ORIGINAL ARTICLE

Design, Development and Characterization of Verapamil Hydrochloride Pulsincap: *In Vitro* and *In Vivo*

K. Kranthi Kumar[1], Suriyakala Perumal Chandran[2], Kalpana Nagpal[3]

[1]School of Pharmacy, Lincoln University College, Selangor, Malaysia, [2]Biochemistry and Genetics Unit, Faculty of Medicine, Lincoln University College, Selangor, Malaysia, [3]Department of Pharmaceutics, Amity University Noida India, Faculty of Health and Allied Sciences, Noida, Uttar Pradesh, India

Abstract

Introduction: In this present study, design and development, of pulsatile capsule for the timed release of verapamil hydrochloride (HCl), utilizing the pulsincap method for irregular heartbeats. **Materials and Methods:** Using hydroxy propyl methyl cellulose (HPMC), E15 sugar spheres were sealed. The verapamil HCl was sprayed on sugar spheres using Fluidized Bed (bottom spray) technology. By using FBP HPMC E15 and polymeric solution of cross-Carmellose Sodium also coated a layer on sugar spheres. The formaldehyde-treated 0-sized capsules filled with coated pellets and sealed with 1:1 of HPMC K4 and lactose as a plug. **Results and Discussion:** The Eudragit L100 was used to release the drug in an extended release. The *in vitro* drug release was conducted using pH 7.4 phosphate buffer for 17 h with the cumulative percentage release from 99.827%. The formulation V7, which demonstrated 99.827% drug release at 17 h with a 5-h lag time, was identified as the optimized formulation. The *in vivo* Pharmacokinetic and dynamic studies were conducted in the rabbit model and estimated. The C_{max} 54.62 ± 0.42 ng/mL, $t_{1/2}$ 8.54 ± 0.013 h, and $AUC_{0-\alpha}$ 944.8 ± 2.07 ng/mL. It was observed that there is a significant difference ($P < 0.05$) between the pharmacokinetic parameters of the oral solution and pellets of verapamil HCl. **Conclusion:** A significant lag time of V7 is shown in plasma concentration when compared with the oral solution. The formulation has successfully demonstrated programmed pulsatile release over a 12-h period, aligning with the requirements of Pulsincap drug delivery.

Key words: C_{max},t_{max}, Eudragit L100, pulsincap, rabbit, verapamil HCl

INTRODUCTION

A pulsatile drug delivery system releases drug after a specified time delay (i.e., lag time). Pulsatile systems are designed to deliver medication to the target site at the optimal time and in the precise dosage. These methods are beneficial for drugs with considerable first-pass metabolism, those indicated for conditions demonstrating chrono-pharmacological patterns, pharmaceuticals with specific absorption sites in the gastrointestinal tract targeting the colon, and scenarios requiring nocturnal dosing.[1,2]

Capsule-based systems

In delayed release systems, the drug remains inside the capsule for a predetermined lag time, and then after the barrier (such as a polymer coating or hydrogel plug) dissolves or erodes, the drug releases, providing a pulsatile or targeted release at the desired site. The plug is pulled out following a certain delay due to expanding, erosion, or dissolution. The Pulsicap® system consists of a water-insoluble capsule body containing a medication formulation. The open end of the body is sealed with a swellable hydrogel stopper. Subsequently, interact with the dissolving media or gastrointestinal fluids. Subsequently, the plug expands. In pulsatile drug delivery, "exiting the capsule after a delay" means the drug is released only after a preset lag time. The capsule stays intact initially, then after the delay, the swollen polymer plug is expelled, allowing a rapid burst release of the drug at the desired time.

Address for correspondence:
K. Kranthi Kumar,
Lincoln University College, Selangor, Malaysia. Phone: 08985298175.
E-mail: pdf.kranthikumar@lincoln.edu.my

