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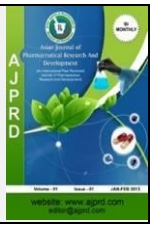

Open Access Research Article

Formulation and Evaluation of Gastro-Retentive Floating Tablets of Verapamil Hydrochloride

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ABSTRACT

Background: Verapamil Hydrochloride has a short biological half-life and undergoes extensive first-pass metabolism, necessitating frequent dosing. Gastro-retentive floating drug delivery systems offer prolonged gastric residence and sustained drug release, thereby improving therapeutic efficacy and patient compliance.

Objective: The present study aimed to formulate and evaluate gastro-retentive floating matrix tablets of Verapamil Hydrochloride using HPMC K4M and Xanthan Gum.

Methods: Tablets were prepared by the direct compression method using a 3^2 full factorial design. The formulations were evaluated for drug–polymer compatibility, pre-compression and post-compression characteristics, buoyancy, swelling index, in vitro drug release, drug release kinetics, and stability.

Results: FTIR and DSC studies confirmed drug–polymer compatibility. All formulations exhibited satisfactory physical properties and remained buoyant for 12 h. Floating lag time ranged from 62 ± 0.595 to 128 ± 0.598 s, while cumulative drug release after 12 h ranged from 85.1 ± 0.42% to 94.0 ± 0.23%. Drug release followed the Korsmeyer–Peppas model for most formulations, whereas a few exhibited Zero-order kinetics. Formulation F3 showed the shortest floating lag time (62 ± 0.595 s), highest drug release (94.0 ± 0.23%), and satisfactory stability under different storage conditions.

Conclusion: The optimized formulation (F3) demonstrated excellent buoyancy, sustained drug release, and stability, indicating its potential as a gastro-retentive floating drug delivery system for Verapamil Hydrochloride.

Keywords: Verapamil Hydrochloride, Gastro-retentive drug delivery system, Floating matrix tablets, HPMC K4M, Xanthan Gum, Direct compression, Sustained drug release, Drug release kinetics.

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INTRODUCTION

Hypertension is one of the most prevalent chronic cardiovascular disorders worldwide and remains a major risk factor for cardiovascular morbidity and mortality. Long-term pharmacotherapy is essential for effective blood pressure control; however, conventional oral dosage forms often require frequent administration due to their short duration of action, resulting in fluctuations in plasma drug concentration, reduced patient compliance, and suboptimal therapeutic outcomes. These limitations have encouraged the development of novel drug delivery systems capable of providing prolonged drug release and improved therapeutic efficacy.

Verapamil Hydrochloride is a calcium channel blocker widely prescribed for the management of hypertension, angina pectoris, and certain cardiac arrhythmias. The drug possesses a relatively short biological half-life of approximately 2.8–7.4 hours and undergoes extensive first-pass hepatic metabolism, leading to reduced oral bioavailability. Consequently, frequent dosing is required to maintain therapeutic plasma concentrations. A sustained-release gastro-retentive formulation may therefore improve drug availability, reduce dosing frequency, and enhance patient compliance.(1-4)

Gastro-retentive drug delivery systems (GRDDS) have emerged as an effective approach for prolonging gastric residence time and enhancing the bioavailability of drugs that are preferentially absorbed in the upper gastrointestinal tract or require prolonged gastric

retention. These systems remain in the stomach for an extended period, allowing controlled drug release, improved absorption, reduced plasma concentration fluctuations, and enhanced therapeutic effectiveness.(5,6)

Among the various gastro-retentive approaches, floating drug delivery systems have attracted considerable attention because of their simplicity, safety, and effectiveness. Floating tablets possess a bulk density lower than that of gastric fluid, enabling them to remain buoyant in the stomach without interfering with the normal gastric emptying process. This prolonged gastric residence facilitates sustained drug release and improves therapeutic performance while reducing dosing frequency.(7,8)

Hydrophilic polymers such as Hydroxypropyl Methylcellulose K4M (HPMC K4M) and Xanthan Gum are extensively employed in floating sustained-release formulations because of their excellent swelling, gel-forming, and release-retarding properties. Upon hydration, these polymers form a viscous gel barrier around the tablet that regulates drug diffusion, maintains matrix integrity, and prolongs drug release. Gas-generating agents such as sodium bicarbonate and citric acid react in the acidic gastric environment to produce carbon dioxide, which becomes entrapped within the hydrated polymer matrix, reducing tablet density and enabling buoyancy. The combined use of suitable polymers and gas-generating agents plays a crucial role in achieving desirable floating behavior and sustained drug release.

The present study was undertaken to formulate and evaluate gastro-retentive floating tablets of Verapamil Hydrochloride using HPMC K4M and Xanthan Gum by the direct compression method. The prepared formulations were evaluated for pre-compression and post-compression characteristics, floating behavior, swelling index, in vitro drug release, and drug–excipient compatibility using FTIR and DSC studies. The objective of the study was to develop a stable gastro-retentive floating tablet capable of providing prolonged gastric residence and sustained drug release, thereby improving therapeutic efficacy and reducing the frequency of drug administration.(9)

MATERIALS AND METHODS

Materials

Verapamil Hydrochloride was obtained from Yarrow Chem Products, Mumbai, India. Hydroxypropyl Methylcellulose K4M (HPMC K4M), Xanthan Gum, Sodium Bicarbonate, and Citric Acid of pharmaceutical grade were procured from S.D. Fine Chem Ltd., Mumbai, India. Microcrystalline Cellulose, Talc, Magnesium Stearate, and Polyvinylpyrrolidone K30 were used as excipients. All chemicals and reagents used in the study were of analytical grade.

