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Design and Optimization of Gastro Retentive Bilayer Foating Tablet of Verapamil HCL

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ABSTRACT:
This study explores the development of floating tablets of Verapamil HCl for controlled oral drug delivery. Conventional oral forms often face issues like fluctuating drug levels and frequent dosing. Gastro Retentive Drug Delivery Systems (GRDDS) can address these problems by extending gastric retention time and improving drug absorption. Tablets were formulated using Hydroxypropyl Methylcellulose (HPMC K 100 M), Eudragit RS 100, and xanthan gum via direct compression. Evaluation included pre and post-compression tests, buoyancy, and dissolution studies. Results showed effective tablet buoyancy and sustained drug release, with the F2 formulation performing best across various kinetic models. The study confirms that these floating tablets offer a viable solution for enhanced drug delivery and patient adherence.

Keywords: Verapamil HCl, Floating tablets, Gastro Retentive Drug Delivery Systems, Controlled release, Hydroxypropyl Methylcellulose, Eudragit RS 100, Xanthan gum

I. INTRODUCTION:

Oral drug delivery is the most widely used and accepted route due to its convenience and cost-effectiveness. Conventional oral dosage forms like tablets and capsules provide immediate drug release but suffer from drawbacks such as frequent dosing, fluctuating blood drug levels, and potential side effects(1). Controlled release drug delivery systems (CRDDS) have been developed to address these issues by maintaining steady drug levels over extended periods, enhancing treatment efficiency, minimizing side effects, and improving patient compliance. Despite advancements, most CRDDS only manage 12-hour release, with 24-hour oral delivery feasible for certain drugs absorbed throughout the GI tract. Challenges in developing CRDDS include ensuring prolonged drug absorption and addressing the variable nature of gastric emptying.(2) Gastro retentive drug delivery systems (GRDDS) have emerged to extend the gastric retention time, thereby enhancing drug absorption and bioavailability. GRDDS uses various mechanisms, such as floating and bioadhesive systems, to retain the drug in the stomach, enabling prolonged and controlled drug release for better therapeutic outcomes. Understanding the GIT's complex anatomy, physiology, and variations in acidity, bile salts, enzymes, and mucosal surfaces is crucial for modulating GI transit time and enhancing drug absorption via GRDDS. The stomach, divided into fundus, body, and antrum, acts as a reservoir and mixing site, with mucus and gastric acid playing key roles in protection and pH regulation. Continuous GIT motility includes digestive and interdigestive modes, with the interdigestive myoelectric cycle cycling every 2 to 3 hours during fasting.(3) Phase I (basal phase) lasts from 30-60 minutes with rare contractions. Phase II (preburst phase) lasts for 20-40 minutes with intermittent action potential and contractions, increasing gradually in intensity and frequency. Phase III (burst phase), or housekeeper wave, lasts for 10-20 minutes with intense, regular contractions that sweep undigested material into the small intestine. Phase IV, lasting 0-5 minutes, occurs between phases III and I of consecutive cycles. These phases, cycling every 90-120 minutes, determine gastric retention time (GRT) and influence drug delivery systems (DDS). Successful gastric absorption hinges on physicochemical factors like pH-dependent solubility, physiological factors like absorption mechanisms, and biochemical factors like intestinal metabolic enzymes. Optimal functioning of an oral gastro-retentive DDS (GRDDS) requires understanding the drug's physicochemical properties, pharmacokinetic profile, and interaction with GI tract anatomy and physiology. Factors like dosage form density, size, shape, single or multiple units, fed or unfed state,

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meal nature and frequency, gender, age, posture, concomitant drug administration, and biological conditions control GRT. Floating DDS (FDDS) enhance bioavailability by remaining buoyant in the stomach, using mechanisms like non-effervescent and effervescent systems, improving sustained and site-specific drug delivery. Despite their advantages, FDDS have limitations, including the need for sufficient gastric fluids, poor suitability for drugs unstable in gastric environments, and potential irritation to gastric mucosa.Verapamil, marketed as Calan, Isoptin, Verelan, and Covera-HS, is a calcium channel blocker used for hypertension, angina, and arrhythmias. Its molecular formula is $C_{27}H_{38}N_2O_5$ with a molecular weight of 454.46 g/mol. The drug, which blocks L-type calcium channels, can cause side effects like dizziness and constipation, and interacts with CYP3A4 inhibitors. It's contraindicated in severe hypotension and bradycardia, requires caution during pregnancy (Category C), and is available only by prescription.Hydroxypropyl methylcellulose (HPMC) and Eudragit polymers (S100 and L100) enhance film-forming and controlled release. Xanthan gum thickens, while polyvinyl pyrrolidone (PVP K-30) binds. Sodium bicarbonate buffers, microcrystalline cellulose adds bulk, Aerosil improves flow, and magnesium stearate acts as a lubricant.