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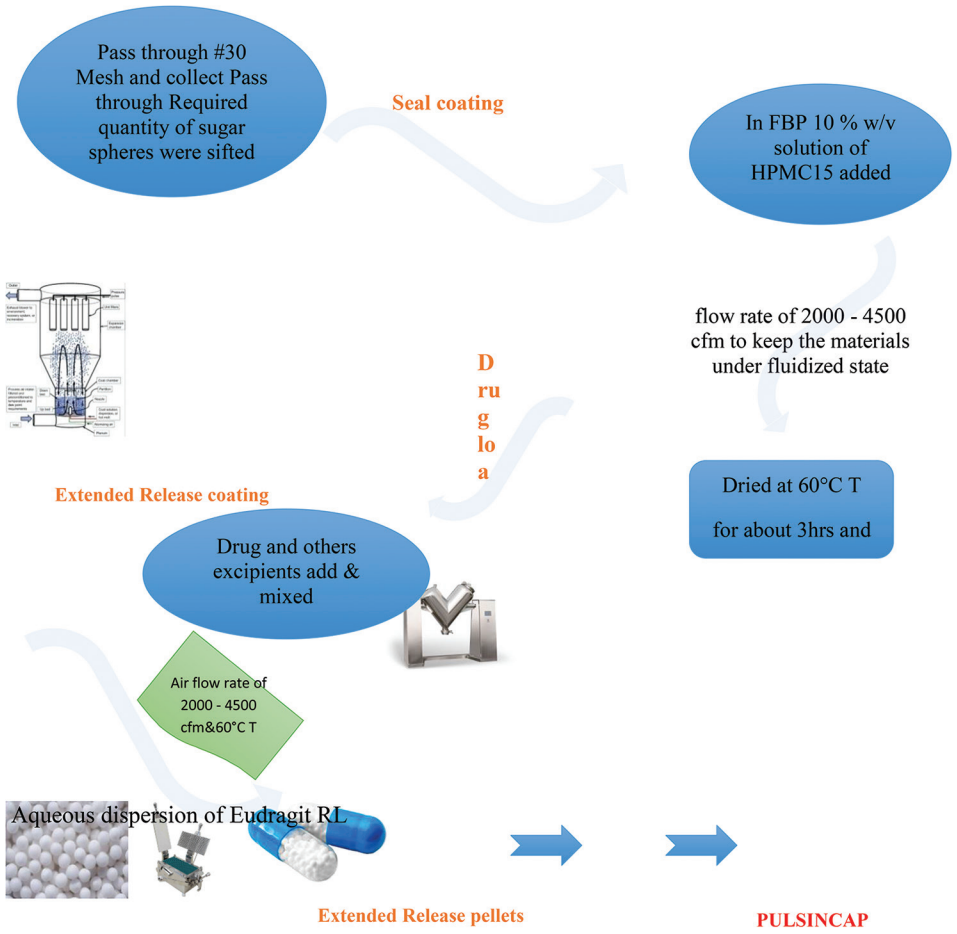


Figure 1: Formulation of verapamil HCl Pulsincap with Eudragit L100

Table 1: Preparation of hydrogel plugs for pulsatile capsule

Code	Ration (1:1)	Amount in mg
	HPMCK100:lactose	
HP1	37.5:37.5	75
HP2	50:50	100
HP3	62.5:62.5	125
HP4	75:75	150

This is succeeded by a fast drug release. The plug material comprises insoluble yet permeable and swellable polymers (polymethacrylates), as well as erodable compressed polymers such as hydroxy propyl methyl cellulose (HPMC), polyvinyl alcohol, and polyethylene oxide. A high melt index like PEGylated, monooleate glyceryls, and polyesters.[3]

MATERIALS[4]

Chemicals

Verapamil hydrochloride (HCl) Indian pharmacopeia (I.P.) was a free sample from VPL Chemicals Pvt. Ltd. Remaining all the ingredients are as per I.P. specifications.

METHODS

Solubility studies

The phase solubility studies were performed in different solvents like ethanol, chloroform, methanol, acetone, and distilled water. A 100 mL conical flask held 10 mL of solvent and was diluted with verapamil HCl until saturation was reached. An orbital shaker was used to spin the saturated solutions for 1 h, followed by overnight storage at room temperature. An ultraviolet (UV) spectrophotometer was used to measure the saturation solutions at 278 nm.[5-8]

Formulation of cross-linked gelatin capsules

A zero-sized hard gelatin capsules were used to pulsatile system designed. After that, the capsule bodies were set on a wire mesh. Formalin vapours were produced by adding a pinch of potassium permanganate to 25 mL of 15% v/v formaldehyde contain desiccator [Figure 1].[3] Twelve hours were spent on the reaction. The bodies were then taken out and dried for 30 min

Table 2: Verapamil hydrochloride formulations with different grade Eudragit in different concentrations

Ingredients	VF 1	VF 2	VF 3	VF 4	VF 5	VF 6	VF 7	VF 8	VF 9
Sugar spheres (30/35)	144	144	144	144	144	144	144	144	144
Hydroxy propyl methyl cellulose 15 cps	6	6	6	6	6	6	6	6	6
Purified water (10% solids)	S.A	S.A	S.A	S.A	S.A	S.A	S.A	S.A	S.A
Weigh of pellets after seal coating (mg)	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**
Drug loading									
Seal coated pellets	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**
Verapamil hydrochloride	80	80	80	80	80	80	80	80	80
PVP-K30	36	36	36	36	36	36	36	36	36
SSG	34	34	34	34	34	34	34	34	34
Purified water (15% solids)	S.A	S.A	S.A	S.A	S.A	S.A	S.A	S.A	S.A
weigh of pellets after drug loading	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Extended layer coating									
Drug coated pellets	300	300	300	300	300	300	300	300	300
Eudragit S100	35	26.25	17.5	35	26.25	17.5	35	26.25	17.5
Hydroxy propyl methyl cellulose 15 cps	3	2.25	1.5	3	2.25	1.5	3	2.25	1.5
Tween 80	7	5.25	3.5	7	5.25	3.5	7	5.25	3.5
Talc	10	3.75	2.5	10	3.75	2.5	10	3.75	2.5
Final weight	350	337.5	325	350	337.5	325	350	337.5	325

I.P: Indian pharmacopeia, VF: Verapamil formulation, S.A: Sufficient amount, PVP-K30: Poly vinyl pyrimidine K30, SSG: Sodium starch glycolate

Table 3: Pharmacokinetic study design of optimized formulation (V7)

