

CENTRAL COMPOSITE DESIGN WITH BCS CLASS-I ANTI-EPILEPTIC DRUG USING *IN VITRO* FLOATING DEVELOPMENT AND OPTIMISATION

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Abstract

Levetiracetam (Lev) is a widely used antiepileptic drug known for its excellent solubility and permeability. The present study aimed to statistically optimize the formulation of gastro-retentive floating tablets using Design-Expert software. A central composite design (CCD) was employed to evaluate the effects of three independent variables: Methocel K100M Premium (X1), Methocel K15M Premium (X2), and cetostearyl alcohol (X3). The prepared tablets were assessed for swelling–erosion behavior, buoyancy, dissolution characteristics, and drug release kinetics. Comparisons were made between the optimized formulation, formulation F9, and the marketed tablet (Levipil, manufactured by Sun Pharma). Additional analyses included response surface plots and counter plots. The order of drug dissolution among the tested formulations was as follows: F13 > F1 = F3 = F5 = F6 = F8 = F10 = F11 = F15 > F7 = F12 > F2 = F9 > F4 = F14. The marketed tablet achieved 100% drug release within 10 min, while formulation F13 and the optimized formulation released 100% of the drug in 7.0 h and 9.5 h, respectively. The optimized formulation followed zero-order release kinetics and exhibited non-Fickian diffusion (diffusion exponent = 0.54), indicating a controlled and sustained release mechanism. These findings demonstrate that the optimized gastro-retentive floating tablet is well suited for extended-release delivery of Lev. The optimized formulation was further validated through statistical analysis, confirming that it met all dissolution criteria and theoretical predictions.

Keywords: Extended Release; Floating; *In vitro*; Levetiracetam; Optimization

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Introduction

Levetiracetam (Lev), an antiepileptic drug (AED), exhibits high permeability and high solubility, consistent with the characteristics of Biopharmaceutics Classification System Class I drugs. Several studies have reported on the use of Lev in combination therapy involving two or more AEDs, highlighting clinically significant drug interactions (Cui *et al.*, 2019). Lev has also been used in combination with anticonvulsants as adjuvant therapy for partial, myoclonic, and tonic-clonic seizures. The development of new formulations has been shown to potentially improve patient compliance with oral therapy (Paliwal *et al.*, 2016). Formulations containing various ratios of croscopovidone and croscarmellose sodium have been evaluated for product quality assurance (Gunda *et al.*, 2019). Extended-release tablets incorporating hydroxypropyl methylcellulose (HPMC) K100, HPMC K15, and ethyl cellulose have also been developed (Challa and Madhuri, 2022). For individuals with partial-onset seizures, the Food and Drug Administration has approved Lev as an adjunct to other AEDs. Sustained-release matrix tablets of Lev have been developed using hydrophilic polymers such as HPMC as release-retarding agents (Ulloa *et al.*, 2009; Sonmezturk and Azar, 2011; Hao *et al.*, 2012; Pinto *et al.*, 2019; Parimi *et al.*, 2021).

Recent investigations have explored the use of 3D printing for personalized medication manufacturing (Aita *et al.*, 2019). Studies have reported formulations combining Lev and carbamazepine for epilepsy treatment (Kandilli *et al.*, 2021), as well as the application of electronic tongue technology to develop additives for 3D-printed instant-dissolving tablets (IDTs) to enhance palatability (Wang *et al.*, 2021). Research has also evaluated 5% and 10% Lev formulations, focusing on how drug concentration affects physicochemical properties (Djekic *et al.*, 2021). A gastro-retentive patch containing Lev was developed using a simple lattice design to enhance reliability (Sivaneswari *et al.*, 2017), while colon-specific sustained-release tablets were also reported (Dangi *et al.*, 2013). The intranasal route has been investigated for direct brain delivery of Lev (Gonçalves *et al.*, 2019). A central composite design (CCD) was employed to assess the effects of three independent variables and optimize formulation parameters (Haney *et al.*, 2015). CCD has also been used to determine optimal conditions for solid lipid nanoparticle preparations incorporating α -tocopherol (de Carvalho *et al.*, 2013; Lalge *et al.*, 2019; Cui *et al.*, 2020; Bhattacharya, 2021;

Hassan *et al.*, 2020; 2021). Floating gastro-retentive drug delivery systems have been developed to prolong gastric residence time and enable sustained drug release (Challa *et al.*, 2018; Mo *et al.*, 2019; Qin *et al.*, 2018; Hu *et al.*, 2011). Various statistical studies have reported single and combined effects of independent variables on formulation outcomes, including investigations involving multiple active pharmaceutical ingredients (APIs) (Chowdary and Challa, 2011; Challa and Chowdary, 2015; Challa and Lavyna, 2015; Challa *et al.*, 2017; 2018; Challa and Jami, 2022; Challa and Madhuri, 2022b; Challa and Preethi, 2022; Challa and Reshma, 2022).