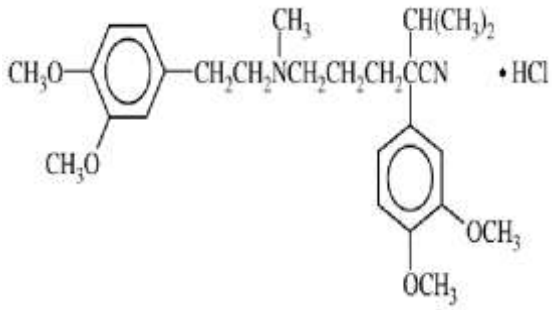

Figure 1: structure of Verapamil Hcl

II. MATERIALS AND METHODS:

2.1. Materials:

Verapamil HCl is supplied by Pharma Train, while Hydroxypropyl methylcellulose K 100M, Eudragit RS 100, and xanthan gum are provided by Colorcon. Polyvinyl pyrrolidone (PVP K-30), sodium bicarbonate, microcrystalline cellulose (MCC), talc, and magnesium stearate are sourced from SD Fine Chemicals in Mumbai.

The equipment includes an Electronic Weighing Balance (Scale-Tec), a Friabilator (Roche Friabilator, Electrolab, Mumbai), a Compression Machine (CMD Cadmach), and a Tablet Hardness Tester (Pfizer Hardness Tester, Mumbai). Other items are a UV spectrophotometer (Labindia UV 3000+), a Dissolution Apparatus (Electrolab TDT-08L), and Vernier Calipers (CD-6" CS).

2.2.Method:

I. Analytical Method Development

Preparation of 0.1 N Hydrochloric Acid (pH 1.2)

8.5 ml of concentrate hydrochloric acid was taken and diluted with distilled water up to 1000 ml.

Determination of λ_{max} of Verapamil HCl in 0.1N HCL:

Procedure:

Working standard: 100mg of Verapamil HCl was weighed and dissolved in 10ml methanol and then make up to a volume of 100ml with 0.1N HCL it gives 1000µg/ml concentrated stock solution.

Dilution 1: From the working standard solution 10ml was diluted to 100ml with 0.1N HCL it will give 100µg/ml concentrated solution.

Dilution 2: From dilution-1, 10ml was diluted to 100ml with 0.1N HCL it will give 10µg/ml concentrated solution.This solution was scanned at a range of 200-400nm wavelength light corresponding scan spectrum curve was noted. The corresponding wavelength having highest absorbance is noted as λ_{max}..

Calibration Curve of Verapamil HCl in 0.1N HCl: Weigh 100 mg of Verapamil HCl, dissolve in 10 ml methanol, and dilute to 100 ml with 0.1N HCl to make a 1000 µg/ml stock solution. Dilute 10 ml of this stock solution to 100 ml with 0.1N HCl for a 100 µg/ml solution. Prepare 2, 4, 6, 8, and 10 µg/ml solutions from this by taking 0.2, 0.4, 0.6, 0.8, and 1 ml, respectively, and diluting to 10 ml. Measure absorbance at λmax=242 nm.

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Table 1: Formulation of Verapamil HCl floating tablets by direct compression method

INGREDIANTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
VERAPAMIL HCL	80	80	80	80	80	80	80	80	80
HPMC K 100 M	20	40	60	-	-	-	-	-	-
EUDRAGIT RS 100	-	-	-	20	40	60	-	-	-
XANTHUM GUM	-	-	-	-	-	-	20	40	60
PVP K30	6	6	6	6	6	6	6	6	6
SODIUM BICARBONATE	30	30	30	30	30	30	30	30	30
MCC	80	60	40	80	60	40	80	60	40
AEROSIL	2	2	2	2	2	2	2	2	2
MG.STEARATE	2	2	2	2	2	2	2	2	2
TOTAL WEIGHT	220	220	220	220	220	220	220	220	220

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies

A)Pre Compression studies:

The angle of repose is the maximum angle between the surface of a powder pile and the horizontal plane, determined using the funnel method. An accurately weighed powder blend is poured through a funnel, which is adjusted so its tip just touches the apex of the pile. The diameter of the resulting powder cone is measured, and the angle of repose is calculated using the formula $q = \tan^{-1} \left(\frac{h}{r}\right)$, where h is the height and r is the radius of the cone. This measurement characterizes the flow properties of solids and reflects inter-particulate friction or resistance to particle movement.