Grouping	Verapamil hydrochloride treatment groups		Un treatment group
	Oral solution (5 mL)	Nil	Controlled
Dose of drug (mg)	4	Group-III	Nil
Treatment groups	Group I	06	Group-III
Number of the animals	06	06	06

Table 4: Preformulation studies of verapamil hydrochloride

Serial number	Characteristics	Specifications of verapamil hydrochloride
1	Melting point (°C)	163
2	% LOD (%)	0.21
3	Bulk density (g/cc)	0.334
4	Tapped density (g/cc)	0.542
5	% Compressibility index	38.37
6	Purified water	Freely soluble
7	Methanol (mg/mL)	>28
8	Ethanol (mg/mL)	>37
9	Acetone (mg/mL)	>34
10	Chloroform (mg/mL)	>46

at 50°C after reaction between the formaldehyde vapour and the gelatine was finished. To help remove any remaining formaldehyde, the remains were allowed to dry.[9-12]

Preparation of hydrogel plug

A hydrogel plug was created to seal the capsule body by compressing different amounts of HPMC K4M and lactose using 7 mm punches and dies on a rotary tablet press.[13-16]

Formulation of verapamil HCl pellets by FBP[17-22]

Verapamil HCl pellets were prepared using sugar spheres as cores. The process involved three main steps:

1. Seal Coating: Sugar spheres were coated with 10% w/v HPMC E15 solution in a fluidized bed to harden them and prevent agglomeration [Table 1].
2. Drug Loading: Verapamil HCl was blended with superdisintegrants (cross-carmellose sodium, sodium starch glycolate) and bound onto the sugar spheres using PVP K-30 solution in a fluidized bed, followed by drying and sizing [Table 2].
3. Extended Release Coating: Drug-loaded pellets were coated with varying concentrations of Eudragit polymers (S100, RLPO, L100) using HPMC as a pore former, Tween 80 as plasticizer, and talc as anti-tacking agent, producing controlled release pellets.

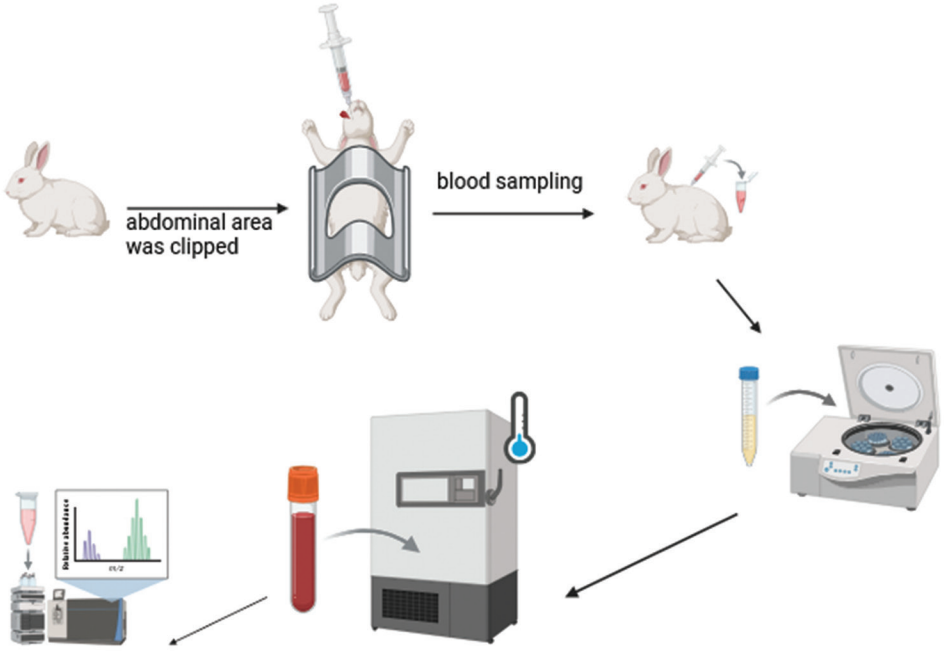


Figure 2: *In vivo* study design

Table 5: Standardization of verapamil hydrochloride

Concentration (µg/mL)	Absorbance (Mean±Standard deviation)		
	0.1N hydrochloric acid	6.8 phosphate buffer	7.4 phosphate buffer
0	0	0	0
2	0.052±0.003	0.092±0.003	0.098±0.003
4	0.107±0.004	0.180±0.002	0.196±0.002
6	0.163±0.003	0.270±0.002	0.291±0.002
8	0.215±0.002	0.361±0.003	0.380±0.003
10	0.263±0.002	0.456±0.002	0.488±0.002
R^2	0.9997	0.9999	0.9998

By randomized cross over design method in vivo performance of Verapamil hydrochloride oral solution and Verapamil Hydrochloride Pellets were evaluated in rabbits. The study adopted a non-blinded, open-label design [Table 3].

Characterization

Preformulation studies of verapamil HCl

The phase solubility studies melting point were performed and reported in Table 4.