Materials and Methods

Lev was obtained as a gifted sample from Aurobindo Pharma. Methocel K100 and Methocel K15 were provided by Colorcon Asia Pvt. Ltd., Verna Industrial Estate, Verna. Cetostearyl alcohol, talc, and magnesium stearate were procured from Loba Chemie Pvt. Ltd., Mumbai. Microcrystalline cellulose was also gifted by Colorcon Asia Pvt. Ltd., Verna Industrial Estate, Verna. Hydrochloric acid was obtained from Merck Life Science Private Limited, Mumbai.

Formulation of Tablets

Tablet formulations were developed using a central composite design (Tables 1 and 2). Each tablet contained 60 mg of Lev along with sodium bicarbonate, cetostearyl alcohol, HPMC K100, and HPMC K15 in varying weight ratios. The central composite design was based on three independent variables (X1, X2, and X3), each tested at five levels: $(-)\alpha$, -1 , 0 , $+1$, and $(+)\alpha$. The corresponding levels were as follows: X1 (Methocel K100) at 91.893, 95, 102.5, 110, and 113.106 mg; X2 (Methocel K15) at 42.92, 45, 50, 55, and 57.07 mg; and X3 (cetostearyl alcohol) at 16.96, 18, 20.5, 23, and 24.03 mg. All formulations were adjusted to an average tablet weight of 300 mg by incorporating diluents such as microcrystalline cellulose (MCC 102), talc, and magnesium stearate, along with other excipients (Chowdary, 2016; Challa and Laxmi, 2024). The final blends were compressed into tablets using a rotary compression machine.

UV-Spectrophotometric Method

To prepare a 100 $\mu\text{g/mL}$ solution, 10 mL of a 1 mg/mL stock solution was transferred to a 100 mL volumetric flask and diluted with 0.1N hydrochloric acid buffer. Serial dilutions of 0.5 mL,

Table 1. Central composite design

Variable	Levels				
Code level	(-)α	(-1)	0	1	(+)α
X1: Methocel K100 M Premium (mg)	91.893	95	102.5	110	113.106
X2 :Methocel K15 M Premium (mg)	42.92	45	50	55	57.07
X3: Cetosterylalcohol (mg)	16.96	18	20.5	23	24.03
Response	Constrains		Goal		
	-	+			
X1: Methocel K 100 M (mg)	90	135	107.68		Range
X2:Methocel K15 (mg)	42	60	48.13		Range
X3:Cetosteryl alcohol X3 (mg)	16.96	25	20.25		Range
Y1: Swelling Index (%)	63.04	68.77	64.56		Range
Y2:Floatinglagtime (sec)	34.92	136	111.93		Range
Y3:%Drug release 1 h (%)	11.833	42.3	16.542		Range
Y4: %Drug release 3 h (%)	45.6	61.94	49.69		Range
Y5:T50 (h)	2.5	4.85	4.29		Range
Y6:T100	5	12	9.82		Maximize

Table 2. Coded Levels as per CCD of Gastro Retentive Floating Tablets

Formulations	X1	X2	X3
F1	0	0	0
F2	0	0	(-)α
F3	0	(+)α	0
F4	1	1	-1
F5	(-α)	0	0
F6	(-1)	-1	-1
F7	1	-1	1
F8	0	0	0
F9	(+)α	0	0
F10	0	0	0
F11	0	0	0
F12	0	0	(+)α
F13	0	(-)α	0
F14	-1	1	1
F15	0	0	0

1.0 mL, 1.5 mL, 2.0 mL, 2.5 mL, 3.0 mL, 3.5 mL, and 4.0 mL of this solution were further diluted with 0.1N hydrochloric acid buffer to obtain concentrations of 5 µg/mL, 10 µg/mL, 15 µg/mL, 20 µg/mL, 25 µg/mL, 30 µg/mL, 35 µg/mL, and 40 µg/mL, respectively. The maximum absorbance of each solution was measured at 210 nm using a UV spectrophotometer (ELICO Double Beam SL 210) (n = 6), as described by Challa and Madhuri (2022).

Characterization

Tablet preparations were evaluated for active drug content, hardness, friability, dissolution rate, swelling index, and buoyancy.

Assay

Tablet powder equivalent to 60 mg of Lev was subjected to extraction using 6×10 mL of methanol. The extract was filtered through Whatman filter paper (0.5 µm pore size). The maximum absorbance of the resulting solutions was measured at 210 nm using a UV spectrophotometer (ELICO Double

Beam SL 210) (n = 6), following the method described by Challa and Madhuri (2022).

Hardness

Tablet hardness was evaluated using a Monsanto hardness tester (Challa and Reshma, 2017). Each tablet (n = 6) was placed between the movable and stationary jaws. The screw knob was turned to apply pressure through the moving jaw until the tablet fractured. The force at the point of fracture was recorded using the scale, and the hardness was expressed in kilograms per square centimeter.

