RESEARCH ARTICLE

Formulation and Evaluation of Floating-pulsating Drug Delivery System containing Fixed-dose Combination for Chronotherapy of Hypertension

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ABSTRACT

This project aims to build a floating, pulsatile hypertension therapy. This work examined the 3-factor, 2-level box-behnken design and optimization technique for the floating pulsatile tablet. The quantity of polyox WSR N12K and polyox WSR205 was chosen to be the independent variable. Drug release, lag time, and swelling index are chosen to function in terms of dependent variables. ANOVA was intended to assess the data statistically, and *p-value* of 0.05 was regarded to have statistical significance. The tablet containing bisoprolol fumarate (BF) and hydrochlorothiazide (HCTZ) was chosen for preparation. The system comprises of 2 parts: an outer layer comprised of an erodible material with a gas-generating agent and a center core tablet holding the active medicinal component. Super disintegrants and active ingredients are to be used to prepare rapid release core tablets (RRCT). The improved formulation's release kinetics provided the best fit for the zero-order models. The floating-pulsatile release (FPRT) F13 revealed a lag-time of 4 hours with > 90% of the drug being released at level 0 (65 mg) for polyox (WSR-205) and level +1 (65 mg) for polyox (WSR-N12K). After the burst, drug release is restricted. The tablets floated well and released drug for 6 hours. The concept of floating pulsatile is to be applied to improve retention in a gastric environment of dosage forms that have a lag phase after bursts release.

Keywords: Bisoprolol fumarate, Factorial dsign, Hydrochlorothiazide, Hypertension, Polyox (WSR-205), Polyox (WSR-N12K), Pulsatile floating.

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INTRODUCTION

Chronodelivery uses natural biological cycles to deliver drugs. Chronomodulated DDS improves safety, efficacy, and drug effectiveness. The third-generation drug delivery systems (DDS) time control feature may enhance disease treatments. Biological rhythm might be used for pharmacological treatment by synchronizing drug concentration with disease activity. Pulsatile DDS might be arranged to deliver medicine to a specified site in gastrointestinal tract (GIT) (e.g., colon) or device after a long time.[1,2]

Humans have an internal biological clock 24 hours daily cycle. In asthma, epilepsy, arthritis, allergic rhinitis, migraine, cardiac disease [stroke, angina pectoris and MI (myocardial infarction)], peptic ulcer, circadian rhythm pattern is well established and severe symptoms arise at particular times. If symptoms appear at night or early in morning, immediate-release dose forms may not be feasible. Blood flow (BF) is a selective β 1-adrenergic blocker.

It is used to treat secondary MI, cardiac failure, angina pectoris, and hypertension ranging from mild to high, possessing a $T_{1/2}$ of around 12 hours. Hydrochlorothiazide (HCTZ) is used for treating edema and hypertension and has a 5.6 to 14.8 hours plasma half-life. [3-5]

This work designs and optimizes a compressed-coated floating-pulsatile system comprising BF and HCTZ using water-soluble polyox. After experimental designs and identifying the ideal formula, they rehydrate by water or gastric juice and expand to generate a hydrogel with regulated drug delivery properties. Modern antihypertensive medicines have improved medication delivery. Most patients have insufficient blood pressure control.

Recent guidelines say those with high cardiovascular risk and >20/>10 mmHg systolic/diastolic blood pressure should start dual therapy. This experiment included HCTZ and BF, combining these two drugs with different mechanisms of action may be 2–5 times more effective than monotherapy *i.e.,* coronary events may be reduced by 40%, and cerebrovascular events by 54% compared to 29 and 40% in monotherapy also provide better organ protection than monotherapy.[6-8]

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Concept of pulsatile floating is appraised to increase residence time of dosage form in gastric environment which delivers drugs based on circadian rhythm.

MATERIALS AND METHODS

Materials

BF and HCTZ gift from Atra Pharmaceuticals, Aurangabad (Maharashtra, India), polyox (WSR-205), and polyox (WSR-N12K) was gifted from IPCA Laboratories Ltd. SEZ Pithampur, Indore (M.P., India). Modern Labs Sanwer Road, Indore provided croscarmellose sodium and microcrystalline cellulose super disintegrants (M.P., India).

Preformulation Studies[9]

Organoleptic

The descriptive color, odor, taste and for crystal morphology using a compound microscope.

Melting Point Determination

The sample's melting point helps us determine its purity. The melting point was established by filling a closed capillary with drugs and melting it. The temperature at which solid drug turns liquid has been studied.

Partition Coefficient

The study measures hydrophobicity and membrane permeability in drug design. The partition coefficient is the ratio between the drug's n-octanol and water concentrations.

$$Po/w = (C_{Oil}/C_{water}) \text{ equilibrium}$$

Physicochemical Characteristics

Angle of repose (AOR), densities (tapped and bulk), Hausner's ratio, Carr's index, and blend homogeneity were examined.

