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Original Research Article

A Chronotherapeutic Floating Pulsatile Delivery System for Valsartan and Hydrochlorothiazide: Formulation, Optimization and In-vitro Evaluation

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Conflict of interest: Nil

Abstract:

Background: Hypertension is a chronic cardiovascular disorder characterized by persistently elevated arterial blood pressure and remains one of the leading causes of global morbidity and mortality. A key physiological feature of hypertension is its circadian rhythm, particularly the early morning surge in blood pressure, which is associated with an increased risk of adverse cardiovascular events such as myocardial infarction and stroke.

Objective: The present study aimed to design, develop, and evaluate a gastroretentive floating pulsatile drug delivery system (FPDDS) of Valsartan and Hydrochlorothiazide to achieve time-specific drug release aligned with circadian rhythm for improved antihypertensive therapy.

Methods: Core tablets containing Valsartan and Hydrochlorothiazide were prepared by direct compression using suitable diluents and superdisintegrants. These core tablets were subsequently compression-coated with hydrophilic polymers (Polyox WSR-205 and Polyox WSR N12K) along with effervescent agents (sodium bicarbonate and citric acid) to impart floating behavior and pulsatile drug release. Preformulation studies, including physicochemical characterization and drug-excipient compatibility (FTIR and DSC), were performed. The prepared formulations were evaluated for hardness, friability, weight variation, drug content uniformity, floating lag time, and total floating duration. In-vitro dissolution studies were conducted using USP apparatus, and drug release kinetics were analyzed using various mathematical models. Stability studies were carried out as per ICH guidelines.

Results: The formulated floating pulsatile drug delivery system of Valsartan (80 mg) and Hydrochlorothiazide (12.5 mg) demonstrated satisfactory preformulation, physicochemical, and in-vitro performance. Powder blends exhibited good flow properties with angle of repose (25–35°), Carr's index (10–20%), and Hausner's ratio (<1.25), indicating suitability for direct compression. The developed UV spectrophotometric method showed excellent linearity with R^2 = 0.996 for Valsartan (2–12 µg/mL) and R^2 = 0.999 for Hydrochlorothiazide (5–25 µg/mL), confirming accuracy for drug estimation. The prepared tablets exhibited acceptable physicochemical properties including uniform weight (~250 mg), adequate hardness, and friability below 1%, indicating good mechanical strength. The optimized formulation showed a floating lag time of <1 minute and total floating duration exceeding 12 hours, confirming effective gastroretentive behavior. In-vitro dissolution studies revealed a distinct pulsatile release pattern with a lag time of 4–6 hours, followed by a rapid drug release of approximately 90–100% within 1–2 hours post-lag.

Conclusion: The developed floating pulsatile drug delivery system successfully achieved chronotherapeutic drug release of Valsartan and Hydrochlorothiazide. This approach holds significant potential for improving the therapeutic management of hypertension by synchronizing drug release with the biological rhythm of the disease.

Keywords: Chronotherapy, Pulsatile drug delivery system, Floating tablets, Gastroretentive systems, Valsartan, Hydrochlorothiazide, Hypertension.

Introduction

Hypertension is a major global health concern and a leading risk factor for cardiovascular morbidity and mortality. It is well established that blood pressure does not remain constant throughout the day but follows a circadian rhythm, characterized by a rise in the early morning hours, a phenomenon often referred to as the "morning surge."[1]

This surge is associated with an increased risk of adverse cardiovascular events such as myocardial infarction, stroke, and sudden cardiac death. Conventional antihypertensive therapies, which deliver drugs at a constant rate, often fail to align drug release with this circadian variation. Consequently, there is a growing interest in chronotherapeutic drug delivery systems that can synchronize drug release with the body's biological rhythms to enhance therapeutic efficacy and minimize side effects.[2]

Among antihypertensive agents, Valsartan and Hydrochlorothiazide (HCTZ) are widely used either alone or in combination. Valsartan acts by selectively blocking the angiotensin II type 1 (AT1) receptors, thereby preventing vasoconstriction and reducing blood pressure.[3] Hydrochlorothiazide, on the other hand, promotes diuresis by inhibiting sodium reabsorption in the distal convoluted tubules, leading to decreased plasma volume and blood pressure. The combination of these two drugs provides a synergistic effect, improving blood pressure control and patient outcomes. However, their conventional formulations may not provide optimal therapeutic benefits due to the mismatch between drug release profiles and circadian blood pressure patterns.[4]

Floating pulsatile drug delivery systems (FPDDS) have emerged as a promising approach to address this limitation. These systems are designed to remain buoyant in the gastric environment for an extended period while releasing the drug after a predetermined lag time.