Standardization of verapamil HCl[23]

A UV spectrophotometric method was used to measure the maximum absorbance of verapamil HCl between 200 and 400 nm using 0.1 N hydrochloric acid and phosphate buffers at pH 6.8 and 7.4. All the results are mentioned in Table 5 and Figure 4.

Table 6: Evaluation of hydrogel plug

Code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Lag time (h)
HP1	75±1.29	2.52±0.021	4.09±0.02	3.6
HP2	100±1.09	3.32±0.034	4.29±0.029	4.1
HP3	125±1.29	4.15±0.057	4.58±0.039	4.6
HP4	150±1.32	5.22±0.079	4.76±0.009	5.01

Table 7: Characterization of verapamil hydrochloride pellets

Code	% yield	Average particle size (µm)	% of drug loading
VF 1	97.53	665.23±0.02	97.13±0.02
VF 2	97.78	654.66±0.04	96.14±0.01
VF 3	98.26	647.31±0.07	96.69±0.04
VF 4	97.83	656.31±0.04	97.91±0.03
VF 5	96.45	644.43±0.02	98.87±0.04
VF 6	97.18	637.32±0.05	98.53±0.02
VF 7	96.29	691.31±0.03	97.68±0.02
VF 8	96.81	679.43±0.06	97.43±0.06
VF 9	97.18	663.41±0.04	96.83±0.05

Evaluations of hydrogel plug[24]

Various evaluations studied such as thickness, hardness, and lag time were performed to the prepared plug.

Table 8: Determination of micromeritic properties of verapamil hydrochloride pellets

Formulation	Angle of repose (θ)	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's index (%)	Hausner's ratio
VF 7	25.42	0.908±0.03	1.066±0.04	14.82±0.04	1.17±0.03
VF 8	24.13	0.917±0.04	1.081±0.07	15.17±0.05	1.18±0.02
VF 9	22.72	0.920±0.06	1.086±0.06	15.28±0.04	1.18±0.03

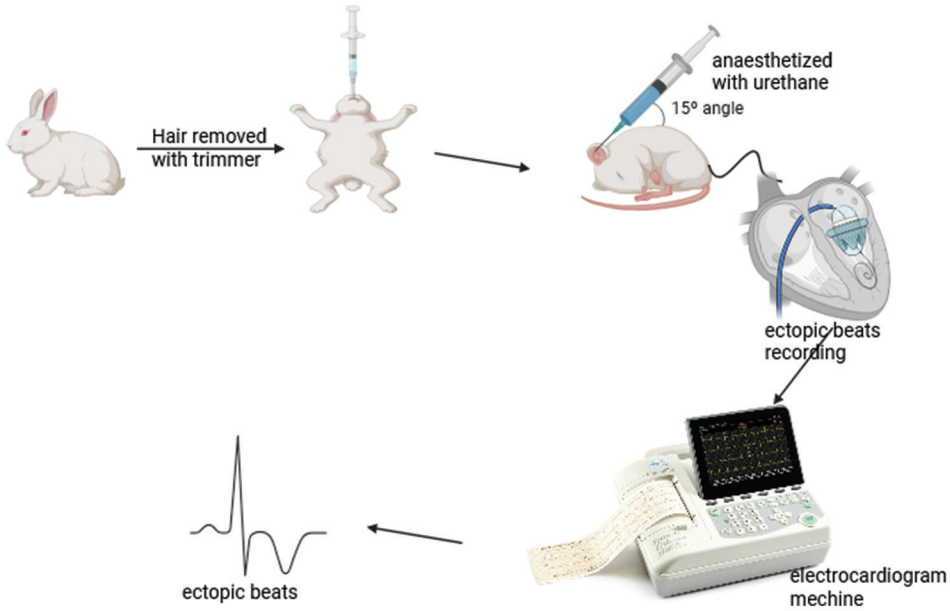


Figure 3: Pharmacodynamic study design

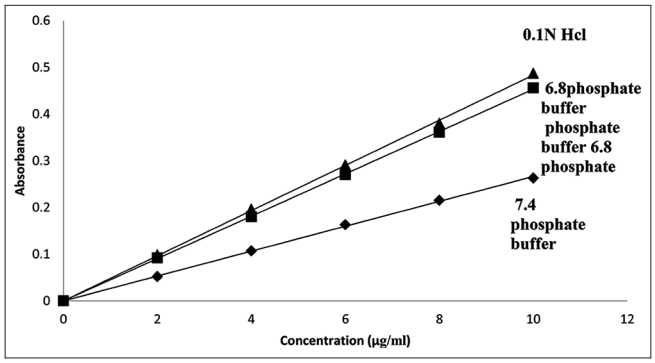


Figure 4: Standardization of verapamil hydrochloride

Thickness

A Vernier calliper was used to measure the thickness of ten plugs, and the average of these measurements was used to calculate the mean tablet thickness.[25] All the results are mentioned Table 6.

Hardness test

The plug's hardness was estimated using Pfizer hardness tester. The force applied on the plug in pill form until it fractured. The hardness measurement was determined by subtracting the initial pressure from the final pressure.[26] All the results are mentioned in Table 6.