Friability

Friability was assessed using a Lab India tablet friability tester (LAB INDIA FT1020) (Chowdary and Challa, 2011). A total of 20 tablets, each weighing 300 mg ±5%, were weighed and placed into the friabilator. The drum was rotated at 25 rpm for a total of 100 revolutions over 4 min. During this process, the tablets experienced mechanical shocks from being dropped onto a plastic surface from

a height of 6 inches. After 4 min, the tablets were reweighed, and friability was calculated as a percentage of weight loss. A weight loss of less than 1% was considered acceptable according to Indian Pharmacopoeia (IP) standards.

Dissolution Study

Lev and its tablet formulations were evaluated for in vitro dissolution using a USP Type II dissolution apparatus (LAB INDIA DS 8000). The dissolution medium consisted of 0.1N hydrochloric acid buffer maintained at 37°C, with a paddle rotation speed of 50 rpm, as described by Challa and Chowdary (2015). At predetermined time intervals 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, and 7.0 h 5 mL samples were withdrawn and analyzed at 210 nm using a UV spectrophotometer (ELICO Double Beam SL 210).

In Vitro Buoyancy Study

The buoyancy of the tablets was evaluated visually in triplicate, following the method described by Challa and Lavanya (2015) and Challa and Bhavyasri, (2018). Floating lag time and total floating time were assessed using the USP dissolution apparatus containing 0.1N hydrochloric acid buffer maintained at 37±0.5 °C. Floating lag time was defined as the time required for the tablet to rise to the surface of the dissolution medium, while total floating time referred to the duration the tablet remained afloat without sinking.

Swelling Studies

Swelling behavior, also referred to as water absorption capacity, was assessed using a petri dish containing a glass plate to hold the tablet. Each tablet was placed in a petri dish with 50 mL of dissolution medium maintained at 37±0.5°C. After a fixed time, the petri dish was removed, and the tablet was blotted with absorbent tissue to remove excess medium before weighing (Challa and Laxmi, 2024; Krishna *et al.*, 2025).

$$\text{Swelling} = [(W_t - W_0)/W_0] \times 100$$

Where W_0 = Weight tablet and W_t is the weight of the wettable.

Comparison

A comparison was conducted between the marketed tablet, the optimized formulation, and the F13 formulation using Levipil 500 mg as the reference. Each film-coated mouth-dissolving tablet contains Levetiracetam IP and is manufactured in India by Sun Pharma Laboratories Ltd., Plot No. 107–108, Namli Block, P.O. Ranipool, East Sikkim

– 737135 (Batch No.: SID1859A; Manufacturing Date: 07/2022; Expiry Date: 06/2024).

FTIR

Fourier-transform infrared (FTIR) spectra of the drug and its tablet excipients were recorded using a Perkin Elmer IR spectrophotometer with a potassium bromide (KBr) disc, as described by Challa and Madhuri (2022a). The resolution was set at 2 cm⁻¹, and the scanning range was 400–4,000 cm⁻¹.

Data Analysis

Data analysis was performed using zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models. Dissolution parameters including swelling index, floating lag time, percentage drug release (% DR) at 1 h and 3 h, T50 (time required for 50% drug release), and T100 (time required for 100% drug release) were analyzed using ANOVA.

Results and Discussion

Lev gastro-retentive floating tablets were optimized using a CCD. Three components X1 (Methocel K100M), X2 (Methocel K15M), and X3 (cetostearyl alcohol) were varied in concentration to develop optimized formulations using Design-Expert software (Challa and Jami, 2022; Challa *et al.*, 2025). Experimental trials were conducted for 15 different combinations of X1, X2, and X3, as presented in Tables 1 and 2.

Tablet Properties

1. All tablet formulations exhibited hardness values ranging from 4.5 to 5.5 kg/cm². The increased hardness reflected improved binding properties of the Lev tablets. The individual and combined effects of the three formulation variables were significant, particularly X1 (Methocel K100) and X2 (Methocel K15), both of which contributed to enhanced binding and retardation properties.

2. The friability test was conducted to assess whether the tablets met the pharmacopeial standard of weight loss not exceeding 1%. The observed friability values ranged from 0.52% to 0.82%, which were within the acceptable limits set by the Indian Pharmacopoeia. Specifically, formulations F1, F8, F10, F11, and F15 prepared with X1, X2, and X3 at the 0 level showed the lowest friability of 0.52%, indicating a favorable combination of individual and interactive effects of the three variables.

3. Based on quality control parameters, the drug content of the tablets was found to be between 98% and 99% of the labeled amount, which is within the acceptable specification range.