Methods

Experimental Design Using 3^2 Full Factorial Design

A 3^2 full factorial design was adopted for the formulation of gastro-retentive floating tablets of Verapamil Hydrochloride. The design consisted of two independent variables at three different levels. The ratio of HPMC K4M to Xanthan Gum (X_1) and the concentration of Citric Acid (X_2) were selected as the independent variables, while Floating Lag Time (Y_1) and Percentage Drug Release (Y_2) were selected as the dependent variables.Based on the selected independent variables and their coded levels, nine formulation batches (F1–F9) were prepared by the direct compression method and evaluated for their floating characteristics and in vitro drug release.(10-13)

Table 1: Coded Levels of Independent Variables Used in 3^2 Full Factorial Design.

Independent variables	Symbol	Coded Values		
		-1	0	+1
HPMC K4M: Xanthan gum (Ratio)	X1	1:2	1:1	2:1
Citric acid (mg)	X2	10	20	30

Table 2: Composition of Gastro-retentive Floating Tablets of Verapamil Hydrochloride (mg/tablet).

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
X1	-1	-1	-1	0	0	0	+1	+1	+1
X2	-1	0	+1	-1	0	+1	-1	0	+1
Verapamil HCl	120	120	120	120	120	120	120	120	120
HPMC K4M	50	50	50	75	75	75	100	100	100
Xanthan Gum	100	100	100	75	75	75	50	50	50
Citric Acid	10	20	30	10	20	30	10	20	30
Sodium Bicarbonate	50	50	50	50	50	50	50	50	50

Microcrystalline cellulose	140	130	120	140	130	120	140	130	120
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Polyvinylpyrrolidone K30	20	20	20	20	20	20	20	20	20

Preparation of Gastro-retentive Floating Tablets

Gastro-retentive floating tablets of Verapamil Hydrochloride were prepared by the direct compression method. Verapamil Hydrochloride, HPMC K4M, Xanthan Gum, Sodium Bicarbonate, Citric Acid, and Microcrystalline Cellulose were passed through a 60-mesh sieve to obtain a uniform particle size distribution. The accurately weighed ingredients were blended thoroughly for 10 min to obtain a homogeneous mixture. Magnesium Stearate and Talc were subsequently added and mixed for an additional 5 min. The final powder blend equivalent to 500 mg was compressed into tablets using a rotary tablet compression machine equipped with 12 mm flat-faced punches.(14)

Evaluation of Formulated Tablets

The prepared gastro-retentive floating tablets were evaluated for drug–excipient compatibility, pre-compression parameters, post-compression characteristics, in vitro buoyancy, swelling index, drug content uniformity, and in vitro drug release using standard pharmacopeial procedures.(15-18)

A. Compatibility Studies

1. FTIR Spectroscopy

FTIR spectroscopy was performed to investigate the compatibility between Verapamil Hydrochloride and the selected polymers. The spectra of Verapamil Hydrochloride and the drug–polymer physical mixture were recorded using an FTIR spectrophotometer over the range of 4000–400 cm^{-1} under standard analytical conditions.(19)

2. Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed to evaluate the thermal behaviour and compatibility of Verapamil Hydrochloride with the selected polymers. The samples were analyzed over a defined temperature range under a nitrogen atmosphere at a controlled heating rate.(20))

B. Evaluation of Powder Blend

The flow properties of the powder blend were assessed prior to compression to ensure uniform die filling and consistent tablet weight. Angle of repose was determined using the fixed funnel method by measuring the height and radius of the powder cone formed after free flow. Bulk and tapped densities were determined using the graduated cylinder method before and after tapping. Compressibility was evaluated by calculating Carr's Index and Hausner Ratio from the density values to assess the flowability and packing characteristics of the powder blend.(21)

C. Evaluation of Tablets

The compressed tablets were evaluated for thickness, hardness, friability, and weight variation using standard pharmacopeial methods. Thickness was measured using a digital vernier caliper. Hardness was determined using a Monsanto hardness tester. Friability was evaluated using a Roche friabilator, while weight variation was determined by individually weighing the tablets and comparing the values with the average tablet weight to ensure dose uniformity. (22-25)

1. Drug Content Uniformity

Drug content uniformity was determined using a validated UV–Visible spectrophotometric method. Twenty tablets were randomly selected, accurately weighed using an electronic balance and finely powdered. A quantity of powdered tablets equivalent to 100 mg of Verapamil Hydrochloride was transferred into a conical flask. The drug was extracted using 150 mL of 0.1 N hydrochloric acid with shaking for 10 minutes. The volume was adjusted to 200 mL with 0.1 N HCl, followed by filtration. From the filtrate, 10 mL was diluted to 100 mL with distilled water, and absorbance was measured at λmax 278 nm using a Double Beam UV–Visible Spectrophotometer (UV-2401 PC, Shimadzu Corporation, Japan).

2. In Vitro Buoyancy Study

Floating behavior was evaluated using a USP Type II dissolution apparatus (Model 84005, Shimadzu Asia Pacific Pvt. Ltd., Singapore) at 50 rpm. Tablets were placed in 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C.

Floating lag time (FLT) was recorded as the time required for the tablet to rise to the surface of the medium, while total floating time (TFT) was recorded as the duration for which the tablet remained buoyant. Buoyancy was visually observed throughout the study.

3. In Vitro Dissolution Study

The in vitro drug release study of Verapamil Hydrochloride from the prepared floating matrix tablets was carried out using a USP Type II dissolution apparatus (paddle method). The dissolution medium consisted of 900 mL of 0.1 N hydrochloric acid (pH 1.2) maintained at 37 ± 0.5°C, which simulated gastric conditions. The paddle rotation speed was set at 50 rpm.