The floating mechanism ensures prolonged gastric retention, which is particularly beneficial for drugs that are primarily absorbed in the upper gastrointestinal tract.[5] The pulsatile release, characterized by a rapid and complete drug release following a lag phase, enables the delivery of drugs at a specific time, aligning with the circadian rhythm of hypertension.[6]

In the context of chronotherapy, a floating pulsatile system can be administered at bedtime, allowing the dosage form to remain in the stomach and release the drug during the early morning hours when the risk of hypertensive events is highest. This targeted delivery not only enhances therapeutic efficacy but also reduces drug wastage and potential side effects associated with continuous drug exposure. Additionally, such systems can improve patient compliance by reducing dosing frequency and providing more effective blood pressure control.[7]

The design of floating pulsatile drug delivery systems involves the use of polymers and gas-generating agents to achieve buoyancy and controlled lag time. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) or polyethylene oxide (Polyox) are commonly used to form a gel barrier that controls drug release.[8] Effervescent agents like sodium bicarbonate and citric acid generate carbon dioxide upon contact with gastric fluid, enabling the dosage form to float. By carefully selecting and optimizing these components, it is possible to tailor the lag time and release profile according to therapeutic requirements.[9]

Thus, the development of a floating pulsatile drug delivery system for valsartan and hydrochlorothiazide represents a novel and effective strategy for chronotherapy in hypertension. It addresses the limitations of conventional dosage forms by providing time-specific drug release, improving therapeutic outcomes, and aligning treatment with the body's natural biological rhythms. This approach holds significant potential for advancing hypertension management and reducing the burden of cardiovascular diseases.[10]

Materials and Methods

Materials: Valsartan was obtained from Lupin Ltd., and Hydrochlorothiazide was procured from Atra Pharmaceuticals, Aurangabad. Polyox WSR-205 and Polyox WSR N12K were supplied by IP-CA Laboratories Ltd., Pithampur. Microcrystalline cellulose, croscarmellose sodium, lactose, and calcium phosphate were obtained from Modern Laboratories and S.D. Fine Chem. Ltd. Sodium bicarbonate and citric acid were used as gas-generating agents. Magnesium stearate and talc were used as lubricants. Methanol, hydrochloric acid, and double distilled water were used as solvents. All reagents used were of analytical grade.

Methods

Preformulation Studies: Preformulation studies were performed to evaluate physicochemical properties of the drugs and their compatibility with excipients. Organoleptic properties such as color, odor, and taste were recorded. The melting point of Valsartan and Hydrochlorothiazide was determined using the capillary method. Solubility studies were carried out in various solvents to assess dissolution behavior.[11] The partition coefficient was determined using an n-octanol and distilled water system to evaluate lipophilicity.

Flow properties of powder blends were assessed by determining angle of repose, bulk density, tapped

density, Hausner's ratio, and Carr's index. Particle size analysis was performed using the sieve method.[12]

Analytical Method Development: A UV spectrophotometric method was developed for simultaneous estimation of Valsartan and Hydrochlorothiazide. The absorption maxima were found at 248 nm for Valsartan and 270 nm for Hydrochlorothiazide. Calibration curves were prepared, and the simultaneous equation method was used for quantification.[13]

Drug–Excipient Compatibility Studies: Compatibility studies were conducted using Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC). Physical mixtures of drugs and excipients were stored under accelerated conditions (40°C ± 2°C / 75% RH ± 5% RH) and analyzed for any interactions.[14]

Preparation of Core Tablets: Core tablets containing Valsartan and Hydrochlorothiazide were prepared by direct compression. The drugs were blended with microcrystalline cellulose as a diluent and croscarmellose sodium as a superdisintegrant. Magnesium stearate was added as a lubricant. The blend was compressed using a rotary tablet compression machine.[15]

Preparation of Floating Pulsatile Drug Delivery System: Floating pulsatile tablets were prepared by compression coating technique. The barrier layer consisted of Polyox WSR-205 and Polyox WSR N12K along with sodium bicarbonate and citric acid as effervescent agents. The core tablet was placed at the center of the die, and half of the barrier layer material was added below and above the core before compression to form the final tablet.[16]

Evaluation of Powder Blend: Pre-compression parameters including angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were evaluated to assess flow properties.[17]

Evaluation of Tablets: Post-compression evaluation included hardness, friability, weight variation, thickness, and drug content uniformity.[18]

Floating Behavior Study: Floating properties were evaluated using a USP type II dissolution apparatus containing 900 ml of 0.1 N HCl at 37 ± 0.5°C and 100 rpm. Floating lag time and total floating time were recorded.[19]

In-vitro Drug Release Study: Dissolution studies were performed using USP type II apparatus in 0.1 N HCl. Drug release profiles were evaluated to determine lag time and pulsatile release behavior.[20]

Optimization and Release Kinetics: Formulations were optimized using factorial design by varying polymer concentrations. Drug release data were fitted to kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the mechanism of drug release.[21]

Stability Studies: The optimized formulation was subjected to accelerated stability studies at 40°C ± 2°C and 75% RH ± 5% RH for one month. Samples were evaluated for physical appearance, drug content, and dissolution profile.[22]

Results

Table 1: Formulations of tablet containing core

Component	Weight (mg)	
	C1	C2
Valsartan	80	80
Hydrochlorthiazide	12.5	12.5
Mannitol	142	132
Povidone	2.5	12.5
Purified Water	q.s	q.s
Microcrystalline Cellulose	5	5
Croscarmellose Sodium	5	5
Magnesium Stearate	3	3
Tablet Weight	250	250

