RESEARCH PAPER

Design Optimization and Characterization of Verapamil Hydrochloride Pulsatile Capsule for Chronotherapeutic Drug Delivery

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ABSTRACT
The aim of the research was to design and test a unique tablet for verapamil hydrochloride to prevent early heart attacks in the morning. A hydrogel plug with HPMC K4 and lactose in a 1:1 ratio (HP4) using 7 mm punches and dies on a rotary tablet press was pressed and placed inside the capsule. With different combinations of Eudragit-S 100 and Eudragit-L 100, trial batches were formulated and optimized by the response surface model with Design Expert version 12 by two-factor, three-level design. A response surface morphological plot model was used to evaluate the correlation between the independent and dependent variables. The optimized batches surface response model consisted of Eudragit S 100 and Eudragit L 100, each at 17.5 mg of X1 and X2, respectively, yielding D = 1. The responses were predicted by the combination of these factors, with the top 10% as Y1 = 0.68 and Y2 = 0.77%. To confirm the model's adequacy for prediction, the optimized batch (VF1) of pulsincap with 5 hours of lag time was released at 5.5 hours with 5.625% and at 17 hours with 99.911%, respectively. The study concluded that pulsatile release was achieved with 5 hours of lag time for the pulsincap, aligning with the needs of chronotherapeutic drug delivery to mitigate the occurrence of cardiac attacks in the early morning.

Keywords: *Verapamil Hydrochloride, HPMC K4, lactose, Eudragit S100 and Eudragit L 100, Design Expert version 12.*
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INTRODUCTION

In a pulsatile drug delivery system (DDS), medication is released at a predetermined rate after a predetermined lag time. The purpose of pulsatile systems is to accurately dose and deliver medication at the right time to the intended site. They are effective when drug has a high first-pass metabolism, if the medications target specific gastrointestinal absorption sites such as the colon, and when nighttime dosing is necessary[1,2]

PULSATILE CAPSULE

The capsule system contains an insoluble polymer mixer that acts as a plug to delay the release of the drug. Once a certain amount of time has passed, the plug is removed as it has expanded, eroded, or dissolved. Using pulsatile capsule technology, a pharmaceutical dosage form is enclosed in a water-insoluble capsule body[3]. As the capsule comes into contact with the dissolved media or gastrointestinal fluids, the plug expands. Eventually, the plug exits the capsule, leading to the slow release of the drug. During this process, the drug is released into the bloodstream, ensuring its therapeutic effects are achieved within a short period of time. The plug mechanism is particularly useful for drugs that require timely release of action or for patients who need fast relief from symptoms. Insoluble, permeable, and swellable polymers (such as polymethacrylates) are used in the plug material, as well as erodable compressed polymers such as HPMC, PVA, and polyethylene oxide. Moreover, PEGylated monooleate, glyceryls, and polyesters are used in swellable plug design[4,5].

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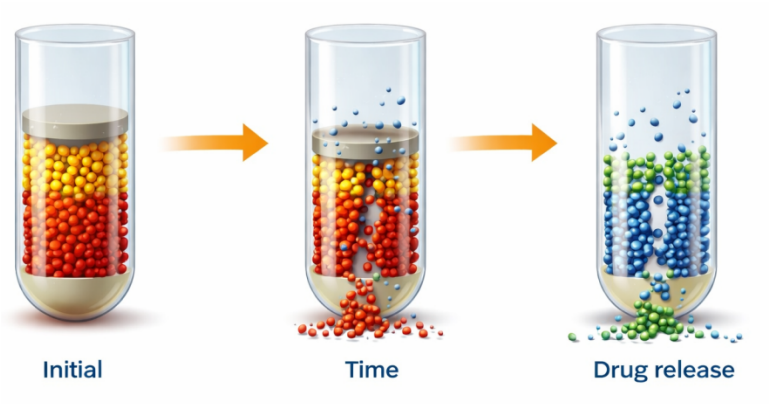

Fig.No.1 Pulsatile Capsule with plug model drug release[6]

MATERIALS AND METHODS

The Verapamil Hydrochloride was received as a gift sample from Biophore Pharma Ltd. All the remaining ingredients are IP grade and were used in the study[7].

METHOLODOGY[8-12]

Preformulation studies:

The below pre-formulation studies were carried[8].

Physical properties:

a. Determination of Melting point: The melting point was determined by melting point apparatus[9].

b. LOD: The test utilized a minimum of 1.0 g of material. A measured sample was placed in a pre-weighed glass bottle, and its weight was noted. The sample underwent heating in a Lindberg/Blue M oven at a temperature range of 105-110°C for a duration of 3 hours. Subsequent to heating, the sample was allowed to cool in desiccators to room temperature prior to reweighing. The transfer from the oven to weighing took approximately 30 minutes. The process persisted until a stable weight was observed, indicating that all moisture had been removed from the sample[10]. All the results are reported in Table 3.

Flow properties of drugs:

The flow properties of Verapamil hydrochloride were determined.