Table 2 : Angle Of Repose Limits
Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

2. Density:

a) Bulk density (BD):

Bulk density is the mass of powder divided by its bulk volume. Weigh 25 g of granules (passed through a 22# sieve) and transfer to a 100 ml graduated cylinder, level the powder, and calculate.

Bulk density = weight of powder / Bulk volume.

$$D_b = \frac{M}{V_0}$$

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b) Tapped density (TD): Tapped density (TD) is the mass of powder divided by its tapped volume. Weigh 25 g of granules (passed through a 22# sieve), place in a 100 ml graduated cylinder, and tap until the volume stabilizes, then calculate using Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f).$$

3. Carr's Index:

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4. Hausner's Ratio:

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Table 3: Compressibility Index Limits

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

B) Post compression studies:

1.General Appearance: Tablets are assessed for shape, color, texture, and odor.

2.Average Weight/Weight Variation:Weigh 20 tablets collectively and individually. Calculate the average weight. Check individual tablet weights against the average weight to ensure no more than two tablets deviate by more than 7.5% (for 300 mg tablets) or double this percentage.

3.Thickness: Measured using Vernier calipers (n=3).

4.Hardness: Determined with a Monsanto hardness tester (n=3). The force required to fracture the tablet is recorded.

5.Friability:

- Tablets are weighed before and after a 4-minute rotation in a Friabilator at 25 rpm.
- Calculate % Friability: $\text{Friability} = \frac{(W1 - W2)}{W1} \times 100$
- Acceptable range: 0.5% to 1.0%.

6.Assay Procedure:To determine the quantity of Verapamil HCl in tablets, first powder ten tablets and transfer a portion equivalent to 100 mg of Verapamil HCl into a 100 ml volumetric flask. Add 10 ml of methanol, shake vigorously for 15 minutes, then dilute to 100 ml with 0.1N HCl and filter. From this solution, take 1 ml and further dilute to 100 ml with 0.1N HCl. Measure the absorbance of this final solution at 242 nm. Calculate the drug content using the standard calibration curve and apply the formula: $\text{Assay} = \frac{\text{Test Absorbance}}{\text{Standard Absorbance}} \times \frac{\text{Standard Concentration}}{\text{Sample Concentration}} \times \frac{\text{Purity of Drug}}{100} \times 100$. This will yield the percentage of Verapamil HCl in the tablets.

7. In Vitro Buoyancy Studies:

- Floating Lag Time (FLT): Time for the tablet to rise and float on 0.1N HCl.
- Total Floating Time (TFT): Duration the tablet remains floating.
- Matrix Integrity: Observed for 12 hours during TFT.

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8. In Vitro Dissolution Study:

Table 4: Dissolution parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	0.1N HCl.
Volume	900 ml
Speed	50rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1,2, 3, 4,6,8,10,12hrs
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	242 nm

1.Zero-Order Kinetics:
-Equation:**$Q=k_0t$.**
Linear relationship between the fraction of drug released (\(Q\)) and time (\(t\)). A plot of \(Q\) versus \(t\) is linear if zero-order kinetics is followed.

2.First-Order Kinetics:
Equation:**Log C= Log C_o-kt/2.303**
Describes drug release with an exponential decrease in surface area. A plot of \(\log C\) versus time yields a straight line if first-order kinetics is followed.

3. Higuchi Equation:
Equation:**Log C= Log C_o-kt/2.303**
Models drug release as a diffusion process. A plot of \(Q\) versus \(t^{1/2}\) is linear if Higuchi kinetics apply.

4. **Peppa's-Korsemeyer Equation (Power Law):**
Equation:**Log C= Log C_o-kt/2.303**
To characterize solvent penetration and drug release, the Peppa's-Korsemeyer equation's diffusion exponent \(n\) is used. A linear plot of \(\log(M_t/M_\infty)\) versus \(\log t\) indicates adherence to this model, with the slope representing \(n\). Regression analysis in MS Excel was employed to determine the drug release mechanism based on correlation coefficients from the kinetic model plots.

Table 11: Drug release kinetics mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non-Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

III. RESULTS AND DICUSSION

1. Construction of Standard calibration curve of Verapamil HCl in 0.1N HCL:

Absorbance was measured at 242 nm using a UV spectrometer with 0.1N HCl as the blank, and the results are listed in Table 12. A graph of absorbance versus concentration confirmed compliance with Beer's law within the 2 to 10 µg/ml range.