Table 2: Preparation of the FPRT trial batches individual polymer

S. No.	Ingredients	Formulation codes					
		P-1	P-2	P-3	P-4	P-5	P-6
1	Polyox WSR-205	160	140	120	—	—	—
2	Polyox WSR-N12K	—	—	—	150	130	110
3	Sodium Bicarbonate	45	45	45	45	45	45
4	Citric acid	15	15	15	15	15	15
5	Calcium Phosphate	—	20	40	10	30	50
	Total Weight (mg)	220	220	220	220	220	220

Table 3: Batch preparation using the 3^2 complete factorial design with Polyox WSR 205 & Polyox WSR N12K as variables

Formulation no.	Polyox WSR 205 (mg)	Polyox WSR N12K (mg)	Sodium bicarbonate (mg)	Citric Acid (mg)	Core Tablet (mg)	Calcium phosphate (mg)	Talc	Lactose	Methanol	Total wt. (mg)
F1	45	65	50	20	250	40	5	25	q.s.	500
F2	45	75	50	20	250	30	5	25	q.s.	500
F3	45	85	50	20	250	20	5	25	q.s.	500
F4	55	65	50	20	250	30	5	25	q.s.	500
F5	55	75	50	20	250	20	5	25	q.s.	500
F6	55	85	50	20	250	10	5	25	q.s.	500
F7	65	65	50	20	250	20	5	25	q.s.	500
F8	65	75	50	20	250	10	5	25	q.s.	500
F9	65	85	50	20	250	—	5	25	q.s.	500

FTIR spectra of Valsartan, Hydrochlorothiazide, Polyox WSR-205, Polyox WSR N12 K

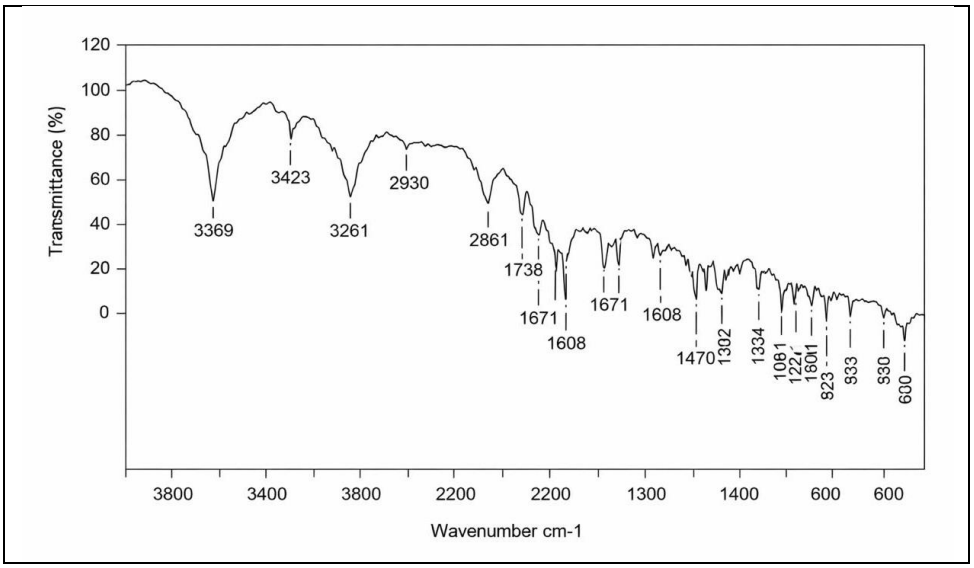

Figure 1: FTIR spectra of Valsartan, Hydrochlorothiazide, Polyox WSR-205, Polyox WSR N12 K