Evaluation of physicochemical properties of pellets[27]

% yield

All the prepared pellets percentage yield was determined. The following calculation was used to get the actual percentage yields of pellets.[27] All the results are mentioned in Table 7.

$$\% \text{ yield of pellets} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Estimation of drug content

We weighed accurately 100 mg of pellets, which was equal to the weight of the pure sample, and dissolve in 100 mL of 6.8 pH phosphate buffer while stirring. To estimate the amount of verapamil HCl, the solution was filtered through a 0.45 µ membrane filter and diluted. The absorbance was measured spectrophotometrically at 278 nm using a blank 6.8 pH phosphate buffer. All the results are mentioned Table 7.

In vitro release study

USP XXIII dissolution test equipment (paddle method) was used for the dissolution investigations. For the capsule to be fully submerged in the dissolving media without floating,

Table 9: *In vitro* dissolution study of verapamil hydrochloride pulsatile capsule

Time (h)	% amount of drug release		
	V7	V8	V9
0	0	**0**	0
0.5	0	0	0
1	0	0	0
1.5	0	0	0
2	0	0	0
2.5	0	0	0
3	0	0	0
3.5	0	0	0
4	0	0	0
4.5	0	0	0
5	0.000	0.000	0.000
5.5	5.940	6.696	8.239
6	11.422	11.773	12.884
6.5	15.643	15.933	17.491
7	20.045	20.462	21.997
7.5	24.156	24.607	26.875
8	27.312	28.931	31.558
8.5	30.580	31.018	36.116
9	32.738	33.076	40.723
9.5	36.065	37.036	44.724
10	40.040	43.536	50.636
10.5	44.037	48.181	55.005
11	47.739	53.166	59.711
11.5	51.460	56.917	64.442
12	54.886	61.002	68.883
12.5	58.644	65.109	75.236
13	62.736	69.236	81.623
13.5	67.164	73.699	89.617
14	72.875	80.705	95.134
14.5	78.931	87.118	99.419
15	83.443	91.044	--
15.5	87.348	94.989	--
16	92.533	99.899	--
16.5	97.113	--	--
17	99.827	--	--

it was secured to the paddle using cotton thread. Various dissolution medium with pH values of 1.2 and 7.4 by change of pH sequentially. The pellets were placed 2 h in pH 1.2 medium and changed with fresh pH 7.4 phosphate-buffered saline. The medium was replaced with pH 6.8 buffer was introduced for the next few hours.[29]

I.P. dissolution conditions

- Dissolution medium volume: -900 mL
- RPM: -100
- Temperature: -37±0.5°C
- Sample volume: -5 mL

The withdrawn samples were analyzed spectrophotometrically at 278 nm in UV spectroscopy, and the cumulative percentage release was calculated.[28] All the results are mentioned in Tables 9, 10, and Figures 5-8.

In vivo studies

Pharmacokinetic study design

By randomized crossover design method, the *in vivo* performance of verapamil HCl oral solution and verapamil HCl pellets was evaluated in rabbits. The study adopted a non-blinded, open-label design. The subjects had a fasting period of not <24 h before the administration of the dosage. The day before the experiment, the hair on the abdomen was removed with a 10 min application of depilatory cream, followed by a washing with distilled water. Rabbits were subjected to an overnight fasting period prior to the experiment and were subsequently randomized into two treatment groups and one control group to facilitate comparative pharmacokinetic evaluation.[30]

Blood sampling

Heblood samples of approximately 1 mL were obtained at 0 (before to medication administration), 0.5, 1.0, 2.0, 3.0, 4.0, and 6.0 h following oral administration and 2, 4, 6, 8, 12, 16, 20, 22,24,26,28,30 and 32 h after administration of transdermal product involved in the study at a dose equivalent to 25 mg of Propranolol HCl. Blood sample volume was replaced by administration of isotonic saline. A heparinized tube containing blood samples was centrifuged at 3000 rpm for 10 min. The collected plasma was stored at –20°C until they were analyzed by liquid

Table 10: Comparative drug release kinetics

Code	Correlation coefficient value				Release rate constant (mg/h) k_0	Exponential coefficient (*n*)	T_{50} (h)	T_{90} (h)
	Zero order	First order	Matrix	Peppas				
VF_7	0.9972	0.7422	0.9223	0.9969	6.60	0.8718	6.06	10.90
VF_8	0.9978	0.7113	0.9208	0.9963	7.14	0.8800	5.60	10.08
VF_9	0.9980	0.7807	0.9251	0.9958	8.17	0.8705	4.89	8.81

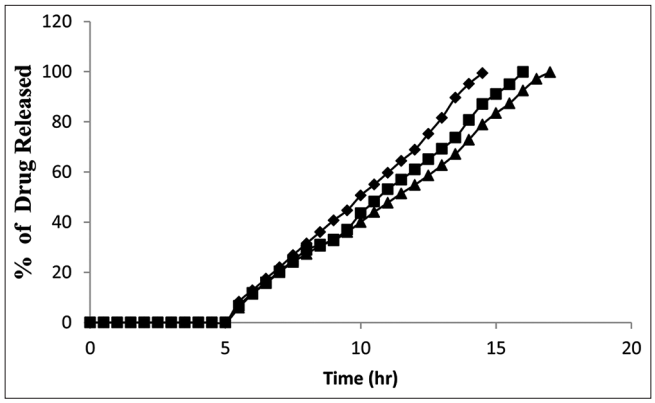


Figure 5: Comparative *in vitro* dissolution study of verapamil hydrochloride pulsatile capsule
(-▲-) VF $_7$: pellets coated with 35% of Eudragit L 100
(-♦-)VF$_8$: pellets coated with 26.25% of Eudragit L 100
(-■-)VF$_9$: pellets coated with 17.5% of Eudragit L 100