Table 5: Standard Calibration graph values of Verapamil HCl in 0.1N Hcl at λ_{Max} = 242 nm

Conc.(µg / ml)	Absorbance at λ_{Max} = 242 nm
0	0
2	0.031
4	0.061
6	0.095

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8	0.125
10	0.158

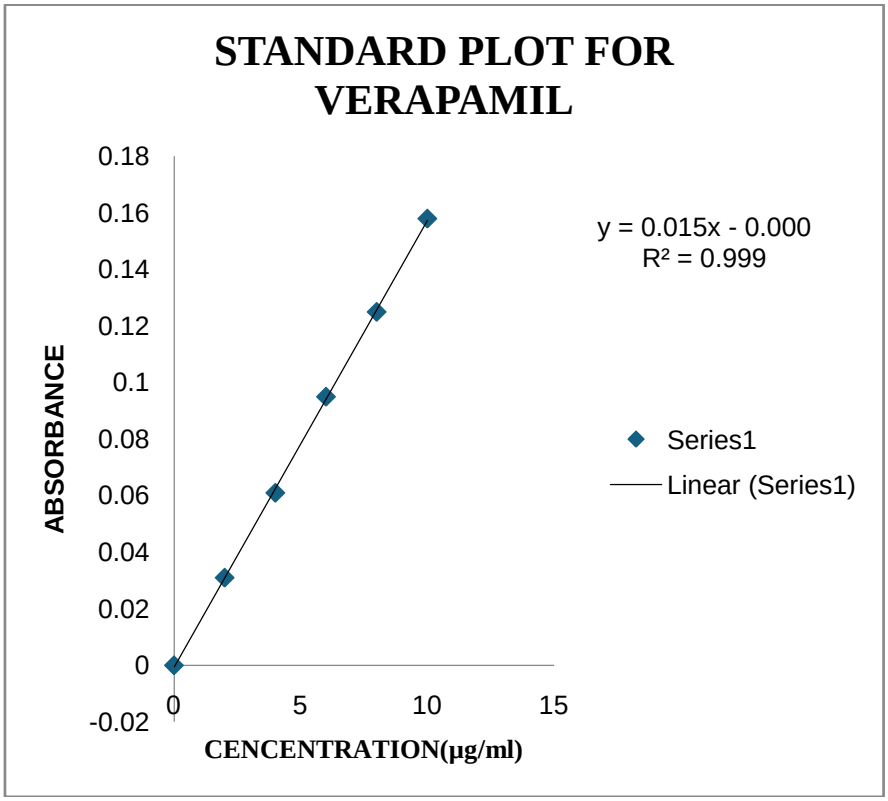

Figure 2: Standard calibration curve of Verapamil HCl in 0.1N Hcl at λ_{Max} = 242nm

Evaluation of Tablets:

Table 6: Precompression studies of Verapamil HCl Floating tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.40	0.48	16	1.2	12.73
F2	0.41	0.50	13.0	1.5	11.29
F3	0.50	0.58	13	1.16	11.58
F4	0.39	0.47	17.0	1.56	12.23
F5	0.37	0.41	9.75	1.1	12.35
F6	0.43	0.52	17.3	1.41	11.62
F7	0.44	0.50	12	1.1	9.92
F8	0.41	0.45	8.8	1.0	11.85
F9	0.39	0.48	18	1.23	11.96

Table 7: Post compression studies of Verapamil HCl floating tablets

Formulation Code	% weight variation	Thickness (mm)	% Friability	% Drug Content	Hardness (Kg/cm^2)
F1	pass	5.06±0.11	0.142	101.3 ±1.2	5.56 ±0.057

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F2	pass	5.06±0.15	0.151	102.3 ±1.7	5.03 ±0.115
F3	pass	5.03±0.057	0.62	100.1 ±1.2	5.01 ±0.1
F4	pass	5.1±0.1	0.154	100.7 ±1.1	5.63 ±0.05
F5	pass	5.03±0.05	0.132	99.6±1.5	5.63 ±0.03
F6	pass	5.03±0.15	0.143	98.9 ±2.3	5.5 ±0.05
F7	pass	4.93±0.05	0.110	100.2± 1.7	5.7 ±0.1
F8	pass	5.1±0.1	0.133	100.5± 1.4	5.53 ±0.04
F9	pass	5.02±0.2	0.13	99.2±1.1	5.69 ±0.05