At predetermined time intervals (30 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h), 5 mL aliquots of dissolution medium were withdrawn and immediately replaced with an equal volume of fresh pre-warmed medium to maintain sink conditions. The withdrawn samples were filtered and diluted to 10 mL, and the drug content was analyzed using a UV–Visible spectrophotometer (UV-2401 PC, Shimadzu Corporation, Japan) at λmax 278 nm.(26,27)

4. Swelling Index Study

The swelling behavior of the gastro-retentive tablets was evaluated to study the hydration and gel-forming characteristics of the polymer matrix. Pre-weighed tablets were placed in 900 mL of 0.1 N hydrochloric acid (pH 1.2) maintained at 37 ± 0.5°C using a USP Type II dissolution apparatus. At predetermined time intervals (30 min, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 h), the tablets were carefully removed, blotted gently with filter paper to remove excess surface liquid, and weighed immediately.

The swelling index was calculated using the following equation:

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

Where:

W_0 = Initial weight of tablet

W_t = Weight of tablet at time t

5. Kinetic Modeling of Drug Release

The dissolution data were fitted to Zero-order, First-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas kinetic models to determine the drug release mechanism. The model showing the highest correlation coefficient (R^2) was considered the best fit..(28,29)

6. Stability Study

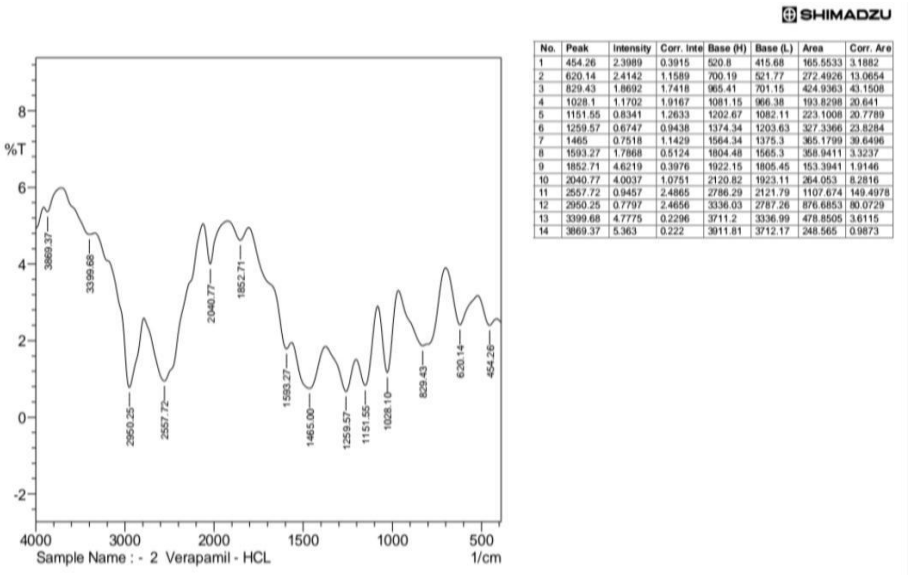
Stability studies were carried out on the optimized formulation by storing the tablets under three different storage conditions: 40 ± 2°C / 75 ± 5% RH, 25 ± 2°C / 75 ± 5% RH, and 10 ± 2°C / 75 ± 5% RH. The samples were evaluated at predetermined intervals for drug content, floating lag time, total floating time, and cumulative drug release to assess the stability of the optimized gastro-retentive floating tablet formulation.(30)

RESULTS AND DISCUSSION

1. Fourier Transform Infrared (FTIR)

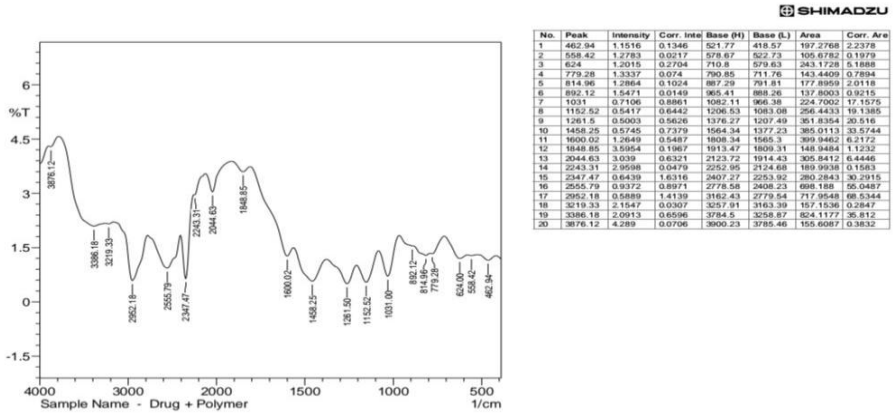
Fourier Transform Infrared (FTIR) spectroscopy was performed to evaluate the compatibility of Verapamil Hydrochloride with Hydroxypropyl Methylcellulose K4M (HPMC K4M) and Xanthan Gum. The FTIR spectrum of pure Verapamil Hydrochloride (Figure 1) exhibited characteristic absorption peaks at 3399.68 cm^{-1} (N–H stretching), 2950.25 cm^{-1} (C–H stretching), 1593.27 cm^{-1} (aromatic C=C stretching), 1465.00 cm^{-1} (C–H bending), 1259.57 cm^{-1} (C–N stretching), 1151.55 cm^{-1} (C–O stretching), 1028.10 cm^{-1} (C–O–C stretching), and 829.43 cm^{-1} (aromatic C–H bending).

The FTIR spectrum of the drug–polymer physical mixture (Figure 2) retained the characteristic peaks of Verapamil Hydrochloride with minor shifts in peak position and slight changes in peak intensity, which may be attributed to physical mixing and weak intermolecular hydrogen bonding between the drug and the selected polymers. No significant disappearance of the characteristic drug peaks or formation of new peaks indicative of chemical interaction was observed. These findings confirmed the compatibility of Verapamil Hydrochloride with HPMC K4M and Xanthan Gum, demonstrating their suitability for the development of gastro-retentive floating matrix tablets.