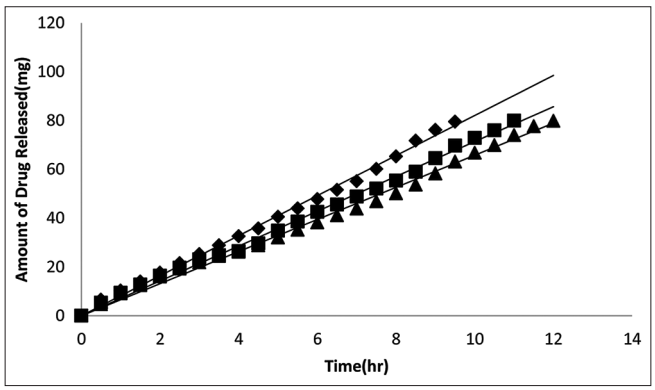
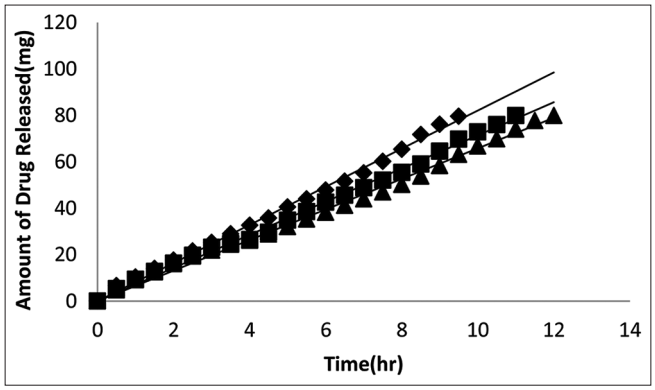


Figure 6: Comparative *in vitro* dissolution study of verapamil hydrochloride pulsatile capsule



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chromatography–tandem mass spectrometry (LC-MS/MS) [Figure 2].

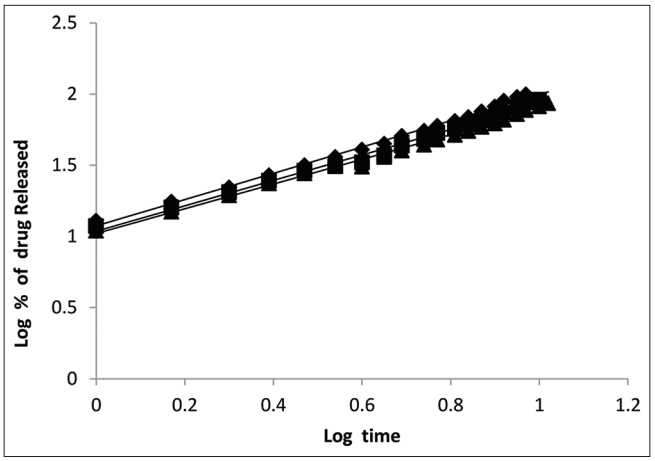

Figure 8: Comparative Peppas plots of verapamil hydrochloride pellets coated with Eudragit L 100in different concentrations
(-▲-) VF $_7$: pellets coated with 35% of Eudragit L 100
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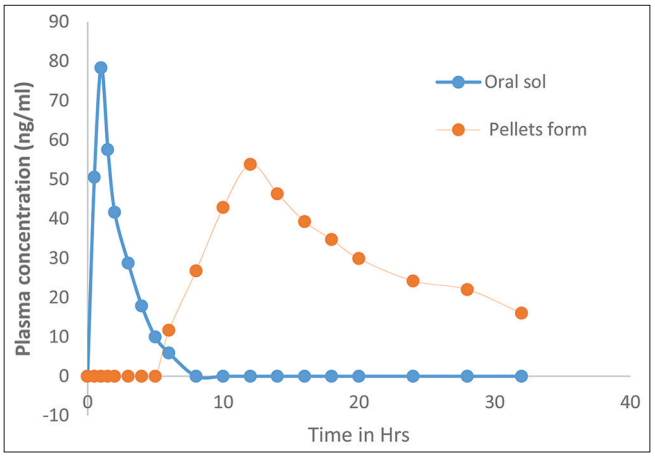

Figure 9: Plasma concentration-time curves of verapamil hydrochloride different formulation

Determination of pharmacokinetic parameters

The non-compartmental pharmacokinetic data analysis software PK Solutions 2.0™ was used to calculate various pharmacokinetic parameters, including the peak plasma concentration (C_{max}), the time at which the peak occurred (T_{max}), the area under the curve (AUC), the elimination rate constant (K_{el}), the biological half-life ($t_{1/2}$), and the mean residence time (MRT). All the results are mentioned in Table 11 and Figure 9.