Phase solubility studies: - Phase solubility studies were conducted in ethanol, chloroform, methanol, acetone, and distilled water. A conical flask with a volume of 100 ml was filled with 10 ml of solvent and diluted with Verapamil hydrochloride to saturation. The saturated solutions were spun with an orbital shaker for one hour, then stored at room temperature overnight. A UV spectra was used to measure the saturation solution concentration at 278 nanometers[11].

Drug-Excipient Compatibility Studies:

With the help of FTIR spectra, drug-excipient compatibility between the selected excipients was determined[12]. All the results are reported in Tables 4, 5 & Fig. No. 1.

Standardization of Pure Drug:

A 100mg sample of the pure drug was dissolved in various solvents, including 0.1N Hydrochloric acid, phosphate buffers at pH 6.8 & 7.4. A serial dilution ranging from 0 to 12 µg was prepared. The spectrophotometric method utilized to measuring extinction at 278 nm[13]. All the results are reported in Fig.No.2.

Preparation of Hydrogel Plug[14]:

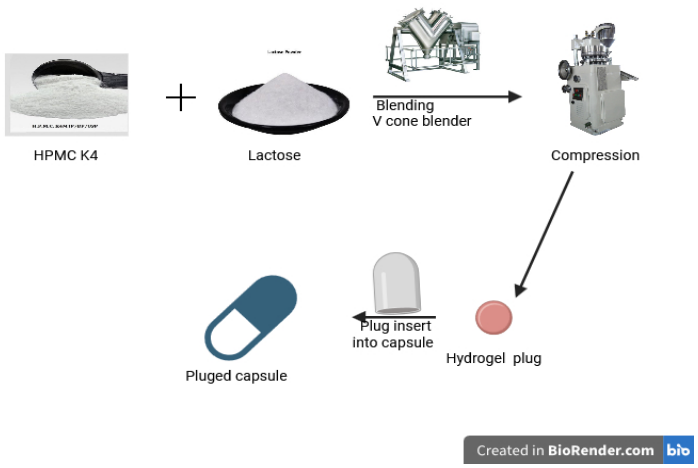

Table 1: Hydrogel Plug Composition

Batch	Ration (1:1)	Amount in mg
	HPMCK100:lactose	
Trial-1	32.5 :32.5	65
Trial-2	55: 55	110
Trial-3	60:60	120
Trial-4	85:85	170

Designing of Pulsincap [15]

The drug-loaded pellets were filled into a capsule and sealed with an optimized plug and prepared pulsincap. The formulations were prepared by using the Response Surface Morphological model DOE version 12. The optimization performed using a two-factor, three-level design was implemented to conduct the experiments. To study how independent variables, influence dependent variables, a response surface morphological plot model was used and reported in Table.2

Table.2 Design of Expert

Trial Batches	Coded Value		Actual Quantity (mg)	
	X_1	X_2	X_1	X_2
VF_1	+1	+1	17.5	17.5
VF_2	+1	0	17.5	13.125
VF_3	+1	-1	17.5	8.75
VF_4	0	+1	13.125	17.5
VF_5	0	0	13.125	13.125
VF_6	0	-1	13.125	8.75
VF_7	-1	+1	8.75	17.5
VF_8	-1	0	8.75	13.125
VF_9	-1	-1	8.75	8.75

X_1 = Eudragit- S 100 X_2 = Eudragit- L 100

Evaluations:

All the 9 formulations were prepared and evaluated. The specific studies were performed for optimized batch only[16].

In Vitro Dissolution Study:

In the USP II apparatus, dissolution was performed using the paddle method. The capsule was tied to the paddle to ensure it stayed submerged. To mimic the pH changes in the gastrointestinal tract, three different pH media were used sequentially: pH 1. 2 for 2 hours, pH 7. 4 for 3 hours, and pH 6. 8 for the remaining hours. Each time, 900 milliliters of media were used. The rpm was 100 & the temperature was kept at 37±0.5°C. Five milliliters of verapamil hydrochloride were drawn at set times and analyzed using UV at 278 nm to determine the % cumulative drug release[17]. All the values are reported in Table.8 & Fig.No.3.

Release Kinetics:

Analyzing how drugs are released from pharmaceutical dosage forms is important and complicated, especially for matrix systems. This process involves using different models to fit dissolution data. Three common release models are diffusion equations, first-order equations, and zero-order equations. Zero-order or first-order kinetics help describe how the drug is released from these matrix systems. To determine the mechanism of drug release from the matrix, the Higuchi equation or the Korsmeyer-Peppas equation is employed[18]. All the results are reported in Table.9 & Fig.No.4.

Stability Studies of Verapamil Hydrochloride Pulsatile Capsule:

A two-group optimized pulsatile capsule containing verapamil hydrochloride formulation was kept in the stability chamber. For three months, each group was placed in a stability chamber set at 25±2°C/60% RH and 40±2°C/75% RH. Each month, the formulation was tested for dissolution to measure the percentage of drugs released[19,20]. All the results are reported in Table.10-12 & Fig.No.3-6.