Table 8: In vitro Buoyancy Studies of Verapamil HCl floating tablets

Formulation Code	**Floating lag time(sec) n = 3**	**Total floating time n = 3**	**Matrix Integrity upto 12 hrs. n = 3**
F1	20 ± 0.51	Up to 12	+
F2	40 ± 0.21	Up to 12	+
F3	80 ± 0.61	Up to 12	+
F4	20 ± 0.71	Up to 10	-
F5	30 ± 0.81	Up to 12	+
F6	35 ± 0.51	Up to 12	+
F7	24 ± 0.31	Up to 10	-
F8	20 ± 0.81	Up to 12	+
F9	36 ± 0.71	Up to 12	+

Table 9: In-vitro Dissolution results for formulation trails

Time (hrs)	**% Drug released**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8`**	**F9**
0	0	**0**	0	0	0	0	0	0	0
1	35	**28**	21	48	40	47	55	45	32
2	48	**37**	38	67	57	59	68	59	43
4	61	**45**	47	86	68	71	81	70	56
6	76	**59**	56	97	88	86	98	81	68
8	88	**71**	63	100	95	98	100	91	76
10	100	**88**	78	100	100	100	100	100	85
12	100	**100**	85	100	100	100	100	100	100

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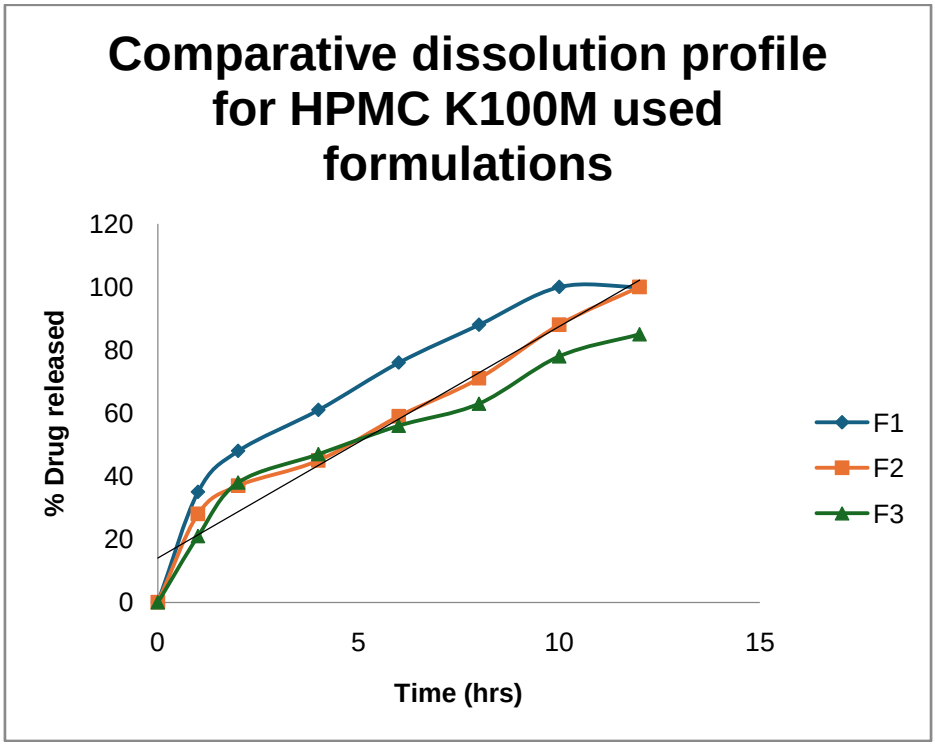