DSC curves of API and Excipients

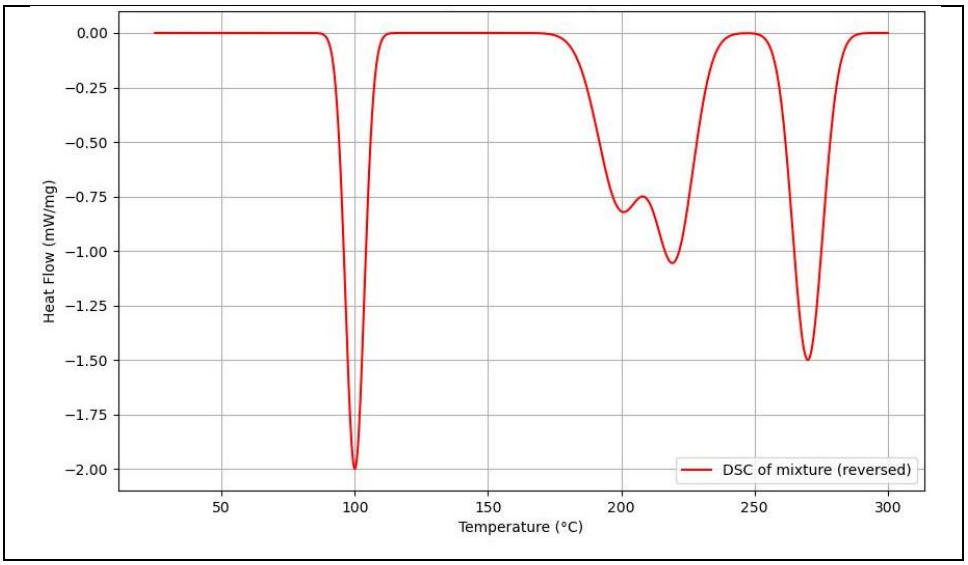

Figure 2: DSC curves of API and Excipients

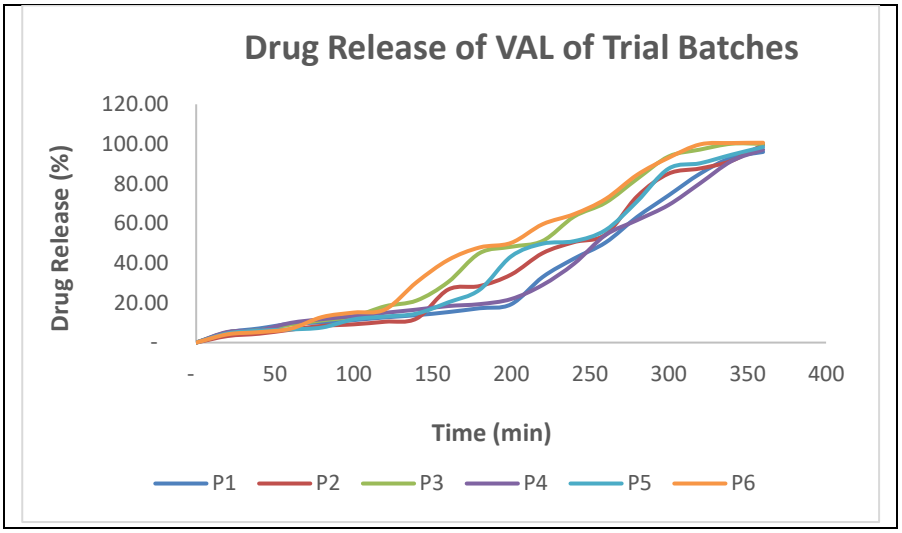

Figure 3: Drug Release of VAL of Trial Batches

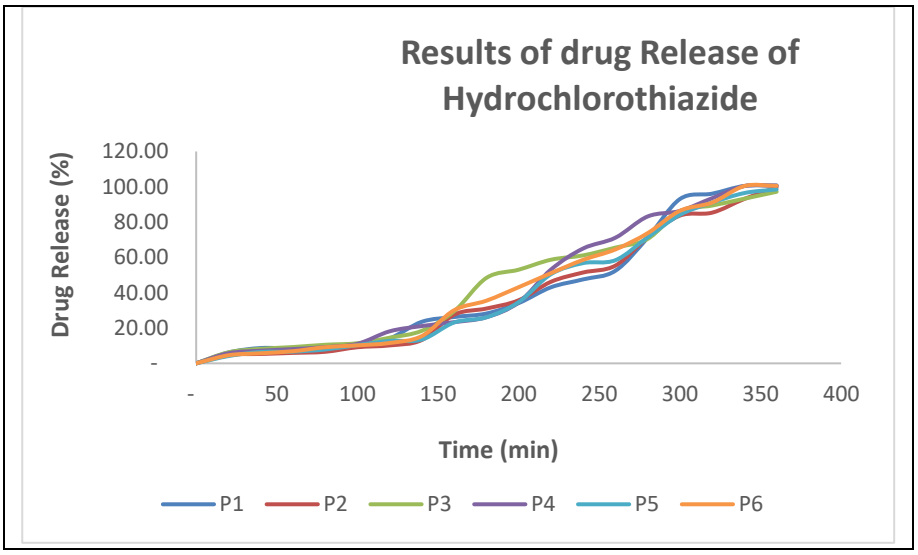

Figure 4: Results of drug Release of Hydrochlorothiazide

Table 4(a): Evaluation of FPRT (Floating-pulsatile release tablet) (F1–F9)

Formulation no.	Tablet weight (mg)	Tablet Thickness (mm)	% drug Content (VAL+HCTZ)	Hardness (Kg/cm^2)
F1	499.12±1.05	2.55±0.07	98.45±0.56	7.2±0.13
F2	498.45±1.25	2.64±0.04	97.27±0.75	7.5±0.25
F3	496.65±1.64	2.58±0.03	98.17±1.34	7.7±0.06
F4	495.47±1.78	2.52±0.05	97.96±0.78	7.6±0.15
F5	496.75±1.38	2.44±0.08	98.62±1.56	7.4±0.08
F6	497.25±1.49	2.63±0.02	97.39±0.50	7.9±0.12
F7	494.98±1.47	2.68±0.10	97.19±2.34	7.9±0.34
F8	499.15±1.45	2.57±0.04	98.82±0.34	8.0±0.26
F9	498.78±1.23	2.62±0.03	96.98±2.78	8.2±0.13

All values are expressed as mean ± standard deviation, n=3

Table 4(b): Evaluation of Floating-pulsatile release tablet (F1–F9)