RESULTS

Preformulation Study:

Table 3: Preformulation study results

Characteristics	Results
M.P (°C)	163
LOD (%)	0.21
Bulkiness (g/cc)	0.334

T.D (g/cc)	0.542
C.I (%)	38.37
Distilled water	Freely soluble
Solubility in CH_3OH(mg/ml)	>28
Solubility in CH_5OH (mg/ml)	>37
Solubility in CH_3COOOH (mg/ml)	>34
Solubility in $CHCl_3$(mg/ml)	>46
Solubility in 0.1N HCL (mg/ml)	>11
Solubility in phosphate buffer at pH 6.8 (mg/ml)	15
Solubility in phosphate buffer at pH 7.4 (mg/ml)	0.22

M.P=Melting point. T.D= Tapped Density, C.I=Compressibility Index,

The studies confirmed that the selected drug conformed primarily with the melting point. Solubility data showed that pH 6.8 has a higher value compared with the other solvents. Finally, 6.8 phosphate buffer was selected for further studies.

Drug-Excipient compatibility studies:

Table 4. Fourier Transform Infrared Spectral assignments for Verapamil HCl

Sr. No	Energy (Wavenumbers cm^{-1})		Assignments
	Reported	Sample	
1	3300-3400	3371.37	OH
2	1500-1600	1518.21	C6H5
3	2800-3000	2948.45	Aliphatic CH
4	1000-1100	1035.36	C-O-C

Table 5. Fourier transform infrared spectral assignments with excipients

S No	Functional Group	Reported Values	Drug	Drug+ HPMC K4	Drug + Lactose
1	OH	3300-3400	3371.37	3373.31	3373.31
2	C_6H_5	1500-1600	1518.21	1519.13	1519.13
3	Aliphatic CH	2800-3000	2948.45	2944.18	2944.18
4	C-O-C	1000-1200	1035.36	1033.86	1033.86

Fig.No.2 FTIR spectra of pure drug with excipients

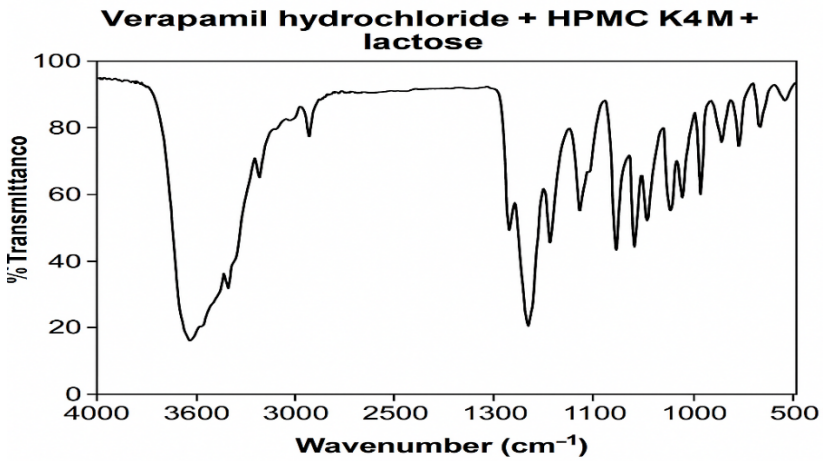

Fig.No.3 Calibration curve of Verapamil hydrochloride

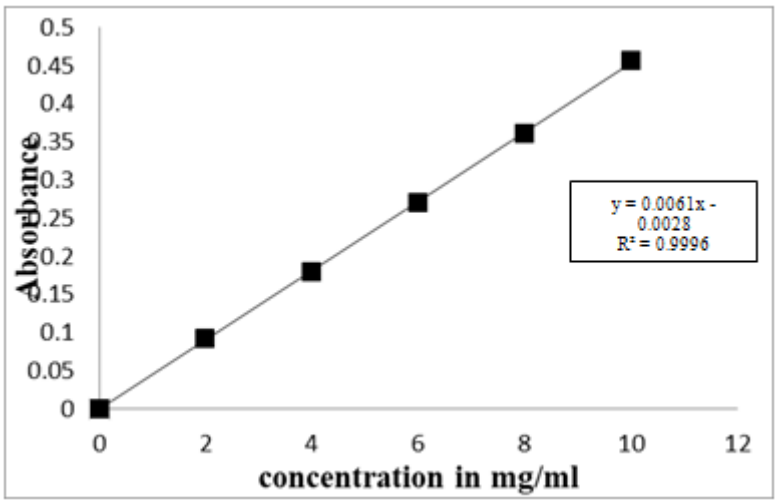

Table.6. % yield, pellets size, and % drug content of Verapamil hydrochloride pulsatile capsule

Formulation	% yield	Avg. Particle Size(µm)	% of Drug loaded
VF 1	96.29	691.31±0.03	97.68±0.02