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	454.26	2.3989	0.3915	520.8	415.68	165.5533	3.1882
2	620.14	2.4142	1.1589	700.19	521.77	272.4926	13.0654
3	829.43	1.8692	1.7418	965.41	701.15	424.9363	43.1508
4	1028.1	1.1702	1.9167	1081.15	966.38	193.8298	20.641
5	1151.55	0.8341	1.2633	1202.67	1082.11	223.1008	20.7789
6	1259.57	0.6747	0.9438	1374.34	1203.63	327.3366	23.8284
7	1465	0.7518	1.1429	1564.34	1375.3	365.1799	39.6496
8	1593.27	1.7868	0.5124	1804.48	1565.3	358.9411	3.3237
9	1852.71	4.6219	0.3976	1922.15	1805.45	153.3941	1.9146
10	2040.77	4.0037	1.0751	2120.82	1923.11	264.053	8.2816
11	2557.72	0.9457	2.4865	2786.29	2121.79	1107.674	149.4978
12	2950.25	0.7797	2.4656	3336.03	2787.26	876.6853	80.0729
13	3399.68	4.7775	0.2296	3711.2	3336.99	478.8505	3.6115
14	3869.37	5.363	0.222	3911.81	3712.17	348.565	0.9873

Figure 1: FTIR spectrum of pure Verapamil Hydrochloride.



No.	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	462.94	1.1516	0.1346	521.77	418.57	197.2768	2.2378
2	558.42	1.2783	0.0217	578.67	522.73	105.6782	0.1979
3	624	1.2015	0.2704	710.8	579.63	243.1728	5.1888
4	779.28	1.3337	0.074	790.85	711.76	143.4409	0.7894
5	814.96	1.2864	0.1024	887.29	791.81	177.8959	2.0118
6	892.12	1.5471	0.0149	965.41	888.26	137.8003	0.9215
7	1031	0.7106	0.8861	1082.11	966.38	224.7002	17.1575
8	1152.52	0.5417	0.6442	1206.53	1083.08	256.4433	19.1385
9	1261.5	0.5003	0.5626	1376.27	1207.49	351.8354	20.516
10	1458.25	0.5745	0.7379	1564.34	1377.23	395.0113	33.5744
11	1600.02	1.2649	0.5487	1808.34	1565.3	399.9462	6.2172
12	1848.85	3.5954	0.1067	1913.47	1809.31	148.9484	1.1232
13	2044.63	3.039	0.6321	2123.72	1914.43	305.8412	6.4446
14	2243.31	2.9598	0.0479	2252.95	2124.68	189.9938	0.1583
15	2347.47	0.6439	1.6316	2407.27	2253.92	280.2843	30.2915
16	2555.79	0.9372	0.8971	2778.58	2408.23	698.188	55.0487
17	2952.18	0.5889	1.4139	3162.43	2779.54	717.9548	68.5344
18	3219.33	2.1547	0.0307	3257.91	3163.39	157.1536	0.2847
19	3386.18	2.0913	0.6596	3784.5	3258.87	824.1177	35.812
20	3876.12	4.289	0.0706	3900.23	3785.46	155.6087	0.3832

Figure 2: FTIR spectrum of the physical mixture of Verapamil Hydrochloride with HPMC K4M and Xanthan Gum.

2. Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) was performed to evaluate the thermal compatibility of Verapamil Hydrochloride with Hydroxypropyl Methylcellulose K4M (HPMC K4M) and Xanthan Gum. The DSC thermogram of pure Verapamil Hydrochloride exhibited a sharp endothermic melting peak at 144.89°C (onset 137.74°C, endset 153.07°C), confirming the crystalline nature of the drug. The DSC thermogram of the drug–polymer physical mixture exhibited endothermic peaks at 147.02°C (onset 138.73°C, endset 157.79°C) and 193.97°C (onset 182.91°C, endset 204.15°C). The slight shift in the melting peak of Verapamil Hydrochloride may be attributed to its uniform dispersion within the polymer matrix and weak physical interactions with the selected polymers. No significant disappearance of the characteristic drug melting peak or appearance of new thermal events was observed, indicating the absence of significant drug–polymer interaction. These findings confirmed the thermal compatibility of Verapamil Hydrochloride with HPMC K4M and Xanthan Gum, demonstrating their suitability for the development of gastro-retentive floating matrix tablets.

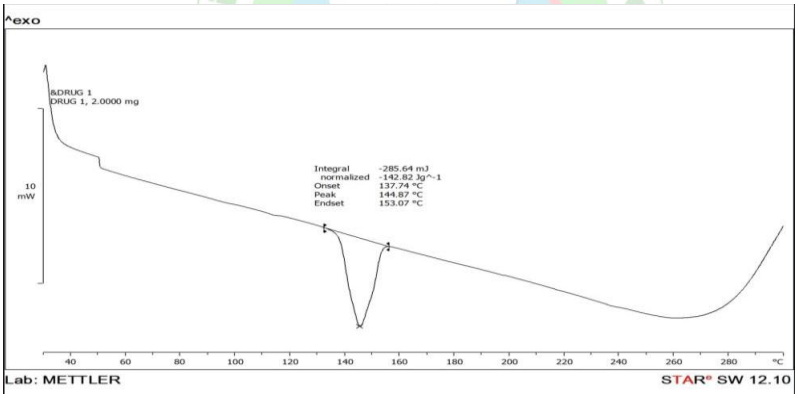


Figure 3: DSC thermogram of pure Verapamil Hydrochloride.