Table 1: Core tablet formulations

Ingredients	*C-1*	*C-2*	*C-3*	*C-4*
BF	20	20	20	20
HCTZ	25	25	25	25
Ac-Di-Sol	6	8	10	12
Mg stearate	3	3	3	3
MCC	8	8	8	8
Lactose	13	11	9	7
Total (mg)	75	75	75	75

AOR

It is obtained when the bulk powder is allowed to flow from a fixed height. Dry powder flow characteristics.

$$AOR = Tan^{-1} h/r$$

Bulk density is mass/volume. Pouring pre-weighed powder in a graduated cylinder measured bulk density of pure drugs and mixtures and is measured by poured volume and mass of powder:

$$P_b = M/V_b$$

Tapped Density

It was calculated by pouring specified quantity of mixed powder in a graduated cylinder, tapping (100 times) until the volume of powder bed was minimal:

$$Pt = M/Vt$$

Hausner's Ratio

It's a basic index that determines powder flow parameters:

$$\text{Hausner's ratio} = TBD/ LBD \times 100$$

Carr's Index

It's a basic index used to interpret powder flow:

$$\text{Carr's index} = TBD- LBD/ LBD \times 100$$

Method of Simultaneous Equations

For simultaneous estimation in a drug combination with a fixed dosage. Double distilled water was used to dilute the stock solutions of BF and HCTZ to produce separate concentrations of 2–6 g/mL of BF and 5–15 g/mL of HCTZ. Two wavelengths, 223 and 271.6 nm, were chosen from the overlapping spectra to produce a simultaneous equation. At both wavelengths, the absorptivity values of both drugs, E (1%, 1 cm), were calculated. A dilution of 2.5:6.25 g/mL and five binary combination solutions of HCTZ and BF were made in ratio of 2:5, which is extremely close to the therapeutic dosage ratio of 2.5:6.25 for the two drugs. Simultaneous equations were solved to estimate the drugs quantitatively.[11]

$$Cx = (A_2\, ay_1 - A_1\, ay_2) / (ax_2\, ay_1 - ax_1\, ay_2) \ldots\ldots.1$$

$$Cy = (A_1\, ax_2 - A_2\, ax_1) / (ax_2\, ay_1 - ax_1\, ay_2) \ldots\ldots.2$$

Where,

Cx is conc. of BF and Cy is conc. of HCTZ, and A1 and A2 are the mixture's absorbance at 223 and 271.6 nm, correspondingly. Similarly, ax_1 and ax_2, ay_1 and ay_2 are absorptivities of x and y at 223 and 271.6 nm, respectively.

Table 2: Individual polymer FPRT trial batches

S. no.	*Ingredients*	*Formulation codes*					
		P-1	*P-2*	*P-3*	*P-4*	*P-5*	*P-6*
1	Polyox-(205)	160	140	120	—	—	—
2	Polyox-(N12K)	—	—	—	150	130	110
3	NaHCO3	45	45	45	45	45	45
4	Citric acid	15	15	15	15	15	15
5	Ca2PO4	—	20	40	10	30	50

Table 3: 3^2 full factorial design

Formulation	*Coded levels*	
	Variable 1	*Variable 2*
F-10	−1	−1
F-11	−1	0
F-12	−1	+1
F-13	0	−1
F-14	0	0
F-15	0	+1
F-16	+1	−1
F-17	+1	0
F-18	+1	+1

Table 4: Factorial design variable concentrations by coded level

Variables	*Coded levels*		
	−1	*0*	*+1*
Polyox (WSR-205)	45	55	65
Polyox (WSR-N12K)	65	75	85

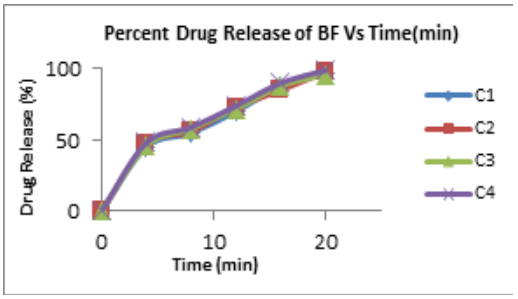
Formulation of Rapid Release Tablets (RRT) (Direct Compression)

Inner core tablets were compressed directly. Table 1 shows that BF, HCTZ, MCC, ac-di-sol with lactose were dry mixed for 20 minutes before being added. C1 to C4 included 5 to 15% ac-di-sol, super disintegrants, and followed by 10 minutes of mixing. Minipress tablet compression machine compresses 75 mg of powder mix using 6 mm circular concave punch and die.