Table.7. Derived properties of Verapamil hydrochloride pulsatile capsule

Formulation	(θ)	B.D	T.D	C.I(%)	H.R
VF_1	25.42	0. 908±0.03	1.066±0.04	14.82±0.04	1.17±0.03

Table.8. *In-vitro* drug release study of pulsatile capsule

Time (hrs.)	% of *In-vitro* drug release
0	**0**
0.5	0
1	0
1.5	0
2	0
2.5	0
3	0
3.5	0
4	0
4.5	0
5	0.000
5.5	5.940
6	11.422
6.5	15.643
7	20.045
7.5	24.156
8	27.312
8.5	30.580
9	32.738
9.5	36.065
10	40.040
10.5	44.037
11	47.739
11.5	51.460
12	54.886
12.5	58.644
13	62.736
13.5	67.164
14	72.875

14.5	78.931
15	83.443
15.5	87.348
16	92.533
16.5	97.113
17	99.827

Fig.No.4 In-*vitro* drug release profile of pulsatile capsule

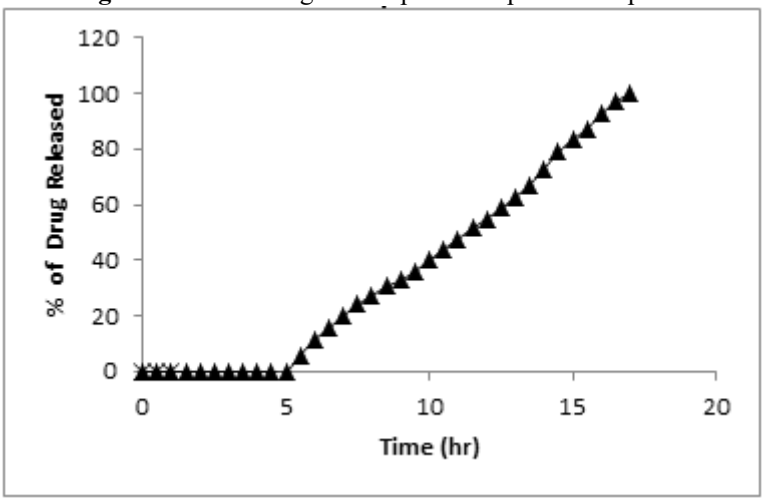

Table.9. *D*rug release kinetic data pulsatile capsule

Formulation	Correlation Coefficient Value (r)				Release Rate Constant (mg/hr)k_0	Exponential Coefficient (n)	T_{50} (hr)	T_{90} (hr)
	Zero Order	First Order	Matrix	Peppas				
VF 1	0.9972	0.7422	0.9223	0.9969	6.60	0. 8718	6.06	10.90

Fig.No.5 Drug release kinetics of pulsatile capsule

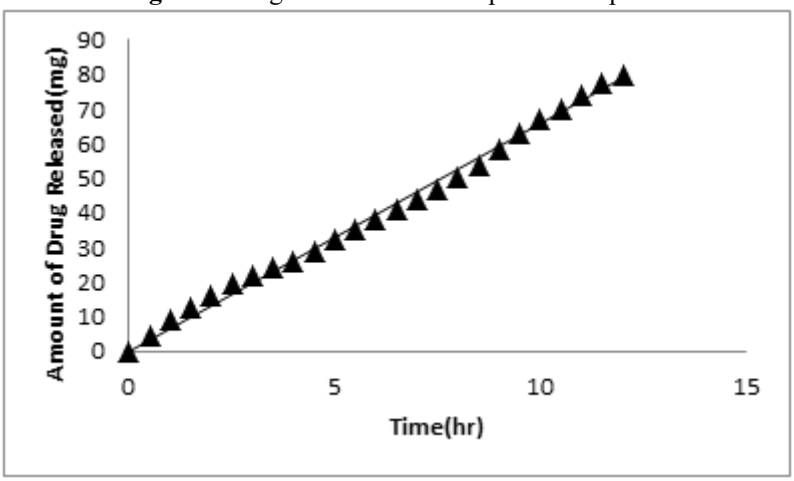

Table.10. Stability studies of pulsatile capsule

Storage	Sample period	Amount of drug	K_o	$t_{50\%}$	$t_{90\%}$
25±2^0 C/ 60±5% RH	**30days**	97.68	6.60	6.06	10.90
	60days	97.64	6.60	6.06	10.90
	90 days	97.61	6.60	6.06	10.90
40±2^0 C/ 75±5% RH	**30days**	97.63	6.60	6.06	10.90
	60days	97.60	6.60	6.06	10.90
	90 days	97.58	6.60	6.06	10.90