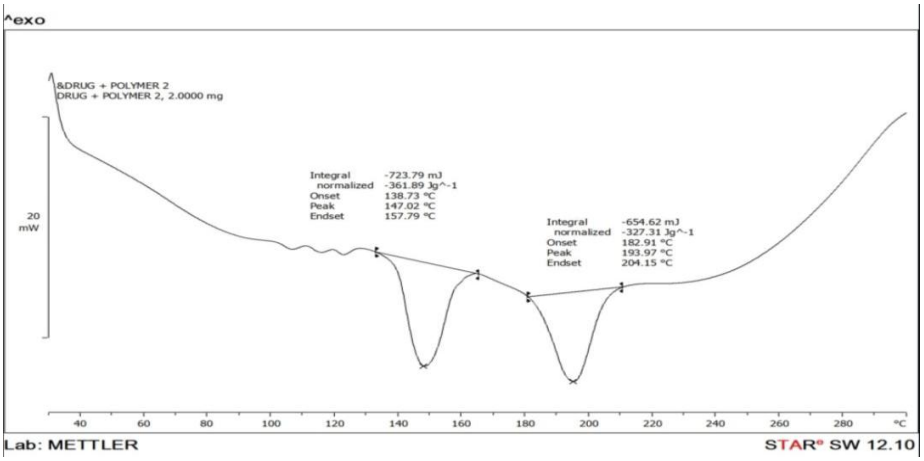


Figure 4: DSC thermogram of the physical mixture of Verapamil Hydrochloride with HPMC K4M and Xanthan Gum.

3. Evaluation of Powder Blend (Pre-compression Studies)

The powder blends of all factorial design formulations (F1–F9) were evaluated for their pre-compression properties. The bulk density and tapped density ranged from 0.566 ± 0.013 to 0.584 ± 0.065 g/cm³ and 0.650 ± 0.008 to 0.663 ± 0.021 g/cm³, respectively, indicating satisfactory packing characteristics. The Carr's Index (11.38 ± 0.72–14.37 ± 0.87%), Hausner's ratio (1.14 ± 0.04–1.16 ± 0.09), and angle of repose (29.2 ± 0.27°–30.4 ± 1.30°) indicated good flowability and compressibility of all formulations. All the values were within acceptable pharmacopeial limits, confirming that the powder blends possessed adequate flow properties and were suitable for the preparation of gastro-retentive floating matrix tablets by the direct compression method.

Table 3: Pre-compression parameters of factorial design batches (F1–F9).

Batch	Bulk Density (g/cm3±SD)	Tapped Density (g/cm3±SD)	Carr's Index (%±SD)	Hausner's Ratio (±SD)	Angle of Repose (θ±SD)
F1	0.566±0.013	0.661±0.014	14.37±0.87	1.15±0.08	29.2±0.27
F2	0.574±0.021	0.658±0.015	12.76±0.45	1.14±0.04	30.1±1.47
F3	0.570±0.009	0.663±0.021	13.45±0.67	1.16±0.09	29.6±1.38
F4	0.568±0.003	0.650±0.008	12.61±0.91	1.16±0.05	29.5±1.19
F5	0.584±0.065	0.659±0.015	11.38±0.72	1.15±0.08	29.2±1.54
F6	0.575±0.012	0.658±0.023	12.61±0.58	1.14±0.09	29.6±1.36
F7	0.568±0.019	0.660±0.009	13.93±0.43	1.16±0.05	29.3±1.26
F8	0.571±0.015	0.661±0.009	13.61±0.46	1.15±0.08	30.4±1.30
F9	0.576±0.075	0.660±0.009	12.72±0.45	1.15±0.08	30.1±1.20

4. Evaluation of Tablets (Post-compression Studies)

The prepared Verapamil Hydrochloride gastro-retentive floating matrix tablets were evaluated for post-compression parameters, including weight variation, hardness, thickness, diameter, friability, floating lag time (FLT), total floating time (TFT), and drug content. The tablets exhibited uniform weight (500.1 ± 1.3–503.8 ± 1.5 mg), diameter (12.05 ± 0.155–12.09 ± 0.147 mm), and thickness (2.970 ± 0.13–2.985 ± 0.14 mm), indicating uniform die filling and dimensional consistency. The hardness ranged from 5.2 ± 0.045 to 6.2 ± 0.059 kg/cm², providing adequate mechanical strength for handling. Friability values ranged from 0.44 ± 0.025 to 0.54 ± 0.035%, which were well within the pharmacopeial limit of less than 1%, indicating good tablet integrity. Overall, all formulations complied with pharmacopeial specifications and were considered suitable for further evaluation.

5. Drug Content Uniformity

The drug content of the factorial design batches (F1–F9) ranged from 96.46 ± 0.82% to 98.78 ± 0.80%, indicating uniform distribution of Verapamil Hydrochloride within the matrix tablets and compliance with pharmacopeial limits. Formulations F3 and F8 showed the highest drug content (98.78 ± 0.80%), whereas F2 exhibited the lowest (96.46 ± 0.82%). The minimal variation in drug content confirmed uniform drug distribution throughout the matrix tablets and demonstrated the reproducibility of the direct compression process.

6. In Vitro Buoyancy Study

The in vitro buoyancy study was carried out in 0.1 N HCl (pH 1.2) to evaluate the floating performance of the prepared tablets. The floating lag time (FLT) ranged from 62 ± 0.595 to 128 ± 0.598 s, while all formulations remained buoyant for 12 h, demonstrating excellent floating ability.

The buoyancy behavior was influenced by both the HPMC K4M:Xanthan Gum ratio and the concentration of citric acid. Formulations containing a higher proportion of HPMC K4M exhibited longer floating lag times because of the formation of a more viscous gel barrier, whereas increasing the concentration of citric acid reduced the FLT by enhancing carbon dioxide generation through its reaction with sodium bicarbonate.

Among all formulations, F3 exhibited the shortest floating lag time (62 ± 0.595 s), whereas F7 showed the longest (128 ± 0.598 s). The prolonged floating duration of all formulations indicated good matrix integrity throughout the study. Among all formulations, F3 was considered the optimized formulation because it exhibited the shortest floating lag time while maintaining a total floating time of 12 h.

Table 4: Post-compression parameters of factorial design batches (F1–F9).