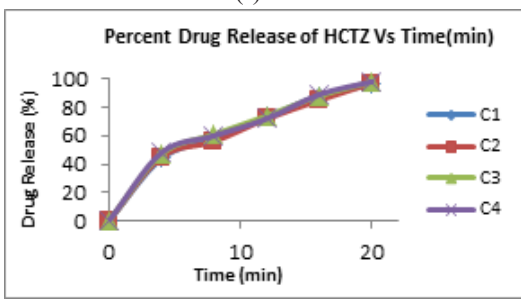
Preparation of the Trial Batches of Individual Polymer for FPRT (Floating-pulsatile Release Tablet)

Table 2 shows that polyox (WSR-205) and polyox (WSR-N12K) polymers, $NaHCO_3$, and citric acid were used as gas generating agent in FPRT. The sodium bicarbonate content in the gas-generating agent ranged from 25% (50 mg) to 10% (20 mg) of citric acid.

After calculating the optimal gas-generating agent concentration, the polymer concentrations were employed in factorial design. After weighing and placing half barrier layer material in an 8.5 mm die, core tablet was added. The die was filled with the remaining barrier layer material before compression.



(a)



(b)

Figure 1 : In-vitro drug release profile of core tablet containing (a) BF (b) HCTZ.

FPRT Formulation

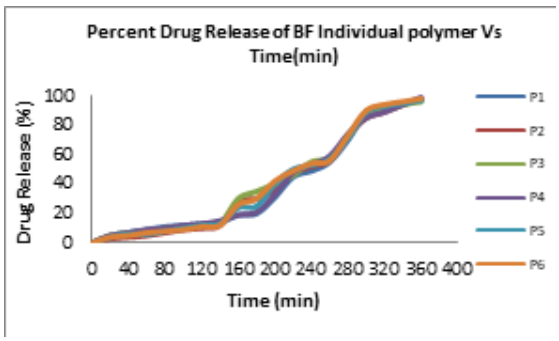
Experimental Design

Optimization employs a 3^2-factorial design. It permits analysis of quadratic response surfaces and building of a 2^{nd} order polynomial model to optimize time-lagged coating process. Using design-expert, mathematical modelling, data-fitting, and RSM (response surface modeling) were done. This study employed a 3^2-randomized reduced factorial design with two components at each of three levels. Experiments were done at each of nine feasible combination preparations using Table 3. Independent factors were polyox WSR205/WSR N12K ratios. The dependent variables were 4 hours delay, drugs release, and swelling index. Response surface analysis is used to examine factorially produced batches and each variable's impact.

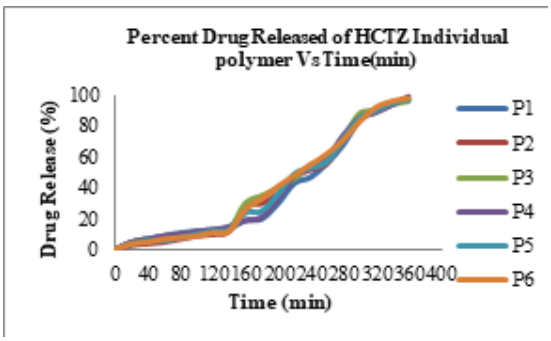
$$Y = b_0 + P_1X_1 + P_2X_2 + P_{12}X_1X_2 + P_{11}X_1^2 + P_{22}X^2_2$$

Where,

Y is dependent variable, b_0 is arithmetic mean of 9 runs, and bi (P_1, P_2, P_{12}, P_{11}, and P_{22}) is estimated coefficient for factor Xi



(a)



(b)

Figure 2: *In-vitro* release profiles of batch P1–P6 (a) BF (b) HCTZ

Table 5: 3^2 full factorial batches using Polyox (WSR-205) and (N12K) as variables

Formulation no.	*Polyox (WSR-205)*	*Polyox (WSR-N12K)*	*$NaHCO_3$*	*Citric Acid*	*Core tablet*	*Ca_2PO_4*	*Total wt. (mg)*
F-10	45	65	50	20	75	40	295
F-11	45	75	50	20	75	30	295
F-12	45	85	50	20	75	20	295
F-13	55	65	50	20	75	30	295
F-14	55	75	50	20	75	20	295
F-15	55	85	50	20	75	10	295
F-16	65	65	50	20	75	20	295
F-17	65	75	50	20	75	10	295
F-18	65	85	50	20	75	—	295

(X_1, X_2, X_1X_2, X_{12}, and X_{22}), which reflects average outcome of altering 1 factor at time from low to high. Interaction (X_1X_2) demonstrates in what way 2 variables influence response. Polynomial terms (X_1^2 and X_2^2) examine nonlinearity.

