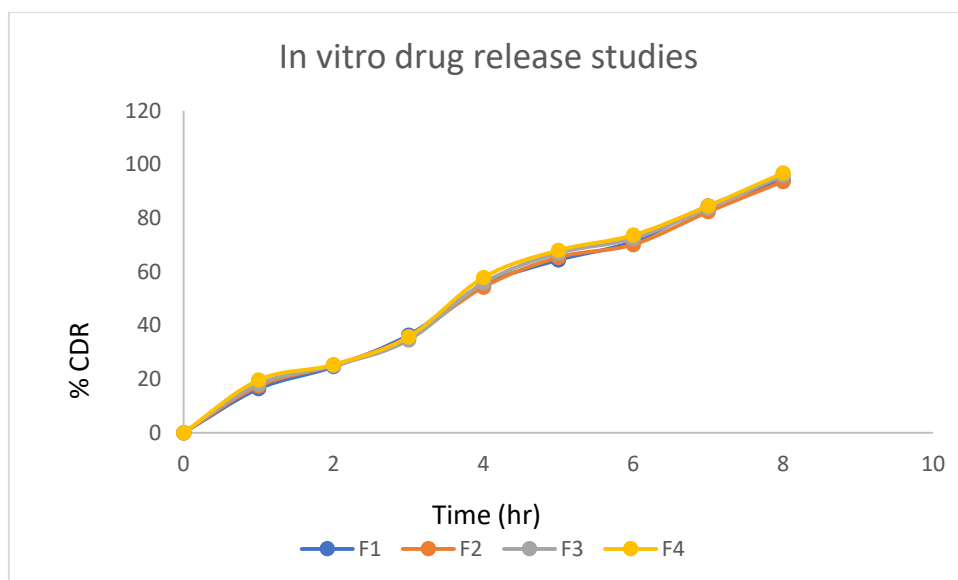


Fig-9: Dissolution Profile of F1 to F4 formulations

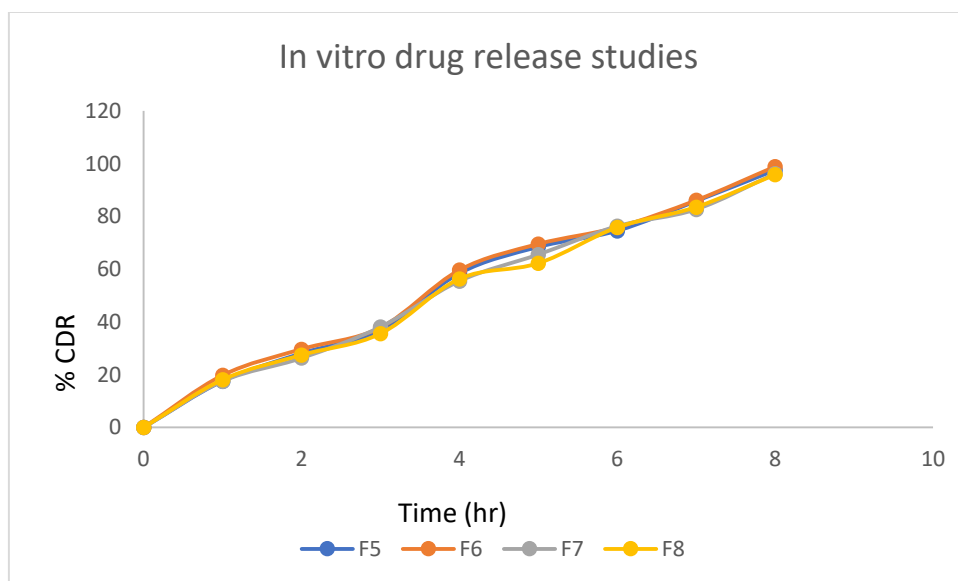


Fig-10: Dissolution Profile of F5 to F8 formulations

Cumulative Drug release of F6 formulation shows 98.89 % within 8 hr. better drug release when compared with other formulations.