Formulation no.	Swelling Index	Lag time Buoyancy (sec)	Lag time (hr)	% drug release	
				VAL	HCTZ
F1	112.41 ± 2.13	108±2	3.0±0.7	99.69 ± 0.32	98.15 ± 0.12
F2	125.17 ± 1.04	109±3	3.2±0.4	99.33 ± 0.14	99.10 ± 0.44
F3	121.16 ± 1.47	113±5	3.5±0.2	99.23 ± 0.56	97.15 ± 1.24
F4	134.41 ± 0.21	102±3	4.1±0.4	99.84 ± 0.21	99.14 ± 0.34

F5	145.60 ± 0.12	116±2	4.6±0.4	84.49 ± 0.52	87.26 ± 0.42
F6	147.01 ± 1.33	115±2	5.0+0.3	81.64 ± 0.47	79.34 ± 0.35
F7	151.13 ± 3.01	111±3	5.2±0.1	78.11 ± 1.34	77.29 ± 1.46
F8	140.18 ± 2.42	110±5	5.5±0.4	68.56 ± 1.48	71.42 ± 0.47
F9	152.14 ± 2.71	119±5	6.0±0.2	60.54 ± 1.02	70.21 ± 1.22

All values are expressed as mean ± standard deviation, n=3

***In-vitro* drug release of Floating Pulsatile release tablet**

***In-vitro* drug release profile of Valsartan**

Table 5(a): In-vitro drug release profile of batches F1–F4 containing VAL

Time (min)	Batch			
	F1	F2	F3	F4
0	0	0	0	0
20	6.21 ±0.75	4.71 ± 0.64	6.34 ± 0.56	5.81 ± 0.57
40	8.14 ± 0.56	5.61 ± 0.55	7.65 ± 0.64	7.55 ± 0.65
60	9.61 ± 0.70	6.40 ± 0. 94	8.95 ± 0.45	8.67 ± 0.42
80	10.31 ± 0.97	7.64 ± 0.61	10.42 ± 0.08	11.42 ± 0.68
100	12.61 ± 0.59	10.48 ± 0.57	11.81 ± 1.74	12.34 ± 0.48
120	19.47 ± 0.15	11.69 ± 0.45	12.61 ± 0.11	13.64 ± 1.54
140	48.62 ± 1.24	13.47 ± 0.58	15.07 ± 0.32	16.75 ± 0.45
160	76.74 ± 0.17	17.64 ± 0.45	26.71 ± 0.11	18.61 ± 0.58
180	79.36±0.52	21.77 ± 1.17	54.61 ± 0.11	22.41 ± 0.61
200	81.57±0.45	74.76 ± 0.68	80.65 ± 1.47	26.58 ± 0.48
220	84.61 ± 1.74	77.33 ± 0.47	82.11 ± 0.61	79.22 ± 0.58
240	86.24 ± 0.34	80.68 ± 0.64	83.08 ± 0.17	81.61 ± 0.49
260	88.20 ± 0.47	82.46 ± 1.54	86.13 ± 1.05	83.66 ± 0.85
280	91.12 ± 0.18	84.59 ± 0.56	88.11 ± 0.74	86.34 ± 0.67
300	92.85 ± 0.27	88.34 ± 0.14	91.55 ± 1.05	89.61 ± 0.43
320	94.76 ± 0.68	91.31 ± 0.64	93.62 ± 1.07	91.61 ± 0.61
340	95.58 ± 0.67	93.67 ± 0.71	95.81 ± 0.41	95.64 ± 1.04
360	96.76 ± 0.34	97.69 ± 0.20	98.64 ± 0.64	99.64 ± 0.47

All values are expressed as mean ± standard deviation, n=3

Table 5(b): In-vitro drug release profile of batches F5–F9 containing VAL

Time (min)	Batch				
	F5	F6	F7	F8	F9
0	0	0	0	0	0
20	5.47±1.04	3.65 ± 0.08	4.32 ± 0.30	5.27 ± 0.17	6.07 ± 0.32
40	6.14 ± 0.57	4.36 ± 0.12	6.36 ± 0.45	6.35 ± 0.30	7.64 ± 0.40
60	6.97±0.15	6.65 ± 0.60	8.12 ± 0.24	6.86 ± 0.15	8.57 ± 0.46
80	8.68±1.27	8.54 ± 0.85	10.85 ± 0.09	7.67 ± 0.67	10.33 ± 0.15
100	11.17 ± 0.68	9.28 ± 0.38	11.06 ± 0.78	8.85 ± 0.60	11.36 ± 0.44
120	12.85 ± 0.32	10.65 ± 0.15	13.58 ± 0.67	11.02 ± 0.28	12.21 ± 0.18
140	14.12±0.10	13.98 ± 0.19	15.94 ± 0.51	12.34 ± 1.06	14.54 ± 0.36
160	23.75±0.55	17.67 ± 0.65	18.20 ± 0.70	15.64 ± 1.15	15.03 ± 0.40
180	31.20±0.64	21.67 ± 0.12	21.28 ± 0.20	18.30 ± 0.28	16.34 ± 0.54
200	44.21±0.68	24.95 ± 0.72	25.84 ± 0.54	21.20 ± 0.78	18.41 ± 0.11
220	60.11 ± 0.44	45.98± 0.95	43.64 ± 0.17	34.01 ± 0.97	21.34 ± 0.74
240	64.43±0.79	55.02 ± 1.08	49.36 ± 0.22	43.25 ± 0.50	25.04 ± 1.34
260	69.32±0.68	60.17 ± 0.05	56.42 ± 0.30	59.10 ± 1.48	39.04 ± 2.20
280	73.65 ± 0.67	69.32 ± 0.62	64.03 ± 0.47	66.80 ± 0.38	54.06 ± 0.65
300	88.14 ± 0.22	87.64 ± 0.51	79.34 ± 0.60	75.39 ± 0.42	68.06 ± 0.64
320	94.32 ± 0.10	93.61 ± 0.75	86.15 ± 0.78	82.65 ± 0.65	78.34 ± 0.88
340	96.04 ± 0.07	95.08 ± 0.22	91.68 ± 0.69	93.37 ± 0.95	88.36 ± 0.55
360	98.69 ± 0.09	97.85 ± 0.13	98.08 ± 0.10	97.67 ± 0.60	98.75 ± 0.64