Statistical analysis of the pharmacokinetic parameters

To analyze the pharmacokinetic properties of the formulations tested, paired sample's *t*-tests were used to test for normal

Table 11: Plasma concentration-time curves of verapamil hydrochloride pellets

Time (h)	Plasma concentration (ng/mL) (Mean±SD) (*n*=6)	
	Oral sol	Pellets form
0	0	0
0.5	50.52±1.88	0
1	78.36±2.78	0
1.5	57.52±1.53	0
2	41.64±1.13	0
3	28.76±1.63	0
4	17.83±1.36	0
5	9.95±1.46	0
6	5.92±1.23	011.67±01.04
8	0.00	026.78±01. 06
10	0.00	042.89±01.11
12	0.00	053.78±01.23
14	0.00	046.36±01.16
16	0.00	039.27±01.03
18	0.00	034.69±01.68
20	0.00	029.86±01.56
24	0.00	024.21±01.43
28	0.00	022.01±01.26
32	0.00	016.01±01.12

Table 12: Pharmacokinetic study of verapamil hydrochloride solution and verapamil hydrochloride pellets

Pharmacokinetic parameter	Oral solution	Pellets	Calculated value of "*t*"
C_{max} (ng/mL)	78.3±0.32	54.62±0.42	36.74***
MRT (h)	2.4±0.02	20.2±0.16	75.53***
Half-life (h)	1.32±0.012	8.54±0.013	40.76***
K_{el} (h^{-1})	0.52±0.011	0.08±0.012	8.86***
K_a (h^{-1})	1.43±0.02	0.25±0.01	19.66***
$AUC_{0-\alpha}$ (ng h/mL)	193±1.44	944.8±2.07	256.62***

Null hypothesis (H_o): The pharmacokinetics between verapamil hydrochloride pellets and oral solution do not differ significantly at the 0.001 level and "*t*" with 10 DF is 4.587. Result: At the 0.001 levels of significance, Ho is not accepted as the computed "*t*" value greater than the table value of "*t*" with 10 DF. Thus, it was determined that the pharmacokinetic characteristics of verapamil hydrochloride solution and pellets differed significantly. ***$p < 0.001$; values are expressed as mean ± SD (n = 3). Statistical significance was determined using Student's t-test when compared with the oral solution.

distribution of the serum concentrations of C_{max}, Ka, and AUC 0–24 and AUC 0–α values. The significance level was set at 0.001 for all tests.[30] All the results are mentioned in Table 12.

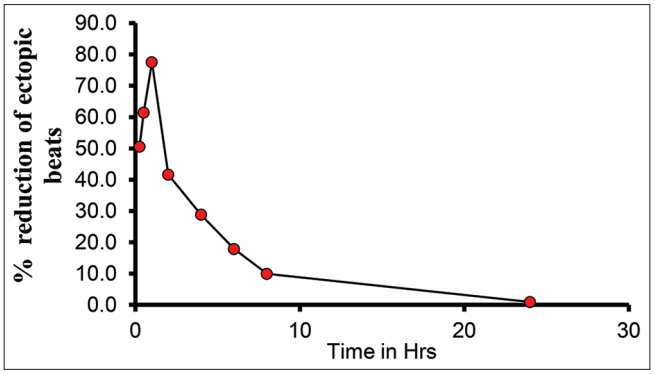

Figure 10: Percent reduction of ectopic beats after administration of verapamil hydrochloride solution and pellets in rabbits

Pharmacodynamic study design

Evaluation of pharmacodynamics of verapamil HCl pulsincap

The degree of reduction in adrenaline-induced arrhythmia was used to measure the pharmacodynamic response in animals following oral and transdermal administration of verapamil HCl. The animals had unrestricted access to water but were fasted for 24 h before the medication formulations were administered. To put the animals to sleep, urethane (1 g/kg I.P.) was used. All animals' normal electrocardiograms (ECG) were recorded after anesthesia. Adrenaline (30 µg/kg i.v.) in normal saline was injected into the marginal ear vein before the drug formulations being administered. An ECG was promptly taken, and these cardiograms were used as a control. The drug formulations were given to the animals as outlined in pharmacokinetic studies, and they were left for an hour. After taking verapamil HCl orally for 1.0, 3.0, and 6.0 h, and transdermally for 4.0, 8.0, 12.0, 20.0, and 24.0 h, adrenaline was given again. At each time interval, the number of ectopic beats before and after the adrenaline injection was counted and recorded as a reaction to the adrenaline challenge. The per se adrenaline response was compared with the net decrease in the number of ectopic beats following the delivery of medication formulations after the adrenaline challenge [Figure 3].[31] All the results are mentioned in Table 13 and Figure 10.

Stability studies of pulsatile capsule containing verapamil HCl pellets

The optimized formulation stability was studied as per ICH guidelines. They divided the batches into two groups and placed separately in stability chamber, which is maintained at 25±5°C/60% RH and 40 ± 5°C/75% RH, respectively, for 3 months. At regular time intervals, the formulation % drug release was calculated.[32] All the results are mentioned in Tables 14 and 15.