Table 3. Characteristics of levetiracetam floating tablets F1 to F15

Formulations	Buoyancy (sec)	Swelling index (%)	Time for floating (h)	DR 1 h	T100 (Time.req to 100% DR)	Hardness (Kg/Cm ²) $\pm$ S.D	Friability (%)	Drug content (%)
F1	82	63.04	>12	11.833	6.5 h	4.5 $\pm$ 0.12	0.52	98.10
F2	79	66.195	>12	20.079	5.5 h	4.6 $\pm$ 0.32	0.56	98.20
F3	46.46	66.35	>12	25.385	6.5 h	4.7 $\pm$ 0.113	0.59	98.25
F4	56.30	68.77	>12	25.810	5.0 h	4.8 $\pm$ 0.19	0.62	98.35
F5	34.92	64.18	>12	22.043	6.5 h	4.9 $\pm$ 0.32	0.66	98.50
F6	39.60	64.46	>12	22.609	6.5 h	5.0 $\pm$ 0.10	0.68	98.65
F7	57.96	67.41	>12	22.560	6.0 h	5.1 $\pm$ 0.06	0.70	98.70
F8	82.22	63.04	>12	11.833	6.5 h	4.5 $\pm$ 0.015	0.52	98.90
F9	120	66.66	>12	19.230	5.5 h	5.2 $\pm$ 0.20	0.73	98.99
F10	82	63.04	>12	11.833	6.5 h	4.5 $\pm$ 0.012	0.52	9.10
F11	82	63.04	>12	11.833	6.5 h	4.5 $\pm$ 0.023	0.52	99.40
F12	110	67.41	>12	18.733	6.0 h	5.2 $\pm$ 0.034	0.77	99.75
F13	136	66.74	>12	22.213	7.0 h	5.3 $\pm$ 0.056	0.80	99.80
F14	70.3	67.60	>12	18.754	5.5 h	5.5 $\pm$ 0.0321	0.82	99.95
F15	82	63.4	>12	11.833	6.5 h	4.5 $\pm$ 0.0234	0.52	98.10
Optimized	117	68.172	>12	20.669	9.5 h	4.5 $\pm$ 0.0123	0.51	98.95

4. Floating behavior of the prepared tablets is presented in Table 3. Floating lag time and total floating time were recorded for all formulations (F1 to F15). Floating lag time ranged from 34.92 to 136 sec. The shortest lag time was observed in the formulation containing X1 at ($-\alpha$) level (91.893 mg of Methocel K100), X2 at the 0 level (50 mg of Methocel K15), and X3 at the 0 level (20.5 mg of cetostearyl alcohol). The longest lag time was recorded in the combination of X1 at the 0 level, X2 at ($-\alpha$) level, and X3 at the 0 level.

5. Swelling behavior was evaluated in 0.1N hydrochloric acid buffer. Significant variation in swelling was observed across all formulations (F1 to F15), indicating the influence of the formulation variables on water absorption and matrix expansion.

FTIR

The primary characteristic absorption bands observed in the FTIR spectra included peaks at 3,196.43 cm⁻¹ (N-H), 2,991.05, 2,938.98, 2,911.02,

and 2,890.77 cm⁻¹ (aliphatic C-H), 1,675.84 and 1,649.8 cm⁻¹ (C=O), 1,383.68 cm⁻¹ (C-N), 1,213.01 cm⁻¹ (C-O), 1,082.83 cm⁻¹ (C-C), and 702.93, 636.39, and 545.76 cm⁻¹ (N-H bending and ring deformation). The IR absorption peaks of Lev were clearly present in the FTIR spectra of the drug-excipient mixtures. As shown in Figure 7, comparison of the spectra of the pure drug and its mixtures with various excipients indicated no significant shifts or disappearance of characteristic peaks, confirming the absence of chemical interactions between the drug and the excipients.

UV Spectrophotometric Method

In 0.1N hydrochloric acid buffer, the maximum absorbance of Lev was recorded at 210 nm. Figure 8(b) shows the standard calibration curve within the concentration range of 0 to 40 μ g/mL, yielding the equation $y = 0.021x + 0.015$ with an R² value of 0.997, indicating excellent linearity.

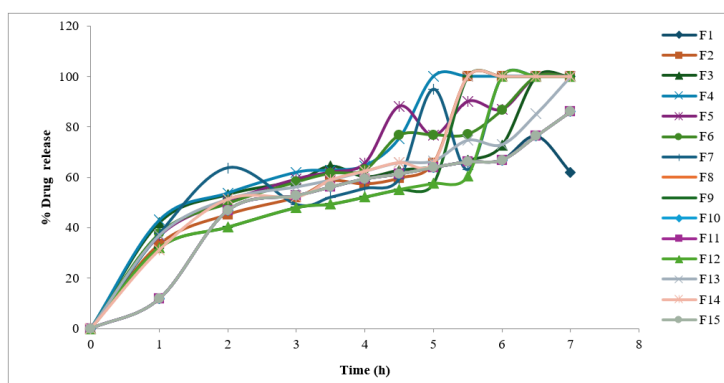


Figure 1. Mean Dissolution profile of Formulations F1 to F15 (n=4)

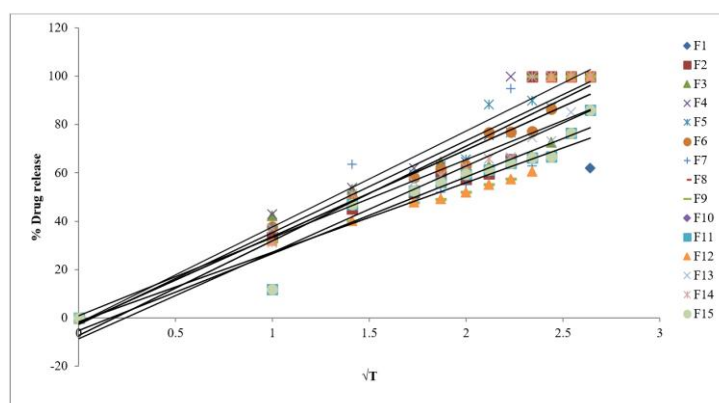


Figure 2. Dissolution Profile of Higuchi plots Formulation of F1 to F15 (n=4)