Batch	Weight Variation (mg±S D)	Hardness (kg/cm^2±SD)	Diameter (mm±S D)	Thickness. (mm±S D)	Friability (±SD)	FLT(sec. ±S D)	TFT(hr. ±SD)	Drug content (%±SD)
F1	503.4±1.5	6.2±0.059	12.08±0.146	2.978±0.15	0.46±0.018	105±0.633	12±0.67	97.6±0.74
F2	501.0±1.4	5.2±0.047	12.08±0.161	2.979±0.14	0.44±0.025	75±0.564	12±0.25	96.46±0.82
F3	502.2±1.5	6.1±0.052	12.06±0.140	2.981±0.17	0.47±0.032	62±0.595	12±0.09	98.78±0.80
F4	503.8±1.4	5.8±0.056	12.07±0.150	2.980±0.15	0.51±0.024	125±0.648	12±0.08	97.04±0.75
F5	500.1±1.3	5.5±0.056	12.05±0.155	2.979±0.14	0.53±0.025	80±0.671	12±0.66	96.86±0.88
F6	502.0±1.8	5.8±0.045	12.09±0.147	2.978±0.13	0.54±0.035	70±0.671	12±0.87	97.64±0.91
F7	503.4±1.6	5.4±0.057	12.08±0.154	2.978±0.16	0.48±0.031	128±0.598	12±0.06	98.76±0.74
F8	503.0±1.5	5.4±0.040	12.06±0.157	2.970±0.13	0.50±0.023	105±0.561	12±0.09	98.78±0.80
F9	503.8±1.4	5.2±0.045	12.07±0.147	2.985±0.14	0.48±0.030	70±0.672	12±0.87	97.64±0.90

7. In Vitro Dissolution Study

The in vitro drug release study was performed in 0.1 N HCl (pH 1.2) for 12 h to evaluate the sustained-release behavior of the gastro-retentive floating matrix tablets. The cumulative drug release was influenced by the HPMC K4M:Xanthan Gum ratio and the concentration of citric acid.

Table 5: Cumulative percentage drug release of factorial design batches (F1–F9) at different time intervals (1–12 h).

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10.5±0.45	9.8±0.25	10.8±0.32	8.2±0.45	11.0±0.18	10.1±0.59	7.4±0.25	7.9±0.25	7.6±0.26
2	19.8±0.35	17.0±0.15	18.2±0.65	24.0±0.58	23.7±0.54	22.0±0.25	11.6±0.43	18.6±0.45	18.2±0.14
3	28.5±0.15	29.6±0.36	26.1±0.14	30.3±0.45	29.7±0.68	29.8±0.36	20.4±0.56	29.5±0.24	23.9±0.23
4	34.4±0.25	39.2±0.15	33.9±0.25	38.0±0.29	34.3±0.49	37.0±0.45	28.1±0.42	32.1±0.24	34.0±0.42
5	43.2±0.56	44.1±0.36	45.1±0.14	48.5±0.75	44.3±0.45	42.7±0.45	35.2±0.75	47.0±0.36	39.5±0.73
6	47.7±0.54	49.8±0.14	56.1±0.14	52.3±0.35	48.2±0.15	51.0±0.25	44.7±0.42	50.9±0.14	46.6±0.42
7	56.3±0.45	57.1±0.25	61.2±0.58	58.9±0.32	55.5±0.25	58.0±0.15	51.3±0.24	57.0±0.59	52.0±0.56
8	60.5±0.25	67.2±0.58	64.8±0.63	65.8±0.25	59.5±0.35	62.0±0.25	58.5±0.42	61.1±0.42	63.3±0.47
9	69.4±0.45	73.5±0.96	71.9±0.48	69.7±0.58	68.8±0.75	71.0±0.31	61.9±0.75	68.3±0.75	68.4±0.31
10	73.3±0.48	76.1±0.75	79.9±0.89	74.2±0.48	75.3±0.56	76.8±0.75	68.2±0.96	75.9±0.42	74.2±0.56
11	82.5±0.35	82.9±0.25	87.1±0.75	80.0±0.75	81.0±0.63	82.3±0.85	79.6±0.63	80.5±0.85	80.6±0.45
12	91.7±0.47	93.1±0.45	94.0±0.23	87.1±0.96	89.2±0.24	91.5±0.45	85.1±0.42	87.3±0.39	89.0±0.36

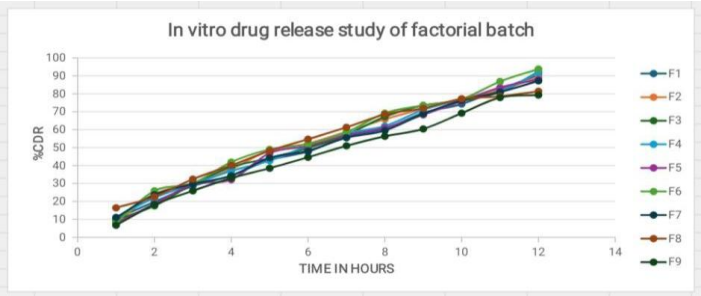


Figure 5: In vitro drug release profiles of factorial design batches (F1–F9).

Formulations containing a higher proportion of Xanthan Gum (F1–F3) exhibited greater drug release than those containing equal proportions (F4–F6) or a higher proportion of HPMC K4M (F7–F9), indicating the release-retarding effect of HPMC K4M. After 12 h, the cumulative drug release of formulations F1, F4, and F7 was 91.7 ± 0.47%, 87.1 ± 0.96%, and 85.1 ± 0.42%, respectively. Within each polymer ratio group, increasing the concentration of citric acid enhances drug release, which may be attributed to increased matrix hydration, pore formation, and improved drug diffusion. The overall drug release pattern was observed as F3 > F2 > F1, F6 > F5 > F4, and F9 > F8 > F7. Among all the formulations, F3 exhibited the highest cumulative drug release (94.0 ± 0.23%) after 12 h, together with a floating lag time of 62 ± 0.595 s and a total floating time of 12 h. Therefore, F3 was selected as the optimized formulation.