Based on trial batches and evaluation, different concentrations for BF and HCTZ tablets were selected. Table 4 shows coded levels and concentrations of formulation variables.

Final batch Preparation

Final batches of tablets were produced using a factorial design. Table 5 shows that batches were made based on concentrations.

Formulation Development of Batches Comprising Polyox WSR (205) and Polyox WSR (N12K)

The 3^2-factor design variables (F10–F18). $NaHCO_3$ concentration remained at the optimal level. Analysis of experimental batches of each polymer determined for optimal level. Polyox WSR205 and N12K concentrations were changed in this factorial design while other components remained constant. Using separate batches, minimum and maximum variable values were established. Both polymer concentrations between 15–30% were used to evaluate their combined effects on lag phase, release pattern, and swelling index. Table 5 is according to factorial design for the batches, including polyox (WSR-205) and polyox (N12K), (F10–F18). Design Expert was used to investigating the effect of parameters on response employing response surface approach and statistical ANOVA (version 8.0.6). Multiple-linear regressions employ equations to model and correlate response variables.

Tablets Manufacturing

Separate quantities of $NaHCO_3$, citric acid, polyox (WSR-205), and polyox (WSR-N12K) were weighed and sieved through mesh 20. Mixing was done for 15 minutes in a plastic bag. Table 1's formula was used to make a rapid-release core tablet. The core tablet was placed at center of an 8.5 mm die after weighing and transferring barrier layer material (half). Before compressing, the die was filled with the remaining material. Hardness was set for 7–9 kg/cm^{-2}.

FPRT[12-15] Evaluation

Physical Evaluation

Prepared tablets were evaluated for weight, thickness, friability, hardness, drug content, swelling index, fourier-transform infrared spectroscopy (FTIR), and differential scanning calorimeter (DSC).

Drug Content Determination

After the tablets were crushed, distilled water was added to 20 mg powder. Stock solutions were membrane-filtered (0.45 mm) and diluted using distilled water. The sample was evaluated using a UV-spectrophotometer. Every sample was triple-analyzed.

Drug-Excipient Interactions

FTIR was used to test drug and excipient physicochemical compatibility. FTIR spectra were obtained using a spectrometer. For FTIR, only F13 was considered. The finest formulations of BF and HCTZ were pulverized and mixed with KBr, an IR transparent matrix, at a 1:10 ratio (Sample: KBr). KBr discs were made by compressing powder in a five-ton hydraulic press for five minutes. Scan resolution was 4 cm^{-1} from 4,000–600 cm^{-1}.

Differential Scanning Calorimetry (DSC)

DSC measures thermal characteristics and excipient-drug interactions in a physical combination. Thermograms were recorded using a DSC. 2–5 mg of BF, HCTZ, polyox WSR (205), and polyox WSR (N12) were heated in the pierced aluminum pan up to 300°C, at heating rate (10°C/min) under nitrogen stream at 50 mL/min. DSC thermograms' thermal data were analysed.

Determination of Swelling Index (SI)

Tablets were incubated at 37 ± 1°C in 200 mL of 0.1 N HCl by weight (W1). Tablets removed from the beaker every hour for 24 hours and excess liquid was swept away. After reweighing swollen tablets (W2), SI was calculated by formula.

In-vitro Buoyancy

The tablet's floating behavior was evaluated using USP-II apparatus in 900 mL 0.1 N HCl kept at 37 (± 0.5°C), 50 rpm. Both floating time and lag time are shown.

In-vitro Drug Release

Three tablets from every batch were tested using dissolution apparatus-II for release rate. Dissolving test employed 900 millilitre 0.1 N HCl at 37 (± 0.5°C) and 75 rpm. Upto 6 hours, a 5 mL sample of solution was collected every 5 minutes for