Table.11. Stability studies of pulsatile capsule

Time (h)	Initial	% drug Released ($\bar{x}$ ± standard deviation)					
		25±2^0 C/60±5% RH			40±2^0 C/75±5% RH		
		30days	60days	90days	30days	60days	90days
0	0.000	0	0	0	0	0	0
5.5	5.940	5.84±0.09	5.76±0.13	5.67±0.06	5.72±0.13	5.64±0.08	5.55±0.05
6	11.422	11.37±0.10	11.28±0.08	11.20±0.09	11.35±0.14	11.31±0.11	11.23±0.05
6.5	15.643	15.52±0.11	15.44±0.05	15.41±0.05	15.57±0.06	15.43±0.10	15.36±0.11
7	20.045	19.99±0.19	19.96±0.11	19.92±0.16	19.97±0.19	19.93±0.19	19.89±0.11
7.5	24.156	24.08±0.09	23.95±0.14	23.92±0.13	24.06±0.13	23.92±0.09	23.8.9±0.12
8	27.312	27.30±0.13	27.26±0.11	27.14±0.15	2719±0.13	27.12±0.06	27.04±0.13
8.5	30.580	30.50±0.13	30.43±0.17	30.33±0.12	30.37±0.16	30.24±0.14	30.18±0.12
9	32.738	32.64±0.14	32.60±0.12	32.57±0.16	32.63±0.13	32.61±0.14	32.58±0.12
9.5	36.065	35.96±0.08	35.87±0.06	35.77±0.08	35.94±0.13	35.91±0.09	35.89±0.08
10	40.040	39.94±0.13	39.91±0.12	39.87±0.12	39.92±0.19	39.89±0.13	39.86±0.13
10.5	44.037	43.95±0.09	43.93±0.07	43.90±0.13	43.94±0.16	43.91±0.09	43.87±0.19
11	47.739	47.60±0.11	47.57±0.06	46.52±0.11	47.66±0.11	47.59±0.06	47.43±0.11
11.5	51.460	51.32±0.14	51.23±0.05	51.12±0.10	51.28±0.13	51.23±0.08	51.13±0.10
12	54.886	54.47±0.09	54.39±0.11	54.26±0.15	54.72±0.05	54.66±0.06	54.57±0.13
12.5	58.644	58.59±0.13	58.56±0.08	58.53±0.09	58.61±0.15	58.56±0.13	58.54±0.15
13	62.736	62.68±0.13	62.65±0.16	62.61±0.12	66.67±0.13	62.59±0.09	62.48±0.15
13.5	67.164	67.13±0.19	67.11±0.13	67.08±0.14	67.15±0.22	67.11±016	67.03±0.09
14	72.875	72.808±0.12	2.69±0.09	72.60±0.09	72.79±0.08	72.72±0.09	72.67±0.13
14.5	78.931	78.84±0.15	8.73±0.06	78.62±0.06	78.67±0.09	78.51±0.11	78.43±0.15
15	83.443	83.37±0.13	3.31±0.08	83.28±0.08	83.36±0.05	83.32±0.09	83.26±0.09
15.5	87.348	87.24±0.08	87.21±0.11	87.16±0.16	87.25±0.11	87.170±0.08	87.13±0.12
16	92.533	92.45±0.19	92.38±0.19	92.33±0.12	92.42±0.09	92.36±016	92.33±0.22
16.5	97.113	97.09±0.13	7.05±0.09	96.96±0.14	97.08±0.15	97.03±0.09	96.98±0.15
17	99.827	99.80±0.10	99.72±0.11	99.62±0.13	99.79±0.09	99.73±0.06	99.66±0.08

Optimization of Designed Pulsicap by Surface Response model

***Invitro* dissolution data**

Table.12. *In-vitro* Dissolution studies

	Time	VF_1	VF_2	VF_3	VF_4
1	0	--	--	--	--
2	4.5	--	--	--	--
3	5	--	--	--	--
4	5.5	5.625	6.003	6.7745	6.4595
5	6	10.255	10.4305	10.986	11.6925
6	6.5	15.7135	15.8585	16.6375	16.1985
7	7	20.2105	20.419	21.1865	20.7295
8	7.5	24.4795	24.705	25.839	25.0645
9	8	28.173	28.9825	30.296	28.903
10	8.5	32.048	32.267	34.816	32.703
11	9	35.266	35.435	39.2585	35.9245
12	9.5	38.922	39.4075	43.2515	39.899
13	10	43.543	45.291	48.841	44.84
14	10.5	47.5585	49.6305	53.0425	48.863
15	11	51.595	54.3085	57.581	52.906
16	11.5	55.652	58.3805	62.143	57.128
17	12	59.1005	62.1585	66.099	61.214
18	12.5	62.409	65.6415	70.705	65.794
19	13	66.521	69.771	75.9645	70.5545
20	13.5	70.812	74.0795	82.0385	75.497
21	14	75.7545	79.6695	86.884	81.095

22	14.5	81.5105	85.604	91.7545	86.88
23	15	86.6655	90.466	94.654	91.5915
24	15.5	90.9025	99.9525	99.7225	99.8035
25	16	96.263	--	--	--
26	16.5	98.5535	--	--	--
27	17	99.911	--	--	--