Figure 3: Comparative dissolution profile for HPMC K100M used formulations

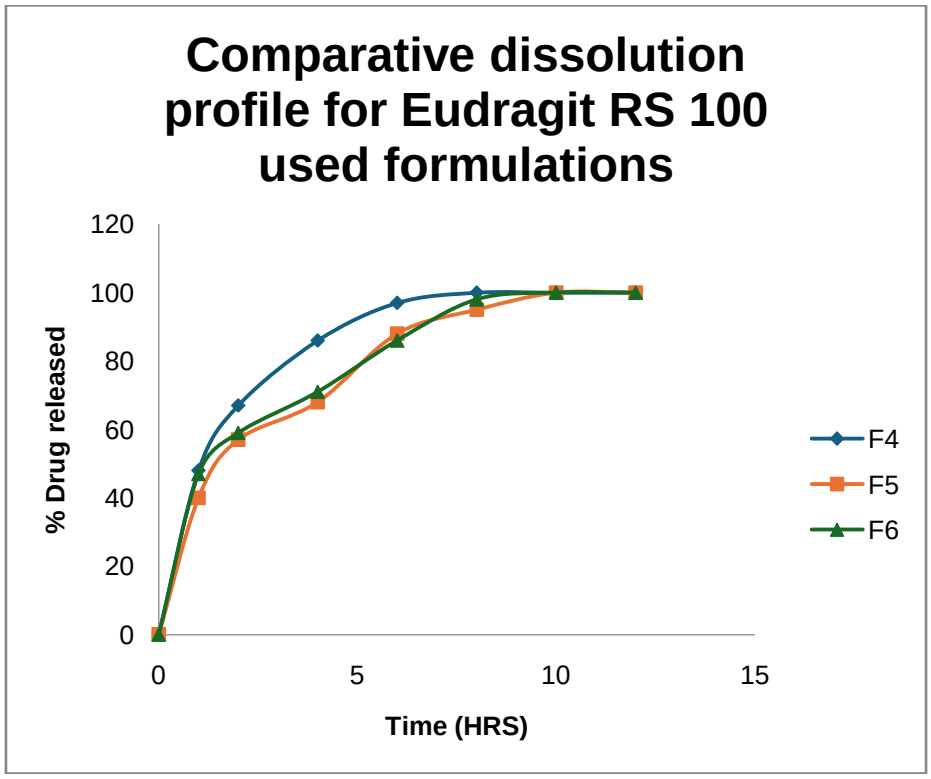

Figure 4: Comparative dissolution profile for Eudragit RS100 used formulations

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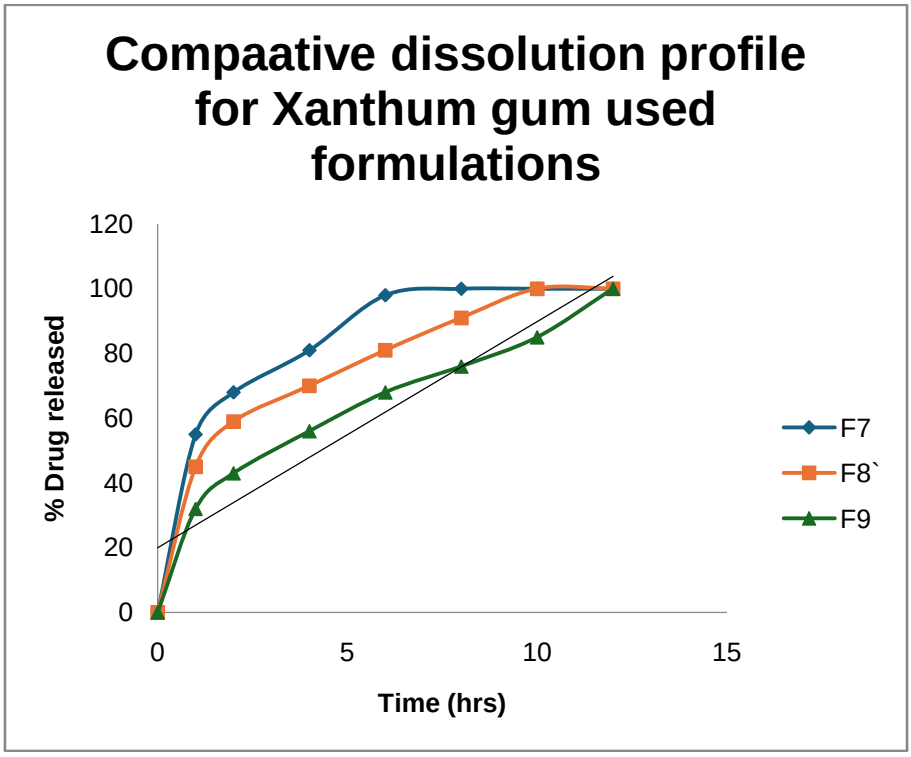

Figure 5: Comparative dissolution profile for Xanthum gum used formulations

Table 10: R^2 value and n result table

Formulation code	R2 value				"n" value
	Zero Order	First Order	Higuchi	Peppas	
F2	0.957	0.923	0.974	0.962	0.503