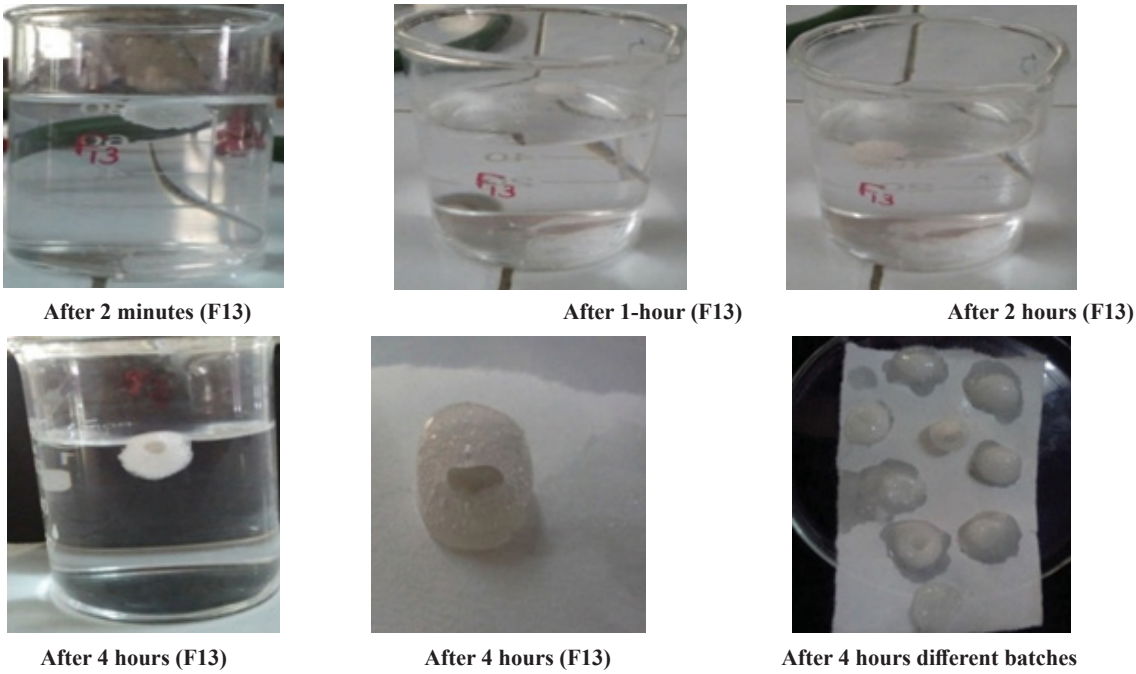
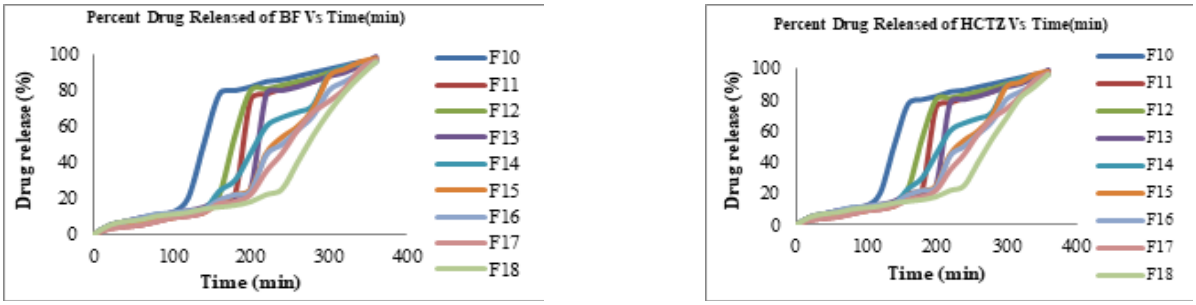


Figure 3 : *In-vitro* floating behavior.



(a) (b)

Figure 4: *In-vitro* drug release profiles of FPRT of F10 – F18 (a) BF (b) HCTZ

the first 15 minutes, then every 30 minutes for the following 45 minutes upto 360 minutes. Replacement was done by fresh media. After filtering using a 0.45 micron membrane, samples were diluted using 0.1 N HCl. Absorbance was measured with the help of double-beam UV-spectroscopy.

Lag Time

Tablet burst and core tablet lost its press-coating during the lag period, which was previously defined. This is thought of as an off-release period that has been planned.

Table 6: Results of preformulation studies

Properties	*Results*	
	BF	*HCTZ*
Description	Amorphous	Crystalline Powder
Taste	Salty	Slightly bitter
Odor	No Odor	No Odor
Color	White	Almost white
Melting Point	100°C	274.00°C
Partition Coefficient	0.89	0.07

Testing the Best Formulation for Stability

As per ICH guidelines, a short-term stability study 1-month on optimized FPRT was done at 40°C (± 2°C) and RH 75% (± 5%). Physical characteristics, drug content, floating lag time, floating duration and *in-vitro* drug release (lag time) were examined after completion of one month.

RESULTS AND DISCUSSION

Preformulation Studies

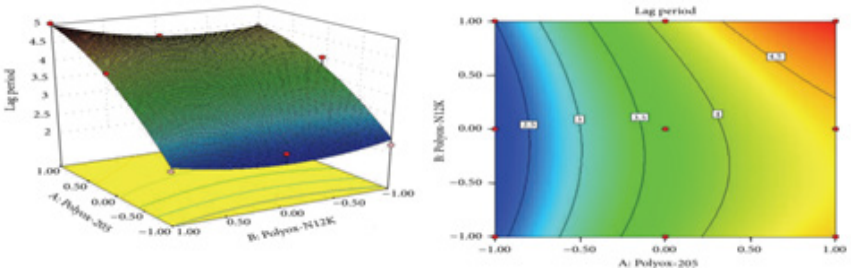
The results of preformulation studies is shown in Table 6.