Table 13: Percent reduction of ectopic beats after administration of verapamil hydrochloride solution and pellets in rabbits

Formulation	% reduction of ectopic beats at							
	1 h	4 h	6 h	8 h	12 h	16 h	20 h	24 h
Oral	99.6±6.1	58.2±4.4	28.4±2.2	---	---	---	---	---
Pellets	----	56.2±5.4	77.3±41	97.6±3.7	96.7±3.1	96.5±3.3	96.3±3.5	96.1±3.4

Table 14: Stability studies of optimized formulation

Storage conditions	Time interval	Drug content	K_o (mg/h)	$t_{50\%}$	$t_{90\%}$
25±2°C/60±5% RH	1st month	97.68	6.60	6.06	10.90
	2nd month	97.64	6.60	6.06	10.90
	3rd month	97.61	6.60	6.06	10.90
40±2°C/75±5% RH	1st month	97.63	6.60	6.06	10.90
	2nd month	97.60	6.60	6.06	10.90
	3rd month	97.58	6.60	6.06	10.90

Table 15: *In vitro* dissolution data of verapamil hydrochloride Pulsicap

S. No.	Time (h)	Initial	Percentage of verapamil hydrochloride released ($\bar{x}$ ±Standard deviation)					
			25±2°C/60±5% RH			40±2°C/75±5% RH		
			1st month	2nd month	3rd month	1st month	2nd month	3rd month
1.	0	0.000	0	0	0	0	0	0
2.	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
3.	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
4.	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
5.	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
6.	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
7.	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.	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.	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
10.	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
11.	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
12.	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
13.	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
14.	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
15.	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
16.	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
17.	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
18.	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
19.	14	72.875	72.808±0.12	72.69±0.09	72.60±0.09	72.79±0.08	72.72±0.09	72.67±0.13
20.	14.5	78.931	78.84±0.15	78.73±0.06	78.62±0.06	78.67±0.09	78.51±0.11	78.43±0.15
21	15	83.443	83.37±0.13	83.31±0.08	83.28±0.08	83.36±0.05	83.32±0.09	83.26±0.09
22	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
23	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
24	16.5	97.113	97.09±0.13	97.05±0.09	96.96±0.14	97.08±0.15	97.03±0.09	96.98±0.15
25	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

RESULTS

Preformulation studies of verapamil HCl

Discussion

The study findings demonstrated that the drug exhibited higher solubility in non-polar solvents, with its solubility profile showing a distinct pH-dependent behavior.

Standardization of pure drug

Discussion

The calibration curve of the pure drug was plotted in the different solvent systems like 0.1N in HCl, 6.8, and 7.4 Phosphate buffer. The absorbance was measured at 278 nm by UV spectrophotometer.

Discussion

The prepared Hydrogel plug evaluation studies were performed, and selected HP4 batch plug composition $HPMCK_{100}$:lactose (75:75 ration) has 5 h lag time, and other studies are as per I.P.

Discussion

The prepared different batch pellets were evaluated, and the selected VF7 batch was optimized. The optimized batch showed a higher % yield of 96.29%, average particle size 691.31 ± 0.03, and entrapment efficiency 97.68 ± 0.02.

Discussion

The optimized batch VF7 was evaluated for micromeritic properties, including bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. Based on these results and the required fill volume, size '0' hard gelatin capsules were selected for the formulation of the pulsatile capsule dosage form.

Conclusion

The dissolution profile of batch VF7 confirmed the desired pulsatile release behavior, with a defined lag time of 5 h and extended up to 12 h, followed by controlled drug release, indicating successful design for chronotherapeutic drug delivery.

Conclusion

The drug release from optimized pulsatile capsule batch VF7 followed Korsmeyer-Peppas kinetics, indicating a diffusion-controlled and possibly anomalous (non-Fickian) release mechanism, suitable for achieving a pulsatile drug delivery profile.

In vivo study

Conclusion

The *in vivo* pharmacokinetic profile of VF7 has a higher AUC 944.8 ± 2.07 as compared with the oral tablet and confirms its pulsatile release behavior, showing a significant lag phase followed by controlled release, making it suitable for chronotherapy of irregular heartbeats, especially for early morning cardiac arrest.

Conclusion

The verapamil HCl pellets demonstrated a greater and more sustained reduction in ectopic beats 96% more when compared to the solution form, indicating their potential effectiveness for chronic therapeutic management of cardiac arrhythmias. The delayed action observed aligns with the pulsatile release design, making it suitable for conditions like early morning arrhythmic episodes.

Accelerated stability studies

Conclusion

The optimized batch VF7 remained stable under accelerated conditions over 3 months, with no significant changes drug content, physical appearance, or pulsatile release profile. The formulation is considered physicochemically stable and suitable for long-term use.

CONCLUSION

The verapamil HCl pellets coated with 35% Eudragit L100 hydrogel plug with HPMCK100: lactose (75:75) extended release up to 300 min. In addition, the optimized formulation (V7) showed that a 12 h release was achieved. According to the evidence from *in vitro* dissolution and pulsing cap characterization, the carrier has a considerable influence on dissolving properties. As the result indicates, the developed verapamil HCl pulsincap formulation showed a promising model to treat of cardiac arrhythmias.

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