Table.13. Drug release Kinetics

Batches	**STATISTICAL DATA**											
	Zero order			**First order**			**Higuchi**			**Korsmeyer-Peppas**		
	A	**B**	**r**	**a**	**B**	**r**	**a**	**b**	**r**	**a**	**B**	**r**
VF_1	26.287	7.239	0.976	2.797	0.124	0.747	46.518	30.952	0.857	0.581	2.162	0.972
VF_2	27.255	7.498	0.976	3.206	0.179	0.725	48.284	32.082	0.857	0.582	2.176	0.974
VF_3	26.488	7.693	0.976	3.013	0.158	0.813	48.756	33.133	0.863	0.518	2.139	0.972
VF_4	26.478	7.422	0.976	2.787	0.125	0.801	47.442	31.802	0.859	0.519	2.118	0.977

Table. 14. Zero Order kinetics

	Time	**VF_1**	**VF_2**	**VF_3**	**VF_4**
1	0	0	0	0	0
2	4.5	0	0	0	0
3	5	0	0	0	0
4	5.5	5.625	6.003	6.7745	6.4595
5	6	10.255	10.4305	10.986	11.6925
6	6.5	15.7135	15.8585	16.6375	16.1985
7	7	20.2105	20.419	21.1865	20.7295
8	7.5	24.4795	24.705	25.839	25.0645
9	8	28.173	28.9825	30.296	28.903
10	8.5	32.048	32.267	34.816	32.703
11	9	35.266	35.435	39.2585	35.9245
12	9.5	38.922	39.4075	43.2515	39.899
13	10	43.543	45.291	48.841	44.84
14	10.5	47.5585	49.6305	53.0425	48.863
15	11	51.595	54.3085	57.581	52.906
16	11.5	55.652	58.3805	62.143	57.128
17	12	59.1005	62.1585	66.099	61.214
18	12.5	62.409	65.6415	70.705	65.794
19	13	66.521	69.771	75.9645	70.5545
20	13.5	70.812	74.0795	82.0385	75.497
21	14	75.7545	79.6695	86.884	81.095
22	14.5	81.5105	85.604	91.7545	86.88
23	15	86.6655	90.466	94.654	91.5915
24	15.5	90.9025	99.9525	99.7225	99.8035
25	16	96.263	--	--	--
26	16.5	98.5535	--	--	--
27	17	99.911	--	--	--

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Fig.No 6 Comparative Zero order plots