All values are expressed as mean ± standard deviation, n=3

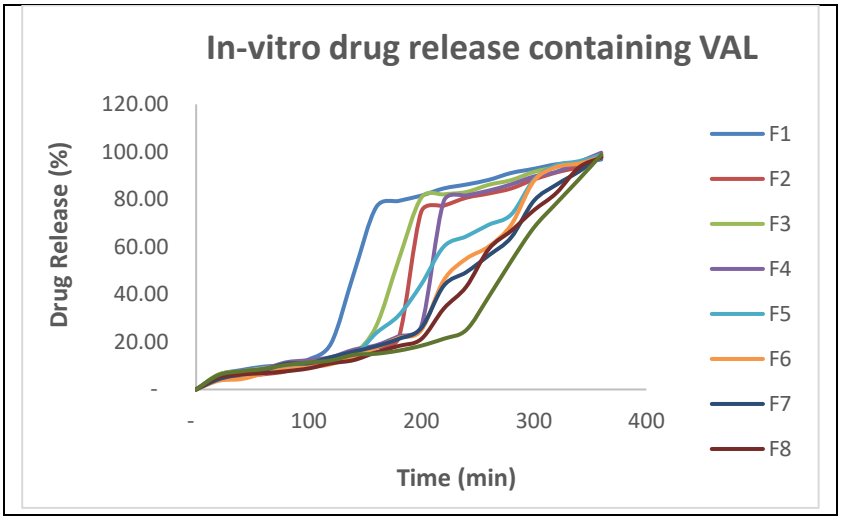

Figure 5: In-vitro drug release containing VAL

***In-vitro* drug release profile of Hydrochlorothiazide**

Table 6(a): In-vitro drug release profile of batches F1–F4containing HCTZ

Time (min)	Batch			
	F1	F2	F3	F4
0	0	0	0	0
20	4.26 ± 0.13	3.94 ± 0.19	5.68 ± 0.16	4.38 ± 0.16
40	6.41±0.82	4.09 ± 0.15	6.44 ± 0.84	6.77 ± 0.52
60	8.22±0.16	5.34 ± 0.67	9.40 ± 0.32	8.26 ± 0.30
80	11.72±0.65	6.37 ± 0.32	10.64 ± 1.10	9.38 ± 0.06
100	12.09±0.28	8.42 ± 0.61	10.98 ± 0.20	11.65 ± 0.59
120	21.48±0.14	11.54 ± 0.47	12.62 ± 0.51	13.04 ± 1.27
140	48.07±0.22	13.30 ± 2.12	14.24 ± 0.15	16.02 ± 0.25
160	74.04±0.85	18.12 ± 0.40	22.41 ± 0.21	19.30 ± 0.62
180	79.36 ± 0.08	25.84 ± 0.13	56.10 ±1.22	22.24 ± 0.23
200	81.68 ± 0.61	72.20 ± 0.80	79.22 ± 0.63	26.32 ± 2.07
220	84.04 ± 0.17	79.02 ± 0.72	81.65 ± 0.05	77.10 ± 0.32
240	87.50 ± 0.36	80.94 ± 0.15	83.03 ± 0.78	80.15 ± 0.05
260	89.07 ± 0.25	82.30 ± 0.94	84.58 ± 0.06	83.27 ± 0.20
280	91.20 ± 0.18	85.41 ± 0.55	86.04 ± 0.19	86.30 ± 0.22
300	93.64 ± 0.52	87.03 ± 0.60	89.20 ± 0.66	88.07 ± 0.15
320	95.10 ± 0.34	93.07 ± 0.05	92.65 ± 0.41	91.40 ± 0.31
340	96.41 ± 0.13	94.28 ± 0.62	95.07 ± 0.12	95.34 ± 0.02
360	98.12 ± 0.20	98.05 ± 0.13	97.02 ± 0.10	99.22 ± 0.10