8. Swelling Index Study

The swelling index of the factorial design batches (F1–F9) was evaluated in 0.1 N HCl (pH 1.2) to investigate the hydration behavior of the polymeric matrix. All formulations exhibited a gradual increase in swelling with time, indicating progressive hydration and gel formation by the polymers. After 12 h, the swelling index ranged from 134.66 ± 0.96% to 152.27 ± 0.96%.

The swelling behavior was influenced by the HPMC K4M:Xanthan Gum ratio and the concentration of citric acid. An increase in the proportion of HPMC K4M resulted in greater swelling because of its excellent hydrophilic and gel-forming properties. Similarly, increasing the concentration of citric acid enhanced matrix hydration and swelling. Among all formulations, F9 exhibited the highest swelling index (152.27 ± 0.96%), whereas F1 showed the lowest swelling index (134.66 ± 0.96%). The enhanced swelling behavior contributed to prolonged tablet buoyancy and sustained drug release by maintaining the integrity of the hydrated polymer matrix throughout the dissolution study.

Table 6: Swelling index (%) of factorial design batches (F1–F9) at different time intervals (1–12 h).

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	10.55±0.65	11.25±0.72	9.71±0.84	8.47±0.73	13.71±0.81	15.39±0.91	19.31±0.88	21.25±0.76	17.55±0.79
2	13.70±0.78	18.92±0.87	22.06±0.88	19.68±0.77	22.72±0.89	20.83±0.85	25.04±0.93	28.66±0.81	23.87±0.84
3	27.70±0.76	41.26±0.88	39.25±0.91	30.22±0.85	36.12±0.92	33.94±0.83	41.86±0.94	46.73±0.78	39.58±0.86
4	43.92±0.82	52.60±0.77	50.83±0.85	52.46±0.90	52.35±0.78	58.69±0.92	62.43±0.89	65.22±0.80	59.61±0.87
5	59.09±0.80	74.71±0.76	72.11±0.87	73.03±0.91	74.90±0.86	81.23±0.91	87.65±0.93	90.78±0.79	83.12±0.85
6	75.35±0.82	91.69±0.89	89.54±0.91	84.57±0.86	88.36±0.85	87.78±0.93	96.25±0.96	99.84±0.82	93.10±0.89
7	92.37±0.91	99.61±0.94	98.54±0.96	97.03±0.92	101.55± .91	103.80±0.95	108.56±0.98	112.05±0.84	105.82±0.93
8	108.59± .93	118.57± .96	125.10± .94	108.65± .91	112.65± .95	112.55± .97	123.55± .99	132.53± .86	124.21±0.94
9	116.80± .96	127.42± .98	132.04± .95	119.26± .94	125.82± .96	123.46± .98	134.75± .96	143.11± .89	136.42± .97
10	124.77± .97	133.54± .94	139.86± .97	129.33± .93	134.72± .98	131.15± .97	141.33± .94	149.62± .91	143.78± .95
11	129.53± .94	138.64± .97	143.25± .96	135.28± .91	140.17± .95	139.33± .96	145.64± .98	153.32± .93	148.63± .94
12	134.66± .96	143.79± .98	148.15± 0.99	146.55± .94	148.82± .97	150.90± .99	148.71± .97	149.94± .95	152.27± .96

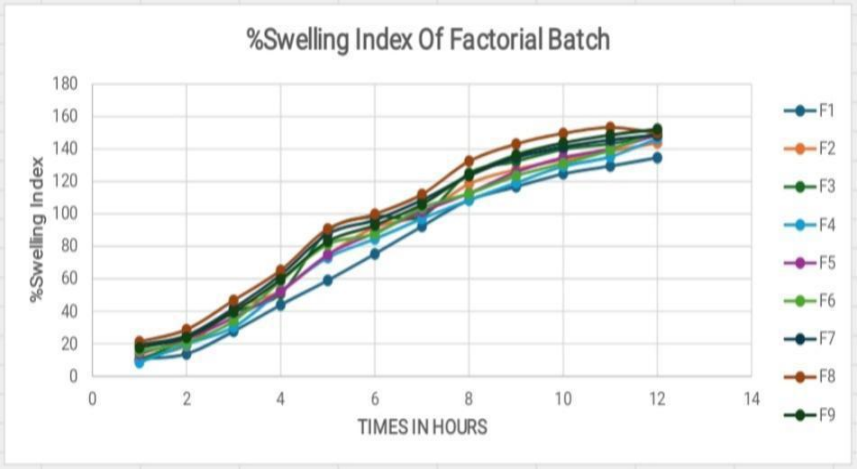


Figure 6: Swelling index profiles of factorial design batches (F1–F9).

9. Drug Release Kinetics

The in vitro drug release data of factorial design batches (F1–F9) were analyzed using different kinetic models, including Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models, to understand the drug release mechanism from the polymeric matrix system.

Based on the regression coefficient (R^2) values, formulations F1, F2, F3, F4, F7, and F8 showed the best fit to the Korsmeyer–Peppas model, whereas formulations F5, F6, and F9 exhibited better fitting with the Zero-order kinetic model, suggesting controlled and sustained drug release from the gastro-retentive floating matrix tablets.

The release exponent (n) values ranged from 0.842 to 0.961. Formulations F1–F8 exhibited n values greater than 0.89, indicating Super Case-II transport mechanism, whereas formulation F9 showed anomalous (non-Fickian) transport mechanism with an n value of 0.842. Among all formulations, F3 showed the best correlation with the Korsmeyer–Peppas model (R^2 = 0.9968), indicating controlled drug release behavior.

Considering the overall evaluation parameters, including floating lag time, total floating duration, swelling behavior, and drug release profile, formulation F3 was selected as the optimized gastro-retentive floating matrix tablet formulation.