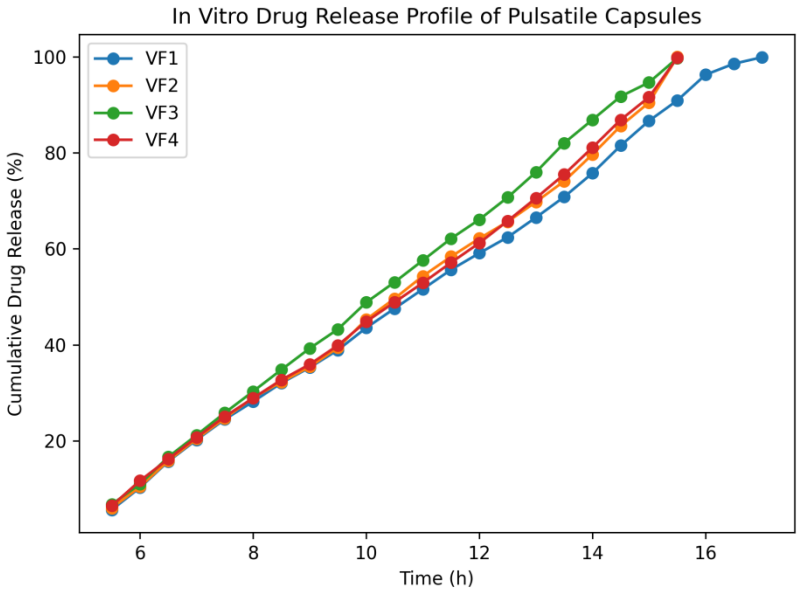


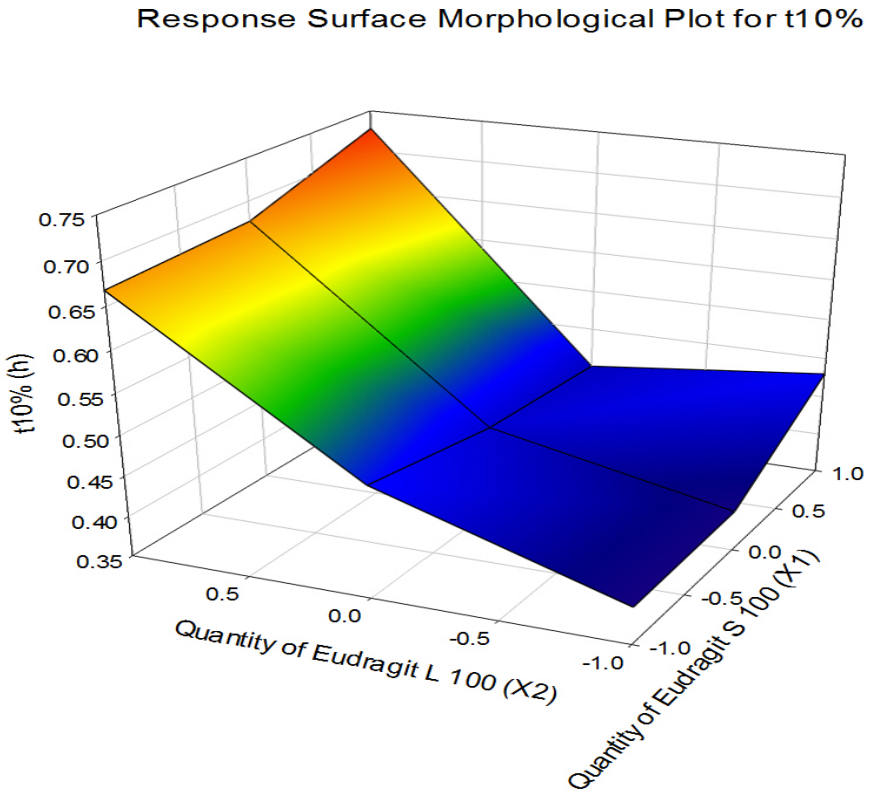
Table.15. DOE data

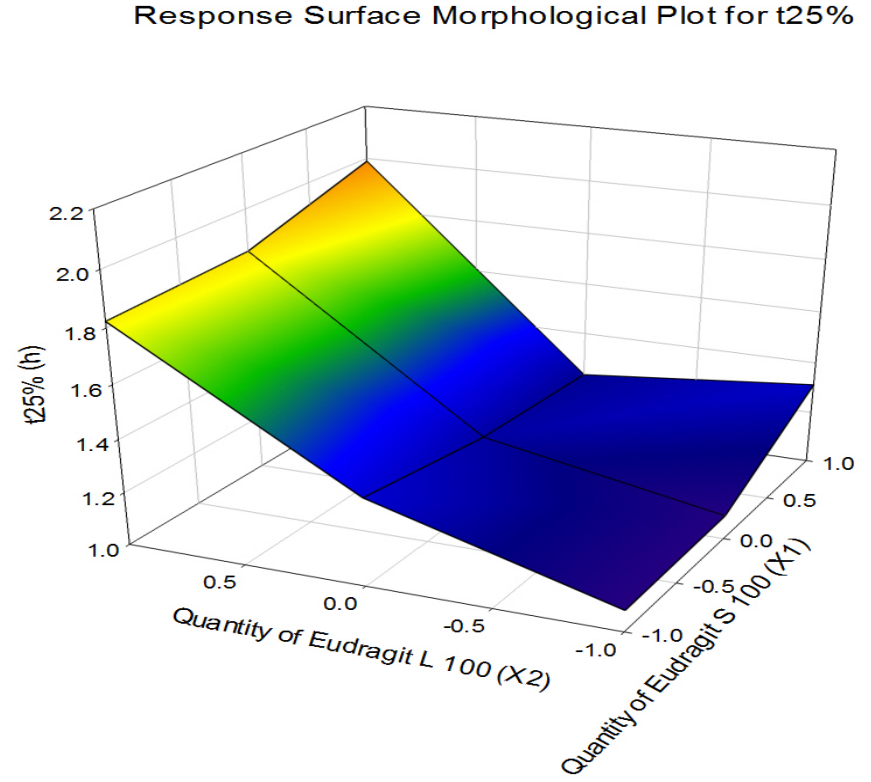
S.NO	Formulation Code	Dissolution Parameters (H)				
		$t_{10\%}$	$t_{25\%}$	$t_{1/2}$	$t_{75\%}$	$t_{90\%}$
1	**VF_1**	0.728	1.989	4.792	9.584	15.925
2	**VF_2**	0.450	1.229	2.961	5.922	9.840
3	**VF_3**	0.480	1.312	3.161	6.322	10.504
4	**VF_4**	0.676	1.845	4.446	8.892	14.775