All values are expressed as mean ± standard deviation, n=3

Table 6(b): In-*vitro* drug release profile of batches F5–F9 containing HCTZ

Time (min)	Batch				
	F5	F6	F7	F8	F9
0	0	0	0	0	0
20	4.58 ± 0.21	5.35 ± 0.64	5.89 ± 0.42	4.68 ± 0.10	5.24 ± 0.31
40	5.30 ± 2.20	6.50 ± 0.28	6.40 ± 0.10	5.24 ± 0.24	7.37 ± 2.06
60	6.22 ± 0.05	7.41 ± 0.11	8.22 ± 0.54	6.80 ± 0.52	8.54 ± 0.10
80	7.24 ± 0.23	8.65 ± 0.45	10.15 ± 0.64	7.95 ± 0.18	10.34 ± 0.34
100	9.10 ± 0.55	9.22 ± 2.01	12.34 ± 0.22	9.84 ± 0.22	11.82 ± 2.27
120	11.65 ± 0.68	10.20± 0.68	14.07 ± 0.04	10.58 ± 0.07	12.10 ± 0.02
140	14.28 ± 0.84	13.42 ± 0.10	17.10 ± 0.12	12.24 ± 0.30	14.37 ± 0.43
160	24.56 ± 0.47	18.33 ± 0.25	20.36 ± 0.67	15.41 ± 0.14	15.69 ±0.38
180	39.20 ± 1.27	21.70 ± 0.32	22.89 ± 2.21	18.63 ± 0.32	16.46 ± 0.05
200	44.05 ± 0.15	26.64 ± 0.65	25.01 ± 0.16	23.75 ± 0.62	18.89 ± 0.36

220	59.15 ± 0.42	44.10 ± 0.12	43.16 ± 1.27	34.42 ± 0.13	22.10 ± 0.74
240	63.40 ± 0.10	53.46 ± 0.57	51.05 ± 0.32	46.12 ± 1.07	28.37 ± 0.18
260	66.41 ± 0.11	61.15 ± 0.20	59.22 ± 0.20	57.38 ± 0.43	46.83 ± 0.10
280	73.17 ± 0.30	72.38 ± 0.67	65.10 ± 0.14	66.07 ± 0.14	56.75 ± 0.04
300	88.02 ± 0.61	86.22 ± 0.18	81.43 ± 0.32	75.18 ± 0.52	69.05 ± 0.15
320	92.10 ± 0.05	92.10 ± 2.27	86.22 ± 0.40	83.14 ± 0.05	82.64 ± 0.53
340	94.15 ± 0.42	95.14 ± 0.30	92.11 ± 2.10	91.54 ± 0.63	89.22 ± 0.18
360	98.02 ± 0.06	98.28 ± 0.15	97.89 ± 0.11	97.84 ± 0.15	96.30 ± 0.10

All values are expressed as mean ± standard deviation, n=3

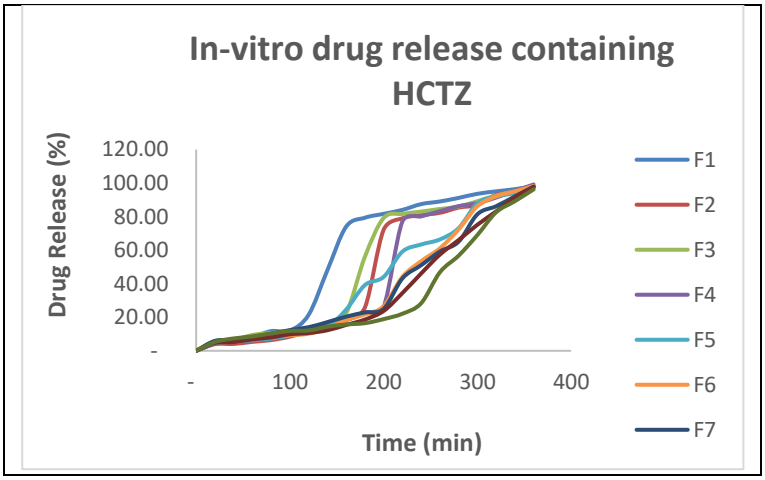

Figure 6: In-vitro drug release containing HCTZ

Discussion

The present study focused on the formulation and evaluation of a floating pulsatile drug delivery system (FPDDS) of valsartan and hydrochlorothiazide intended for chronotherapeutic management of hypertension.[23] The rationale behind this approach lies in the circadian rhythm of blood pressure, particularly the early morning surge, which is associated with a higher risk of cardiovascular events such as myocardial infarction and stroke.

Conventional dosage forms fail to address this temporal variation effectively, as they provide either immediate or sustained drug release without considering the biological timing of disease manifestation.[24] Therefore, the developed system aimed to achieve a programmed lag phase followed by a rapid drug release, synchronized with the body's circadian needs.