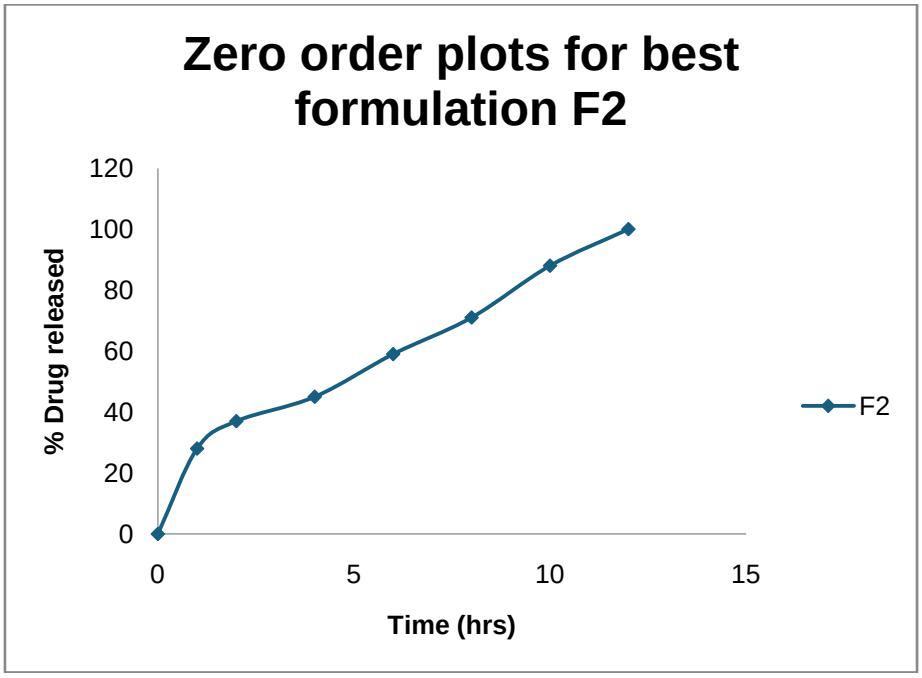

Figure 6: Zero order plot for best formulation F2

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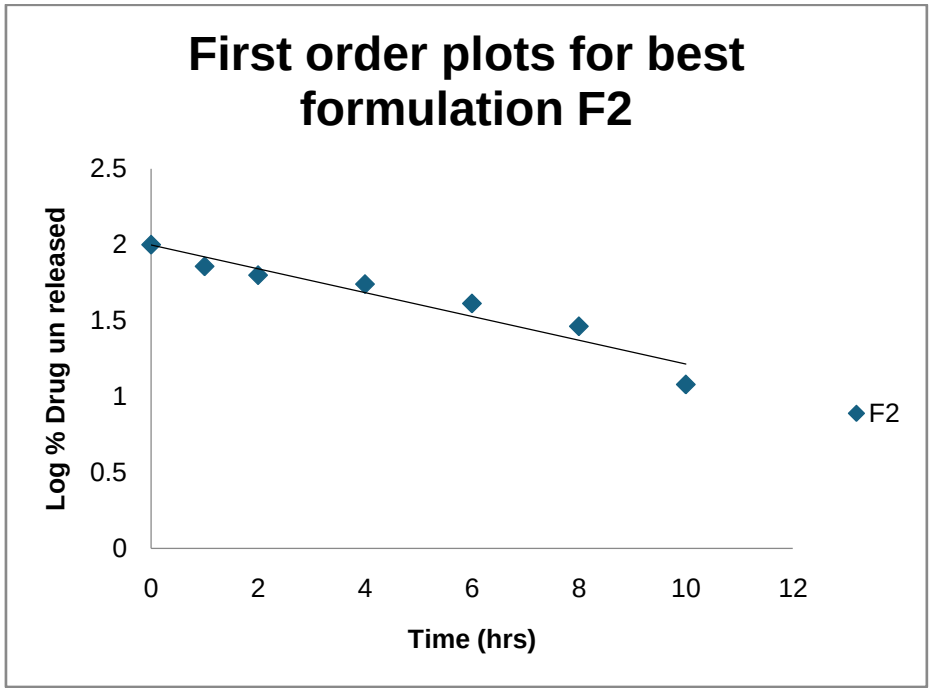