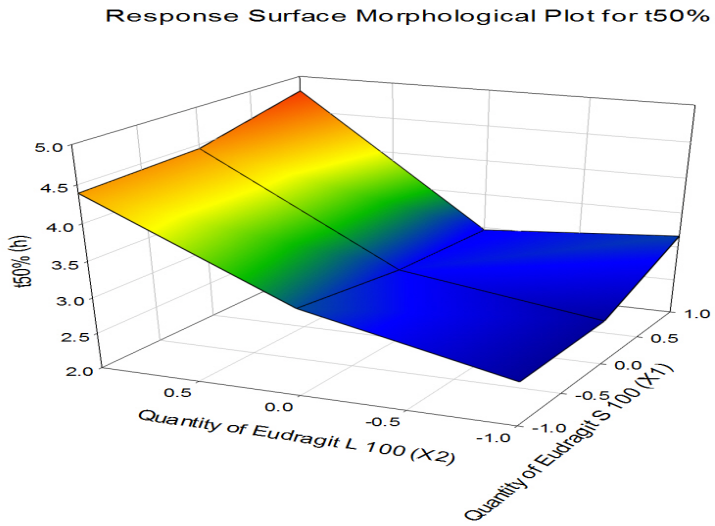
Table 11: ANOVA study

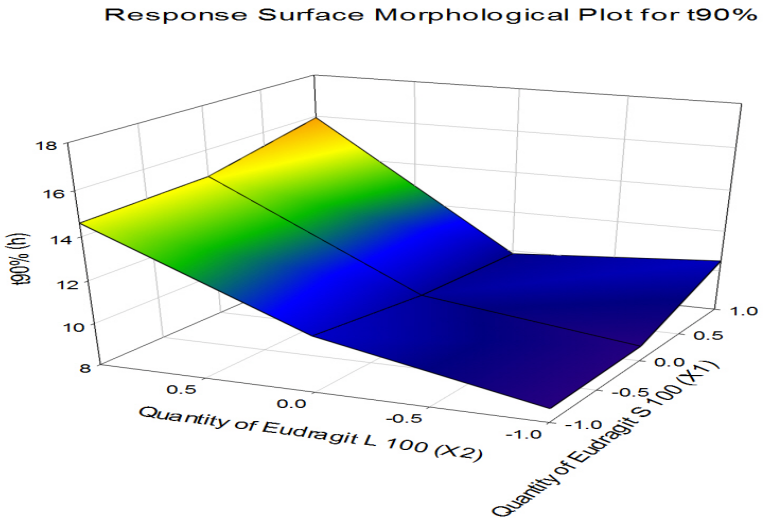
Source	Sum of squares	df	Mean square	F-value	p- value		Press	R2 value
Model	2980.01	4	415.00	253.86	<0.0001	significant	--	--
X_1 Eudragit- S 100	591.20	1	591.20	272.79	<0.0001		48.91	0.99731
X_2 = Eudragit- L 100	522.88	1	522.88	522.97	0.01599		--	--
X_1 X_2	18.79	1	18.79	8.63	0.0077		--	--
X_1	56.06	1	56.06	21.25	0.0108		--	--
X_2	29.99	1	29.99	15.17	0.0074		--	--
Residual	13.82	6	2.71	--	--	--	--	--
Lack of fit	1.32	2	1.16	0.5031	0.6653	not significant	--	--
Pure error	10.51	3	2.5	--	--		--	--
Cor total	2710.85	11	--	--	--		--	--

Fig.No 7 Response surface graphs









The mathematical model of the design used to find the relationship between selected dependent and independent variables. The significance value >1 and P<0.05. From the 3D response surface found that the combination of the polymers pulsatile release the release of the drug in desired rate.

DISCUSSION

The research aimed to create and optimize a controlled release pulsatile capsule (PRC) for verapamil hydrochloride, targeting the prevention of cardiac events in the early morning. A hydrogel plug was developed and incorporated into the capsule, sealed with HPMC K4 and lactose. Trials used Eudragit S 100 and Eudragit L 100 to explore the drug's release, using a specific experimental design to find optimal conditions. The best formula achieved a pulsatile release: after a 5-hour delay, it released 5. 625% at 5. 5 hours and 99. 911% by 17 hours.

The research also involved standardizing a 100 mg sample of Eudragit in various solvents, conducting serial dilutions, and measuring absorbance to determine drug concentrations. Hydrogel plugs were created using design software, and drug-loaded pellets were encapsulated for further analysis. The in vitro release studies tested the capsule in different pH environments to mimic the gastrointestinal tract, using known equations to analyze how the drug was released.

Stability tests showed that the drug's release rate remained consistent over time, while the kinetics of drug release were assessed based on various environmental factors. The study concluded that the Pulsicap' s design was optimized effectively, leading to reduced dissolution times and enhanced efficiency in drug delivery.

Eudragit is noted for its application in a new pulsincap system for verapamil hydrochloride. The hydrogel blend of Eudragit was found to significantly impact drug release, achieving an pulsatile release release duration. Overall, the research presents the developed pulsincap delivery system as a promising approach for treating cardiac arrhythmias, highlighting the importance of the formulation in drug solubility and release rates.

CONCLUSION

A novel Verapamil Hydrochloride pulsincap formulation was developed, utilizing pellets coated with a 17.5:17.5% Eudragit L_{100} & S_{100} hydrogel blend and a HPMCK100: lactose (75:75) hydrogel plug. This design successfully

achieved pulsatile release after 5Hrs lag time, with the optimized formulation (VF1) released up to 12 hours. The DoE study factors have strong effect on dissolution and pulsincap analysis revealed a significant influence of the carrier on drug dissolution, while dependent factors played a more constrained role. These findings suggest the developed Verapamil Hydrochloride pulsincap formulation is a highly promising approach for cardiac arrhythmia treatment.

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