The formulation strategy employed a compression-coated tablet design consisting of a rapidly disintegrating core containing valsartan and hydrochlorothiazide, surrounded by a polymeric barrier layer composed mainly of Polyox WSR-205 and Polyox WSR N12K along with effervescent agents such as sodium bicarbonate and citric acid. This design was intended to ensure buoyancy, prolonged gastric residence time, and a controlled lag phase before drug release.[25] Preformulation studies played a crucial role in ensuring the suitability of drug candidates and excipients. The physicochemical properties such as solubility, melting point, and partition coefficient confirmed that valsartan and hydrochlorothiazide possess characteristics compatible with oral delivery systems.[26] Additionally, flow properties of the powder blends, indicated by parameters like angle of repose, Carr's index, and Hausner's ratio, suggested acceptable flowability and compressibility, which are essential for uniform tablet production. These findings supported the feasibility of direct compression technique for core tablet preparation and compression coating for pulsatile release.[27]

Drug-excipient compatibility studies using FTIR and DSC revealed no significant interactions between the drugs and selected excipients, indicating the stability of the formulation components. This is an important prerequisite for ensuring that the therapeutic efficacy of the drugs is not compromised during formulation development or storage.[28]

The core tablets were designed for immediate release using superdisintegrants such as croscarmellose sodium. Evaluation parameters like hardness, friability, weight variation, and drug content uniformity confirmed that the core tablets met pharmacopoeial standards.[29] Rapid disintegration of the core tablets ensured that once the barrier layer ruptured, the drug would be released quickly, fulfilling the requirement of pulsatile delivery.[30]

The compression coating played a critical role in controlling the lag time and release behavior. The use of hydrophilic polymers such as Polyox WSR-205 and Polyox WSR N12K contributed to the

formation of a gel barrier upon hydration, delaying drug release.[31] The viscosity and molecular weight of these polymers significantly influenced the lag time. Higher polymer concentrations resulted in increased gel strength and extended lag time, whereas lower concentrations led to premature drug release. This observation aligns with previously reported studies where polymer concentration was directly proportional to the delay in drug release.[32]

Effervescent agents, particularly sodium bicarbonate and citric acid, were incorporated to impart buoyancy to the system. Upon contact with gastric fluid, these agents generated carbon dioxide, which became entrapped within the polymer matrix, reducing tablet density and allowing it to float.[33] The floating lag time and total floating duration were found to be within acceptable limits, ensuring prolonged gastric retention. This is particularly beneficial for drugs like valsartan, which exhibit better absorption in the upper gastrointestinal tract. [34]

In vitro dissolution studies demonstrated a clear pulsatile release pattern characterized by an initial lag phase followed by a rapid and complete drug release. The optimized formulation achieved a lag time of approximately 4–6 hours, which is ideal for bedtime administration to target the early morning blood pressure surge.[35] After the lag phase, a burst release of both drugs was observed, ensuring immediate therapeutic action. This release pattern confirms the successful development of a chronotherapeutic drug delivery system.[36]

The drug release kinetics further supported the mechanism of release. The dissolution data, when fitted into various kinetic models, indicated that the release followed a combination of diffusion and erosion mechanisms. The initial lag phase was governed by polymer swelling and gel formation, while the subsequent rapid release was due to the rupture of the outer coating and disintegration of the core tablet. This biphasic release behavior is a hallmark of pulsatile drug delivery systems.[37] Comparing the results with previous studies, the findings are consistent with reports indicating that floating pulsatile systems are effective in synchronizing drug release with circadian rhythms. Studies by Koshta et al. demonstrated that Polyox-based compression-coated tablets could successfully achieve delayed drug release, similar to the present investigation. Additionally, literature suggests that combining antihypertensive drugs like valsartan and hydrochlorothiazide enhances therapeutic efficacy through synergistic action, which further justifies the selection of this drug combination. [38]

The strengths of the present study include the successful integration of floating and pulsatile delivery principles into a single dosage form, the use of well-characterized polymers to achieve controlled lag time, and the comprehensive evaluation of formulation parameters. [39] The system not only improves drug bioavailability through prolonged gastric retention but also enhances patient compliance by reducing dosing frequency and aligning therapy with biological rhythms.[40]

However, certain limitations should be acknowledged. The study primarily focused on in vitro evaluation, and in vivo studies are necessary to confirm the clinical effectiveness of the formulation. Factors such as gastric motility, food intake, and individual variability may influence the performance of the floating system in real conditions. Additionally, large-scale manufacturing of compression-coated tablets may present challenges related to uniformity and reproducibility.[41]

Conclusion

This study successfully formulated and evaluated a floating pulsatile drug delivery system of valsartan and hydrochlorothiazide designed for chronotherapeutic management of hypertension. The optimized formulation demonstrated a well-defined lag time followed by rapid drug release, effectively matching the circadian rhythm of blood pressure variation. The combination of Polyox polymers and effervescent agents proved effective in achieving controlled lag time, prolonged gastric retention, and efficient burst release. The system exhibited desirable physicochemical properties, satisfactory floating behavior, and a pulsatile drug release profile, fulfilling the intended formulation objectives.[42]

Importantly, the developed system addresses the limitations of conventional drug delivery by providing time-specific drug release, thereby enhancing therapeutic efficacy during the early morning surge in hypertension. This approach has the potential to reduce cardiovascular risks and improve patient outcomes. From a clinical perspective, the floating pulsatile system offers a promising strategy for chronotherapy, particularly in diseases exhibiting circadian patterns. Future studies should focus on in-vivo evaluation, pharmacokinetic profiling, and large-scale stability testing to further validate its clinical applicability. In conclusion, the developed FPDDS represents an innovative and effective drug delivery approach that aligns pharmacotherapy with biological rhythms, paving the way for advanced chronotherapeutic systems in hypertension management.

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