Drug-excipient Mixture Results

The flow properties of drugs and excipients is shown in Table 7.

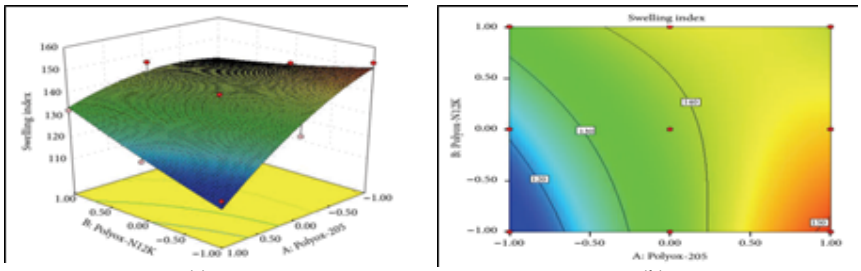
Evaluation of RRT

The quick expansion of tablet may be the cause of the rapid rise in the disintegration of BF and HCTZ within concentration (5–15%). It was shown that when the concentration of ac-di-sol rise, the time it took for a tablet to dissolve decreased. With a drug release of 99.35% and the lowest disintegration time (66 second), formulation C-4 (15% CCS) was used (Figure 1).



(a) (b)

Figure 6: (a) Response surface plot screening impact on drug release and (b) contour plot.



(a) (b)

Figure 7: (a) Response surface plot viewing impact on swelling index and (b) contour plot.

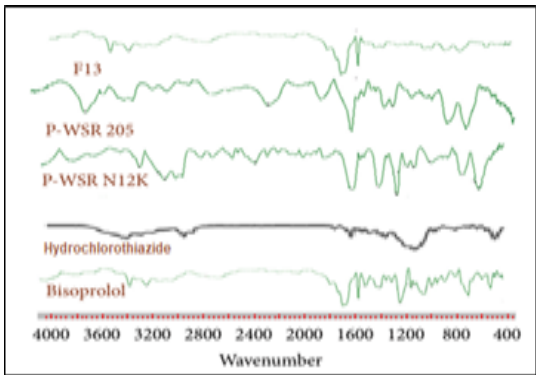


Figure 8: IR of drug, polymers, and formulations.

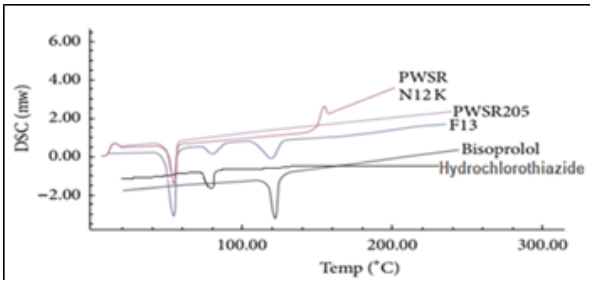


Figure 9: DSC curves of BF, HCTZ, polymers and formulation F13.

The pulsatile delivery development requires a short disintegration time to generate a burst effect. The tablet has a hardness in the (2.4–2.7 ± 0.18 Kg/cm^2) range and a friability of <1%, indicating high mechanical resistance. Both medicines' high (>98.14%) and consistent drug content was observed in all tablet forms. C4 was picked for further research as the main tablet for pulsatile release tablets.

Table 7: Flow properties of drugs and excipients

Flow property	*Physical mixture of BF, HCTZ and excipients*
Bulk density	0.378 g/m^3
Tapped density	0.389 g/m^3
Angle of repose	24.37°
Hausner's ratio	1.33
Carr's index	23.25%

FPRT Evaluation (Floating Pulsatile Release Tablet)

Individual polymers in trial batches. Gas-producing agent conc. affects formulation drug release. $NaHCO_3$ affects formulation hardness and release pattern. Gas-generating agent conc. was adjusted between 25% (50 mg) $NaHCO_3$ and 10% (20 mg) citric acid to get optimum floating and optimum lag time and optimum concentration 45 mg (23%) and 15 mg (8%), respectively was chosen. Polyox (WSR-205) and polyox (WSR-N12K) at 70 to 65% give a burst- effect (after 4 hours) and continuous drug release (for 6 hours).