Kinetic modeling of drug release

All the 8 formulation of prepared matrix tablets of Thyroxine sodium were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)

Zero order kinetics

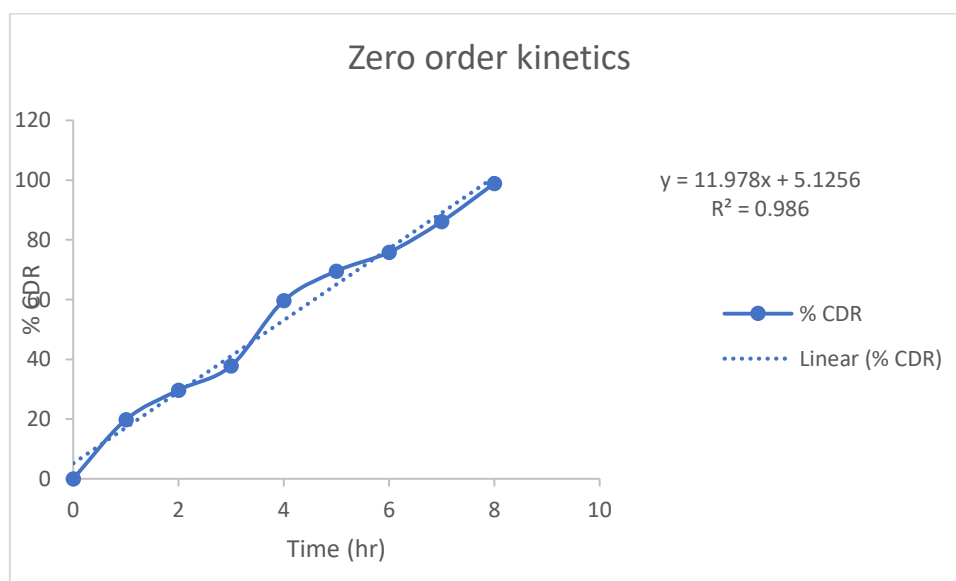
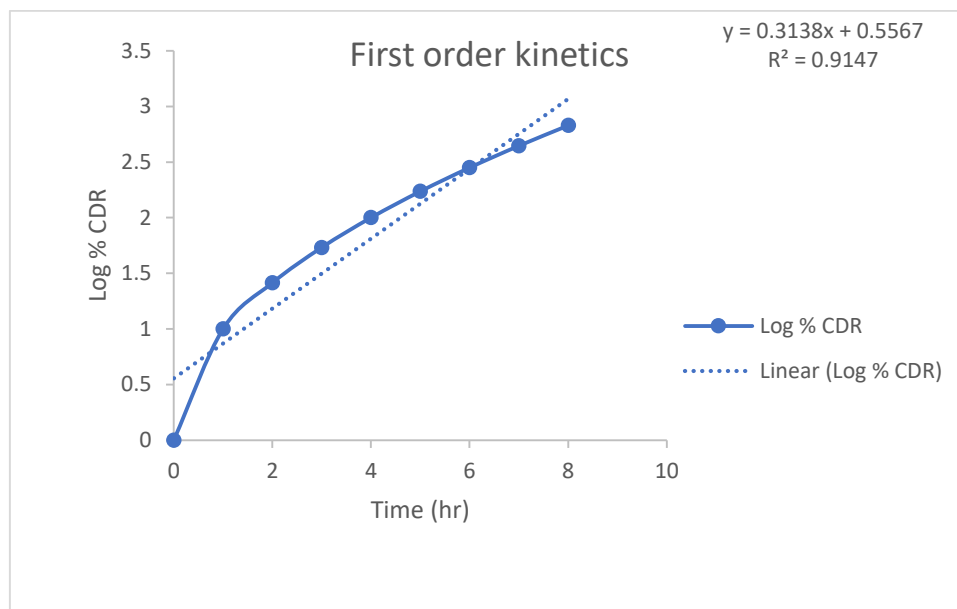
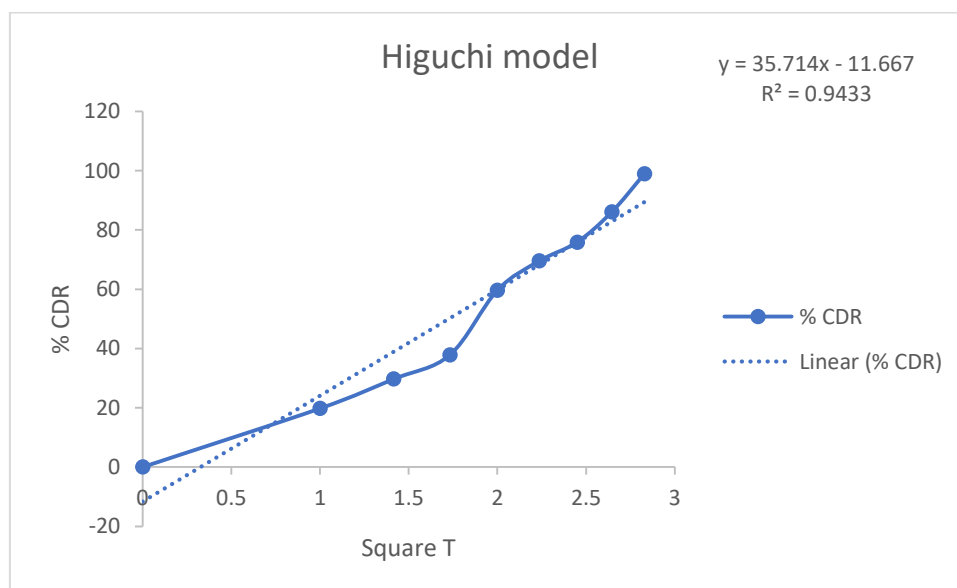