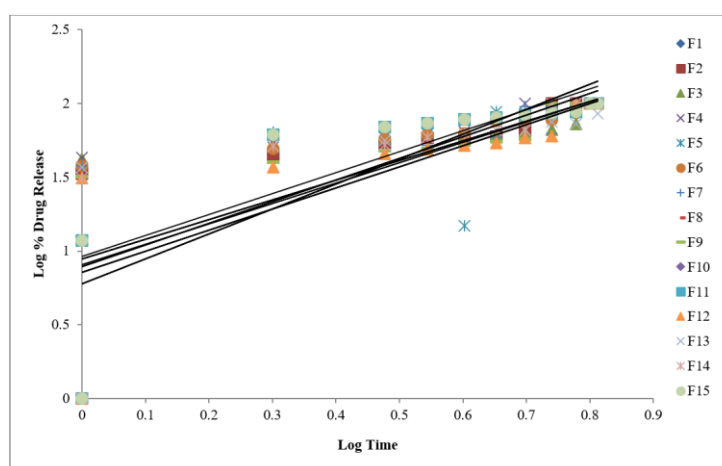


Figure 3. Dissolution Profiles of Peppas plots Formulation of F1 to F15 (n=4)

In vitro Dissolution

Figure 1 presents the in vitro dissolution profiles of the developed gastro-retentive tablets. The formulations F1, F3, F5, F6, F8, F10, F11, and F15 exhibited 100% drug release within 6.5 h. Formulations F2 and F9 achieved complete release in 5.5 h, while F4 showed 100% release in 5 h. Formulations F7 and F12 reached maximum drug release in 6 h. F9 and F14 also exhibited a 5.5-h release profile, whereas F13 demonstrated the longest release period of 7 h. The order of drug release among the batches was as follows: $F13 > F1 = F3 = F5 = F6 = F8 = F10 = F11 = F15 > F7 = F12 > F2 = F9 > F4 = F14$. Formulation F13, which demonstrated the most prolonged release, corresponded to the combination of X1 at the 0 level, X2 at $(-)\alpha$ level, and X3 at the 0 level. Formulations F1, F3, F8, F10, F11, and F15 also shared the X1 variable at the 0 level. Similarly, F1, F5, F8, F10, F11, and F15 included X2 at

the 0 level, and F1, F3, F5, F8, F10, F11, and F15 incorporated X3 at the 0 level. Formulation F5 included X1 at the $(-)\alpha$ level, whereas F6 included X1 at -1, X2 at both $(-)\alpha$ and -1 levels, and X3 at -1. These combinations significantly influenced the drug release profile, with both individual and combined effects of the three variables contributing to the observed outcomes.

Kinetics Drug Release

Drug release kinetics were evaluated to analyze the in vitro release profiles using various mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, as shown in Figures 2 and 3. When fitted to the zero-order model, formulations F2, F3, F4, F5, F6, F7, F9, F12, and F14 exhibited zero-order release behavior, indicating a constant rate of drug release independent of concentration. As shown in Table 4, the coefficient of determination (R^2) values

Table 4. 'r' value of Levetiracetam Tablets (n=4)

Formulations	K _O	K _I	K _H	K _P	Release Exponent ('n')
1	0.2527	0.9694	0.7517	0.8356	0.3183
2	0.9251	0.7308	0.9293	0.6643	0.4609
3	0.0949	0.696	0.9360	0.6895	0.3456
4	0.8694	0.7129	0.9573	0.795	0.2757
5	0.9589	0.8406	0.9682	0.7214	0.3703
6	0.9613	0.0905	0.9822	0.7365	0.3868
7	0.8407	0.6875	0.8711	0.7005	0.3621
8	0.2527	0.9694	0.7517	0.8356	0.3183
9	0.8958	0.6203	0.8876	0.7293	0.3662
10	0.2527	0.9694	0.7517	0.8356	0.3183
11	0.2527	0.9694	0.7517	0.8356	0.3183
12	0.9114	0.6291	0.9010	0.7398	0.4979
13	0.9242	0.9689	0.9908	0.7088	0.2469
14	0.9332	0.6793	0.9435	0.7383	0.4444
15	0.2527	0.9694	0.7517	0.8356	0.3183
Optimized	0.9653	-0.8496	0.9664	0.7386	0.54

Table 5. Analysis of variance (ANOVA) of Swelling Index (Y1)