Figure 7: First order plot for best formulation F2

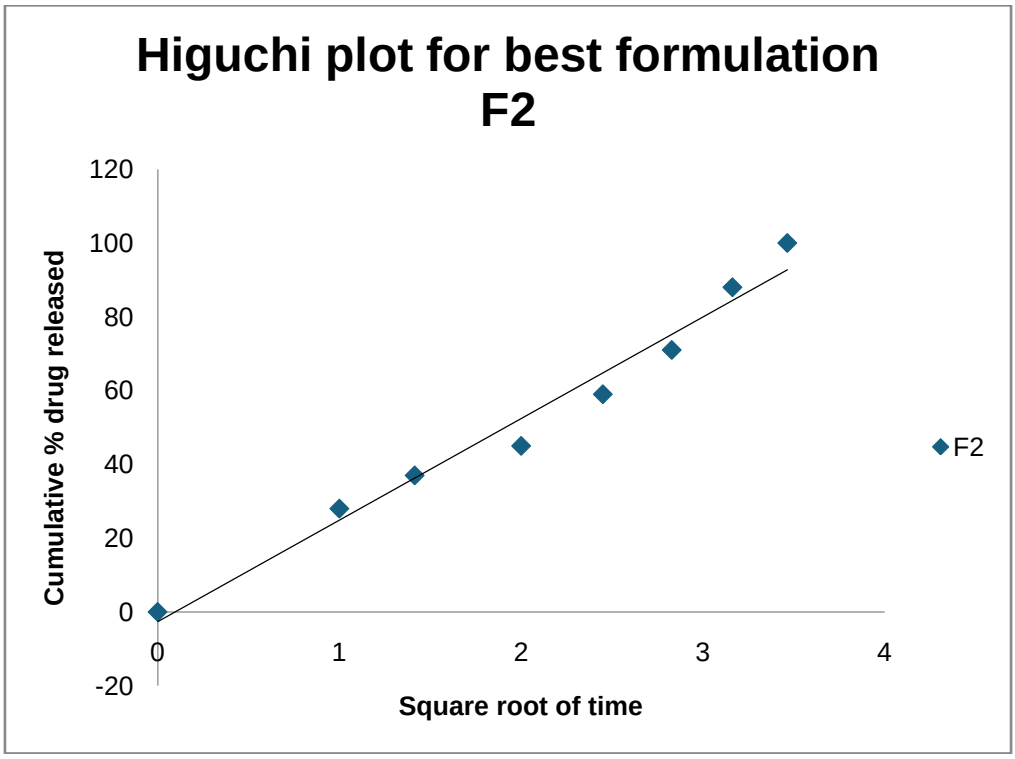

Figure8: Higuchi plot for best formulation F2

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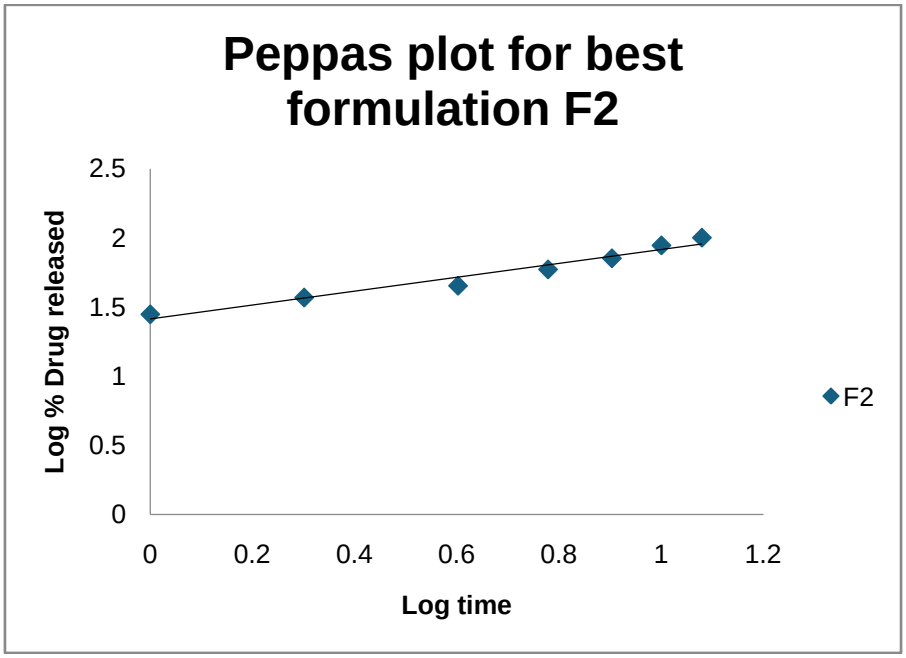

Figure 9: Korsmayerspepas plot for best formulation F2

IV. SUMMARY AND CONCLUSION

The absorbance of the solution was measured at a wavelength of 242 nm using a UV spectrometer, with 0.1N HCl serving as the blank to account for any background absorbance. The measured absorbance values are detailed in Table 12. To evaluate the relationship between absorbance and concentration, a graph was plotted with absorbance on the y-axis and concentration on the x-axis. The resulting graph indicated that the absorbance values were linearly related to the concentration within the range of 2 to 10 µg/ml, demonstrating that the system adheres to Beer's law over this concentration range. This compliance confirms the reliability of the UV spectroscopic measurements for quantifying the substance within the specified concentration limits.

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