Table 7: Drug release kinetic model fitting of factorial design batches (F1–F9)

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero Order (R^2)	0.9961	0.9874	0.9905	0.9855	0.9944	0.9931	0.9759	0.9841	0.9959
1st Order (R^2)	0.9571	0.9322	0.9543	0.8756	0.9447	0.9632	0.9512	0.9606	0.9218
Higuchi (R^2) Model	0.9874	0.9892	0.9894	0.9894	0.9812	0.9922	0.9898	0.9902	0.9820
Peppas (R^2) Model	0.9965	0.9984	0.9968	0.9919	0.9836	0.9781	0.9899	0.9944	0.9891
n value	0.9610	0.953	0.938	0.944	0.936	0.922	0.9470	0.928	0.842
k value	35.16	33.47	31.23	32.21	30.56	30.22	28.88	29.45	28.87
Best Fitted To	Peppas	Peppas	Peppas	Peppas	Zero order	Zero order	Peppas	Peppas	Zero order

Stability Study

The optimized formulation (F3) was subjected to stability studies under different storage conditions, i.e., 40 ± 2°C / 75 ± 5% RH, 25 ± 2°C / 75 ± 5% RH, and 10 ± 2°C / 75 ± 5% RH for a period of 4 weeks, as per ICH guidelines, to evaluate its physical and chemical stability.

The results of the stability study showed that the drug content remained nearly constant throughout the study period under all storage conditions, ranging from 98.78 ± 0.80% to 97.77 ± 0.80%, indicating excellent chemical stability of the optimized formulation.

No significant variation was observed in floating lag time (62 ± 0.595 sec) and total floating time (12 ± 0.09 h) during the entire study period. The cumulative drug

release remained consistent at approximately 94 ± 0.23% under most conditions, as shown in Table 6, indicating that the drug release profile was not significantly affected by the storage conditions.

A slight decrease in cumulative drug release (93 ± 0.23%) was observed at the end of the 4th week under 10 ± 2°C / 75 ± 5% RH condition; however, this change was within acceptable limits and not considered significant.

Overall, the optimized formulation exhibited no significant changes in drug content, floating lag time, total floating duration, and cumulative drug release throughout the storage period, confirming the stability of the developed gastro-retentive floating tablets under the investigated storage conditions.

Table 8: Stability study of optimized formulation (F3) under different storage conditions.

Stability 40 ± 2°C / 75 ± 5% RH	Drug Content (%)	Lag Time(Sec)	Floating Time (Hr.)	Cumulative Drug Release
0 Day	98.78±0.80	62±0.595	12±0.09	94±0.23
1 Week	98.78±0.80	62±0.595	12±0.09	94±0.23
2 Week	98.78±0.80	62±0.595	12±0.09	94±0.23
3 Week	97.77±0.80	62±0.595	12±0.09	93±0.23
4 Week	97.77±0.80	62±0.595	12±0.09	93±0.23

Stability 25 ± 2°C / 75 ± 5% RH	Drug Content (%)	Lag Time in (Sec)	Floating Time (Hr.)	Cumulative Drug Release
0 Day	98.78±0.80	62±0.595	12±0.09	94±0.23
1 Week	98.78±0.80	62±0.595	12±0.09	94±0.23
2 Week	98.78±0.80	62±0.595	12±0.09	94±0.23
3 Week	98.78±0.80	62±0.595	12±0.09	94±0.23
4 Week	97.77±0.80	62±0.595	12±0.09	93±0.23

Stability 10± 2°C / 75 ± 5% RH	Drug Content (%)	Lag Time (Sec)	Floating Time (Hr.)	Cumulative Drug Release
0 Day	98.78±0.80	62±0.595	12±0.09	94±0.23
1 Week	98.78±0.80	62±0.595	12±0.09	94±0.23
2 Week	98.78±0.80	62±0.595	12±0.09	94±0.23
3 Week	98.77±0.80	62±0.595	12±0.09	94±0.23
4 Week	97.77±0.80	62±0.595	12±0.09	93±0.23

CONCLUSION

The present study successfully developed gastro-retentive floating matrix tablets of Verapamil Hydrochloride using Hydroxypropyl Methylcellulose K4M (HPMC K4M) and Xanthan Gum by the direct compression method. FTIR and DSC studies confirmed the compatibility of Verapamil Hydrochloride with the selected polymers, indicating the absence of any significant drug–polymer interaction.

The pre-compression studies demonstrated satisfactory flowability and compressibility of the powder blends, whereas the post-compression evaluation confirmed that all formulations complied with pharmacopeial specifications for weight variation, hardness, friability, thickness, diameter, and drug content uniformity.

All formulations exhibited excellent floating characteristics with a total floating time of 12 h, indicating their suitability for prolonged gastric retention. The in vitro drug release study demonstrated that both the polymer ratio and citric acid concentration significantly influenced the release profile of Verapamil Hydrochloride. Formulation F3 exhibited the shortest floating lag time (62 ± 0.595 s) and the highest cumulative drug release (94.0 ± 0.23%) after 12 h. Although formulation F9 exhibited the highest swelling

index (152.27 ± 0.96%), formulation F3 demonstrated the best overall balance between buoyancy, swelling behavior, and sustained drug release and was therefore selected as the optimized formulation.

Drug release kinetic analysis revealed that most formulations followed the Korsmeyer–Peppas model, while a few formulations exhibited Zero-order release kinetics, indicating controlled drug release from the polymeric matrix. Stability studies demonstrated that the optimized formulation (F3) remained physically and chemically stable throughout the study period, with no significant changes in drug content, floating behavior, or drug release profile under the investigated storage conditions.

Based on the overall findings, formulation F3 can be considered a promising gastro-retentive floating drug delivery system for the sustained release of Verapamil Hydrochloride, with the potential to improve gastric residence time, provide sustained drug release, and enhance the bioavailability and therapeutic efficacy of the drug. However, further in vivo studies are required to establish the in vitro–in vivo correlation and confirm the clinical performance of the developed formulation.

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