Compression-coated polyox (WSR-205) (P-2) and polyox (WSR-N12K) (P-5) with central cord syndrome (CCS) using (C-4 as core tablet) showed appropriate lag periods with burst at 3.40 (± 0.2 hours) and 4.0 (± 0.1 hour) and release of drug at 98.97 and 99.16%, respectively. The coating layer steadily starts to dissolve during dissolution kinetics, finally reaching the coat's limiting thickness. After this point, the existence of the super disintegrants allowed the core tablet to enlarge, which caused the shell to rupture under pressure. This pressure was considerable because CCS has a strong swelling capacity, which led to a burst effect (after 4 hours) and entire drug get released. To evaluate the influence of polymers on optimization, formulations P2 and P5 were taken into account as the final batch. The quantity of coating polymer in batches P1 and P4 was too large to get a high lag time with a low amount of drug release. Because the coating polymer in P3 and P6 was too weak, the tablet's integrity could not be maintained for a prolonged time, leading the complete quantity of drug to

Table 8: Evaluation of FPRT (F-10–F-18)

Formulations	*Tablet weight (mg)*	*Thickness (mm)*	*% Drug Content (Combined)*	*Hardness (Kg/cm^2)*	*Swelling Index*	*Buoyancy Lag time (sec.)*	*% Drug Release*	
							BF	*HCTZ*
F-10	294.12 ± 1.26	2.55 ± 0.07	98.45 ± 0.56	7.5 ± 0.13	188.45 ± 2.34	108 ± 2	99.49 ± 1.32	97.43 ± 0.32
F-11	297.29 ± 2.14	2.64 ± 0.04	97.27 ± 0.75	7.8 ± 0.25	192.66 ± 3.75	109 ± 3	99.23 ± 0.74	98.20 ± 0.44
F-12	298.54 ± 1.35	2.58 ± 0.03	98.17 ± 1.34	7.7 ± 0.06	201.56 ± 2.56	113 ± 5	99.30 ± 0.96	98.18 ± 1.01
F-13	295.23 ± 0.95	2.52 ± 0.05	97.96 ± 0.78	8.1 ± 0.15	206.45 ± 1.34	102 ± 3	99.89 ± 2.01	99.21 ± 0.21
F-14	292.11 ± 1.23	2.44 ± 0.08	98.62 ± 1.56	7.4 ± 0.08	210.55 ± 3.13	116 ± 2	83.60 ± 0.82	85.16 ± 0.42
F-15	294.78 ± 0.87	2.63 ± 0.02	97.39 ± 0.50	7.9 ± 0.12	222.44 ± 1.57	115 ± 2	80.94 ± 0.95	77.54 ± 0.35
F-16	297.89 ± 0.98	2.68 ± 0.10	97.19 ± 2.34	8.2 ± 0.34	226.45 ± 2.18	111 ± 3	75.21 ± 1.74	76.19 ± 1.16
F-17	291.55 ± 1.34	2.57 ± 0.04	98.82 ± 0.34	7.6 ± 0.26	231.61 ± 3.56	110 ± 5	66.96 ± 1.98	70.46 ± 0.80
F-18	298.78 ± 2.15	2.62 ± 0.03	96.98 ± 2.78	7.8 ± 0.13	239.77 ± 2.15	119 ± 5	59.94 ± 2.02	69.41 ± 1.62

Results are Expressed in (mean ± S D) (n = 3)

be released fast. The type and amount of hydrophilic polymer utilized on the core had an influence on drug release Figure 2.

Evaluation of FPRT

Tablet weight (260 ± 0.18–275 ± 0.22 mg), thickness (3.50 ± 0.07–3.60 ± 0.04 mm), hardness (7.3 ± 0.16–7.8 ± 0.18 kg/cm^2), drug content (>97.48) and buoyancy lag time (90–110 second) are presented in Table 8.

***In-vitro* Buoyancy Determination**

Additional polymers in the buoyant layer alter how a tablet floats. The buoyancy lag time for each batch was within three minutes. Each batch had a floating time that exceeded 9 hours Figure 3 shows the *in-vitro* floating behavior of a polyox tablet.

Evaluation of Combination Polymers

Properties for the floating-pulsatile release of F10-18 included weight (ranging from 291.55 ± 1.34 to 298.78 ± 2.15 mm), thickness (2.44 ± 0.08 to 2.68 ± 0.10 mm), hardness (7.4 ± 0.08 to 8.2 ± 0.34 Kg/cm^2), drug content (>97.19% for both medicines), and buoyancy lag time (between 102 - 119 sec). With a shorter buoyancy lag time of 102 seconds, FPRT of the improved batch F13 demonstrated maximal drug release of 99.89 ± 2.01 for BF and 99.21 ± 0.21 for HCTZ.

Experimental Modeling of FPRT Drug release In-vitro using a 3^2-Factor Design (F10–F18)

As can be seen in Figure 4, the F-13 batch of 70 mg polyox (WSR-205) (level 0) and 50 mg polyox (WSR-N12 K) (level +1) showed a 4.20 hour lag time, followed by a sigmoidal release pattern that ended in 100% drug release in 6^{th} hour. When polyox concentration changes from F-10 to F-18, both lag time and drug release are affected.