Source	Sum of Squares	df	Mean Square	F- Value	p-Value	Remarks
Model	58.46	9	6.50	33.93	0.0006	Significant
A-HPMCK100	3.08	1	3.08	16.07	0.0102	
B-HPMCK15	0.0761	1	0.0761	0.3973	0.5562	
C-Cetosteryl Alcohol	0.7381	1	0.7381	3.86	0.1068	
AB	0.0005	1	0.0005	0.0025	0.9621	
AC	3.19	1	3.19	16.66	0.0095	
BC	0.0469	1	0.0469	0.2452	0.6415	
A ²	7.43	1	7.43	38.83	0.0016	
B ²	18.39	1	18.39	96.09	0.0002	
C ²	21.59	1	21.59	112.79	0.0001	
	0.9571	5	0.1914			
	0.9571	1	0.9571			
	0.0000	4	0.0000			
	59.41	14				

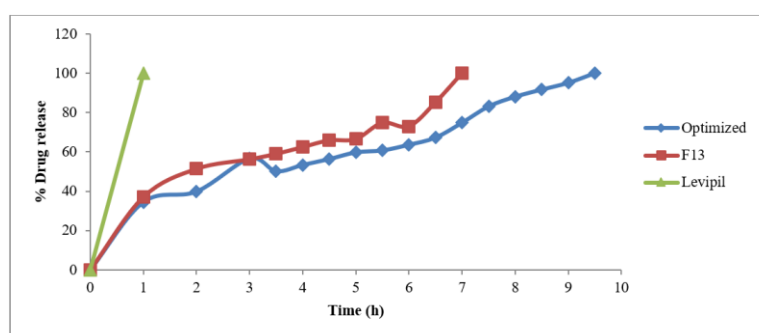


Figure 4. Dissolution Profile of F13, Marketed, and Optimized Formulation (SD±0.225) n=4

increased for formulations F1, F6, F8, F10, F11, F13, and F15 when fitted to the first-order model, suggesting a concentration-dependent release consistent with first-order kinetics. The release exponent (n) values for formulations F2 and F12 indicated non-Fickian (anomalous) diffusion, reflecting a combination of drug diffusion and polymer relaxation mechanisms. In contrast, formulations F1, F2, F3, F4, F5, F6, F7, F8, F9, F10,

F11, F13, F14, and F15 exhibited n values consistent with Fickian diffusion, suggesting that drug release was primarily controlled by diffusion through the polymer matrix.

Comparative Studies

Comparative studies were conducted between the optimized formulation, F13, and the marketed tablet (Levipil 500 mg). The marketed formulation

Table 6. Statistical parameter of Gastro retentive floating tablets

Statistical parameter	(Y1) Swelling index	(Y2) Floating lag time	(Y3)	(Y4)	(Y5)	(Y6) T100 time req for 100%DR
Std. dev	0.4375	19.03	5.52	0.9852	0.3552	0.5297
Mean	65.40	77.37	28.03	53.66	3.70	7.25
c.v	0.6690	24.60	19.70	1.84	9.60	7.31
Press	103.47	59,436.68	16,479.50	524.72	68.19	14.10
2loglikehod	1.29	121.52	77.35	25.64	-4.97	7.02
R ²	0.9839	0.7476	0.9280	0.9826	0.9230	0.9579
Adj R ²	0.9549	0.5584	0.7985	0.6511	0.7843	0.8822
Pred R ²	-0.7415	-4.1756	-6.7800	-0.8862	-7.3292	0.5772
Adeqorecision	16.5404	6.8865	7.1938	18.6455	7.4138	8.7772
BIC	28.37	140.48	104.43	52.72	22.12	34.10
AICC	76.29	151.52	152.35	100.64	70.03	82.02

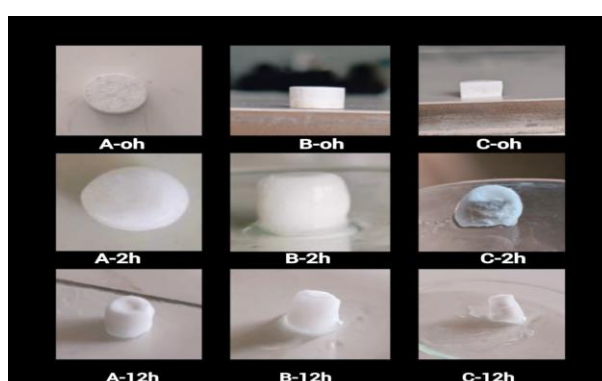


Figure 5. Swelling index – Erosin Studies (n=4)

achieved 100% drug release within 10 min. In contrast, F13 reached complete drug release in 7 h, while the optimized formulation achieved 100% release in 9.5 h. These results indicate that the drug release profiles of F13 and the optimized formulation differed significantly from that of the marketed tablet. The comparative dissolution data are illustrated in Figure 4.

Data Analysis

A summary of the statistical parameters is presented in Table 6.