Fig-11: Zero order kinetics of optimized formulation

First order kinetics**Fig-12: First order kinetics of optimized formulation****Higuchi model****Fig-13: Higuchi model of optimized formulation**

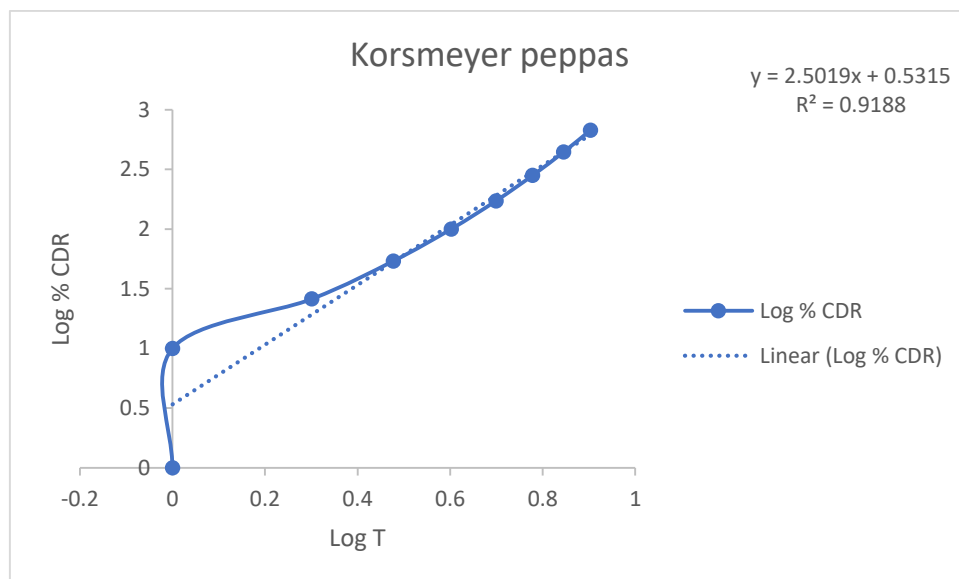
Korsmeyer peppas

Fig-14: Korsmeyer peppas of optimized formulation

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix and Peppas.

Regression values are higher with Zero order release kinetics. Therefore, all the Thyroxine sodium tablets follows Zero order release kinetics.

The table indicates that r^2 values are higher for Higuchi's model compared for all the tablets. Hence Thyroxine sodium release from all the Tablets followed diffusion rate-controlled mechanism.

Stability Study

There was no significant change in physical and chemical properties of the tablets of formulation F-6 after 90 days. Parameters quantified at various time intervals were shown.

Table-4: Stability studies of all formulations

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	25°C/60%RH % Release	98.89	97.82	96.37	95.33	Not less than 85 %
F-6	30°C/75% RH % Release	98.89	97.58	96.24	95.28	Not less than 85 %
F-6	40°C/75% RH % Release	98.89	97.60	96.25	95.25	Not less than 85 %

CONCLUSION

The sustained release matrix tablets of Thyroxine sodium were successfully developed using synthetic polymers such as Ethyl cellulose and HPMC by direct compression method. All formulations met pharmacopoeial requirements for physical parameters and drug content. The optimized formulation F6, containing Ethyl cellulose, showed a controlled and sustained release profile with 98.89% drug release in 8 hours, following zero-order kinetics and Higuchi diffusion mechanism, indicating a diffusion-controlled release process. FTIR spectra confirmed compatibility between the drug and excipients, and stability studies demonstrated that the formulation remained stable for 90 days under accelerated and room temperature conditions.

Overall, the findings suggest that Ethyl cellulose-based sustained release matrix tablets of Thyroxine sodium are a reliable and effective dosage form for maintaining consistent plasma drug levels, reducing dosing frequency, and enhancing patient compliance in the treatment of hypothyroidism.

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