Lag Period

The lag period determines tablets release drugs. Ischemic heart disorders, including angina pectoris and MI occur late at night or early in morning. High blood pressure causes these episodes, often before waking up. BF and HCTZ both have 9–12 hours of half-lives. The lag time for the formulas F10-F18 was 2–6 ± 0.2 hours. F-13 showed the best drug release and lag time (4.2 ± 0.2). Polyox WSR (205) and polyox WSR (N12K) affect lag time. Polymer concentration increased lag time (from level 1 to level 1) (Figure 5).

$$\text{Lag Period} = + 3.67 + 1.13\ A + 0.17\ B + 0.1\ AB - 0.40\ A2 + 0.30B2 \quad (4)$$

Using ANOVA, Design Expert determined all polynomial equations statistically significant ($p < 0.01$)

Figure how polyox WSR205 and N12K affect lag time. In figure, the response shows the surface plot and contour plot illustrate that both polymers affect lag time. Polyox (WSR-205) and polyox (WSR-N12K) concentrations (+1, +1) extend and uniformize lag time. The polymers increased lag time but didn't hinder drug release.

Drug Release

Variables affecting drug release in F10–F18 formulations are presented.

$$\text{Cumulative\% Drug Release} = + 72.30 - 25.86\ A - 10.23\ B - 3.94\ AB - 6.88\ A2 - 0.72\ B2, \quad (5)$$

Formulation variables are A and B. Using ANOVA, design Expert determined all polynomial equations statistically significant ($p < 0.01$) polynomial equations contain intercept, first-order key effects, factors of interaction, and advanced-order effects.

Figure 6 shows how polyox (WSR-205) and (N12K) affect drug release. Drop in polyox (WSR-205) and (WSR-N12K) concentrations (levels -1 and -1) increases drug release by >90%.

Swelling Index

It affects how long drugs remain in the stomach. F10-F18 had swelling indices between 113.61 and 153.13. F16 had the greatest swelling index (153.13 ± 4.1), while F10 the lowest (113.61 ± 3.13). Formulations F10 – F18 indicate the variables' impact on swelling index Figure 7.

$$\text{Swelling index} = + 137.99 + 11.91\ A + 3.33\ B - 8.49\ AB - 4.88\ A2 - 0.88\ B2. \quad (6)$$

Design Expert software's and ANOVA findings indicated all polynomial equations were statistically significant ($p < 0.01$). Figure 7 shows the swelling index after mixing polyox WSR205 and N12K. The response surface plot and contour plot

show that polyox (WSR-205) and (WSR-N12K) concentrations enhance the swelling index (level 0).

FTIR Study

Figure 8 shows no drug-polymer interaction. BF and HCTZ shows peaks at 1652 and 1235 cm^{-1}, respectively. Polyox (WSR-205)'s maxima were 2959, 1942, and 1482 cm^{-1}. Polyox (WSR-N12K) exhibited peaks at 3649, 2854, and 1304 cm^{-1}. The drug and polymer have no chemical interaction, as revealed by the F13 spectra. A few bands in the formulation vanished and merged as a result of the cross-linking of polymers. F13's spectra exhibited 1652 and 1235 cm^{-1} peaks, indicating the drug was pure and had not underwent structural alterations.

DSC

The DSC thermogram for HCTZ, BF and Formulation F13 is displayed in Figure 9. The thermographs produced *via* DSC study show that the melting point of a pure drug is between 110 and 89°C, whereas that of a formulation is between 85 and 112°C. A small but noticeable difference exists between the melting points of the pure medication and its preparations. This shows that the drugs remain unreacted even after being formulated. This demonstrates that the drug and polymer have no chemical interactions.

Stability Testing

For stability studies, the optimized batch F13 was used. Floating duration (7.0-7.4 ± 0.8 hours) and assay (>97.35%) were observed at 40ºC (± 2ºC) and 75% RH (± 5%). No formulation parameters altered, according to stability data. Stability results suggest that no formulation factors altered.

CONCLUSION

Organoleptic characteristics, melting point, and partition coefficient are tested to determine drug purity during the initial stage. Physical mixing of drugs and excipients is undertaken to ensure batch uniformity. Adjusting the concentration of polyox (WSR-205) and (WSR-N12K) in the outer barrier layer using gas generating agent may modify the FPRT formulation's drug release lag time.

The compression-coated, floating-pulsatile release tablet worked well *in-vitro* and *in-vivo*, demonstrating a good ability to delay drug release. Formulation will aid with chronopharmaceutical delivery of the drug. It's mightily promising HCTZ and BF drug delivery technologies.

CONFLICT OF INTEREST

Authors have no conflicting interests.

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