1. Swelling Index (Y1): The swelling index for all formulations ranged from 63.04% to 68.77%, indicating that both X1 (Methocel K100) and X2 (Methocel K15) contributed significantly to drug release. A statistically significant model was reported by Chowdary and Challa (2011), with a p-value < 0.0006, as shown in Table 5 and Figure 5. The polynomial equation describing this response is:

$$Y1 = 343.07518 - 2.05922X1 - 5.91065X2 - 3.28568X3 - 0.000412X1^2 - 0.067354X1X3 - 0.012255X2X3 + 0.017451X1^2 + 0.061765X2^2 + 0.267659X3^2$$

2. Floating Lag Time (Y2): A statistically significant model ($p \leq 0.0389$) was developed for floating lag time. The model equation is:

$$Y2 = 1698.88658 + 42.73328X1 - 61.72065X2 + 101.16997X3 + 0.076537X1X2 - 2.07558X1X3 + 2.31923X2X3$$

The positive coefficients for X1 and X3 suggest that increasing their levels increases the floating lag time, whereas a higher level of X2 results in a decrease.

3. Percentage Drug Release at 1 H (Y3): The model equation for drug release at 1 h is:

$$Y3 = 3453.45732 - 36.89085X1 - 42.91171X2 - 45.99539X3 + 0.051148X1X2 + 0.126494X1X3 - 0.345970X2X3 + 0.153755X1^2 + 0.451348X2^2 + 1.21979X3^2$$

4. Percentage Drug Release at 3 Hs (Y4): This model was statistically significant ($p \leq 0.0007$), and the equation is:

$$Y4 = 355.11243 - 6.10931X1 - 10.70113X2 + 30.29280X3 + 0.063228X1X2 - 0.046635X1X3 -$$

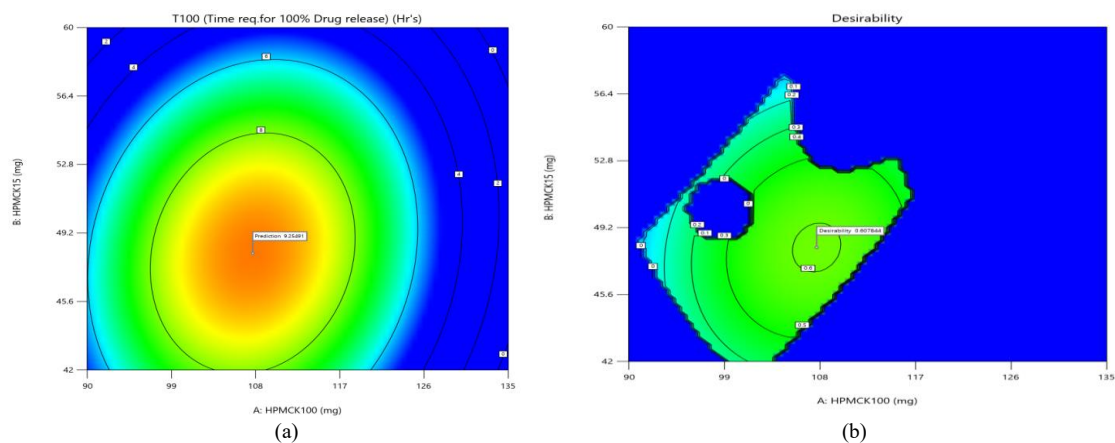


Figure 6. (a) Contour Plots of T100 and (b) Desirability

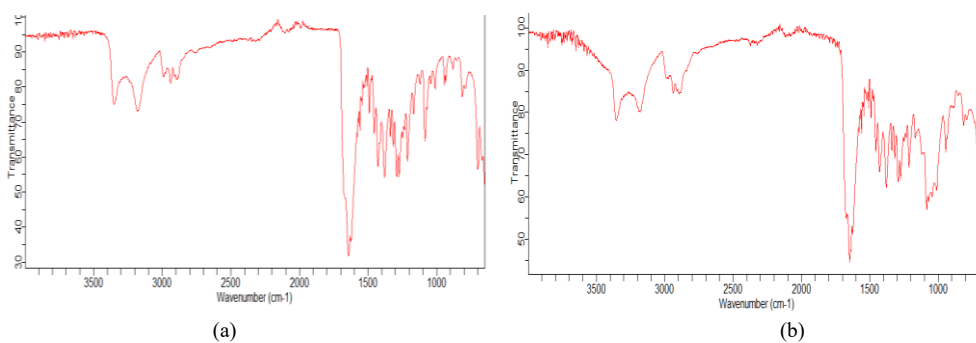


Figure 7. FTIR (a) Pure Drug and (b) Pure drug with Excipients

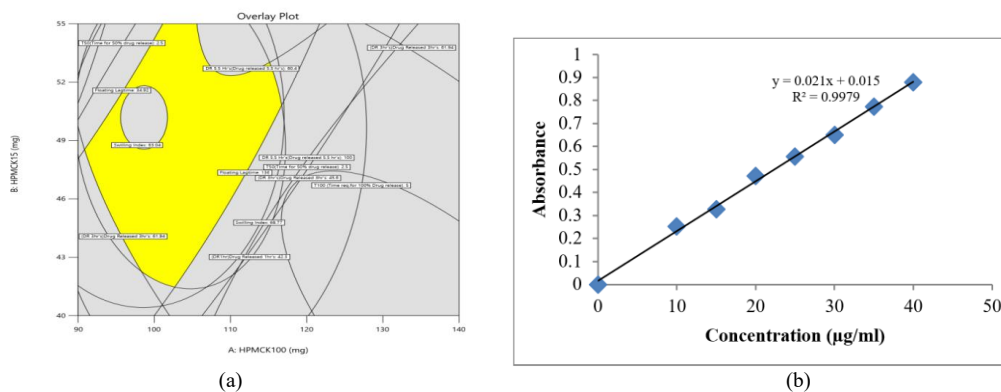


Figure 8. (a) Overlay plot and (b) Estimation of Levetiracetam by using 0.1N Hydrochloric acid buffer (n=4)

$$0.334909X_2X_3 + 0.016431X_1^2 + 0.112570X_2^2 - 0.045355X_2X_3 - 0.006519X_1^2 - 0.018667X_2^2 - 0.236119X_3^2 + 0.066667X_3^2$$

5. T50 – Time Required for 50% Drug Release (Y5): The model equation for T50 is:

$$Y_5 = -3.35632 + 0.436938X_1 - 1.20094X_2 + 1.04580X_3 + 0.020270X_1X_2 - 0.002694X_1X_3 +$$

The positive coefficients for X_1 , X_2 , and X_3 indicate that increasing these variables leads to an increase in the time required for 50% drug release.

6. T100 – Time Required for 100% Drug Release (Y6): This model was also statistically significant ($p \leq 0.0061$). The regression equation is:

$$Y6 = -192.06374 + 2.17742X1 + 0.720030X2 + 6.59253X3 + 0.004714X1X2 - 0.005577X1X3 + 0.090711X3 - 0.010639X1^2 - 0.031837X2^2 - 0.255748X3^2$$

The contour plot and overlay plot supporting this model are shown in Figures 6(a) and 8(b).

Optimization

A higher desirability value reflects a more suitable formulation, and the optimized formula can be identified directly from the desirability function response surface plots, as previously reported (Challa and Reshma, 2022; Challa *et al.*, 2023). The optimized formulation exhibited a desirability value of 0.607844, indicating its suitability, as shown in Figure 6(b). During optimization, each response variable was adjusted to meet its desired target: the swelling index (Y1), floating lag time (Y2), drug release at 1 h (Y3), drug release at 3 h (Y4), and T50 (Y5) were set within specific ranges, while T100 (Y6), the time required for 100% drug release, was set to be maximized. Optimization was carried out using six independent variables, and the final composition of the optimized formulation is presented in Table 1 and Figure 6(b). The concentrations of X1, X2, and X3 were 107.68 mg, 48.13 mg, and 20.25 mg, respectively, corresponding to a desirability function value of 0.607844. The theoretical predictions for the optimized formulation were as follows: swelling index (Y1) of 64.56%, floating lag time (Y2) of 111.93 seconds, drug release at 1 h (Y3) of 16.54%, drug release at 3 h (Y4) of 49.69%, T50 (Y5) of 4.29 h, and T100 (Y6) of 9.82 h. These predicted values closely matched the experimental results, demonstrating the validity and predictive power of the model. The experimental values for the optimized formulation were: swelling index of 63.04%, floating lag time of 82 seconds, drug release at 1 h of 34.45%, drug release at 3 h of 56.57%, T50 of 4.75 h, and T100 of 9.5 h. These findings confirm that the optimized gastro-retentive floating Lev tablets achieved 100% drug release within 9.5 h and validate the individual and interactive effects of the formulation variables (Challa and Pavani, 2023; Challa, and SaiKiranmai, 2023).

Conclusions

The drug release profiles of the formulations followed the order: F13 > F1 = F3 = F5 = F6 = F8 = F10 = F11 = F15 > F7 = F12 > F2 = F9 > F4 = F14. Among all formulations, the correlation coefficients (r values) indicated zero-order kinetics for F2, F3, F4, F5, F6, F7, and F9. Comparisons between the optimized formulation, F13, and the marketed product Levipil revealed non-identical dissolution profiles. ANOVA results for floating lag time, swelling index, drug release at 1 h (%DR at 1 h), drug release at 3 h (%DR at 3 h), T50 (time required for 50% drug release), and T100 (time required for 100% drug release) demonstrated statistically significant models. The optimized formulation exhibited a swelling index of 63.04%, a floating lag time of 82 seconds, 34.45% drug release at 1 h, 56.57% drug release at 3 h, T50 of 4.75 h, and T100 of 9.5 h. The optimized formulation was composed of 107.68 mg of X1 (Methocel K100M), 48.13 mg of X2 (Methocel K15M), and 20.25 mg of X3 (cetostearyl alcohol). This optimized gastro-retentive floating tablet demonstrated 100% drug release within 9.5 h and was found to be highly suitable for extended-release delivery of Lev.

Conflict of Interest

All the authors of this article declared no conflict of interest.

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