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Research article

Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension

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ABSTRACT

The paper aimed to progress an ideal gastro retentive drug delivery system intended for directing Losartan and Hydrochlorothiazide as a fixed-dose combination for anti-hypertensive therapy. The bilayer tablets were primed through direct compression method. Losartan was formulated by means of a floating layer expending hydrophilic swellable polymer Hydroxy Propyl Methyl Cellulose K4M, ethyl cellulose (4cps) as a buoyancy enhancer, sodium bicarbonate as a gas spawning agent. The amount of polymer blends remains optimized using 2^3 full factorial designs. The clout of experimental factors such as swelling agent concentration, buoyancy enhancer and gas generating agent on floating lag time, total floating time, T50% and % drug release remain investigated to get optimized formulation. The responses remain analyzed using Analysis of variance, and polynomial equation stood created for every retort using Multiple linear regression analysis. Entirely preparations floated for more than 12 h. The release pattern of losartan stood fitted to diverse models based on the coefficient of correlation (r). All the formulations, except F2, showed the Korsemeyer-Peppas model as the best fit model. Formulation F2 showed the zero-order model. Diffusion exponents (n) remained indomitable designed for entirely formulations (0.45–0.89), accordingly the chief drug discharge mechanism was non-fickian (anamolous) transport. Formulation F4 containing 20% w/w Hydroxy Propyl Methyl Cellulose K4M, 15% Sodium bicarbonate and 5% ethyl cellulose (4cps) was the best formulation as per the range of drug release remain institute to be more than 95 % in 12h and floating lag time was 20.15 s. The immediate-release layer stood optimized using crospovidone and Indion 414 as a super disintegrant. Formulation A8 containing 2% Indion 414 was considered as optimized formulation as it released 99% drug within 35 min and possessed less disintegration time. Optimized formulation F4 from the controlled-release layer and A8 from immediate-release layer was used to formulate bilayer tablet. The optimized formulation was imperilled to stability reading for three months at 40°C/75% relative humidity. The stability revision exhibited no substantial alteration in the appearance of tablets, floating characteristics, drug content and *in-vitro* drug dissolution. Consequently, a biphasic drug release design was effectively accomplished over the formulation of floating bilayer tablets.

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1. Introduction

The controlled release drug delivery systems (CDDS) owning the capacity to be engaged in the stomach remain entitled as Gastro Retentive Drug Delivery Systems (GRDDSs), then both retain aid in enhancing the oral precise release of medications through unremittingly discharging drug afore absorption window designed for an extended period. Further being capable to persistently and sustainably release medication towards the small intestinal absorption window, the enhancements delivered since GRDDSs embrace: attaining a further substantial then extended therapeutic outcome and consequently falling the incidence of management epochs, only if further effective management of resident stomach ailments, and curtailing equally lower-tract deactivation of the medication and impacts on the lower intestinal flora. Subsequently that, innumerable methodologies of this sort as floating, bioadhesive, swelling and escalating systems obligate remain advanced toward surge the gastric retaining period of a dosage form [1].

Bilayer tablet remains a novel epoch designed for the effective advance of controlled delivery design laterally through numerous sorts to deliver an approach of efficacious drug transport system [2, 3]. Bi-layer tablet remain seemly intended for ensuing discharge of two medications in combination, discrete two discordant constituents then similarly designed for sustained discharge tablet in that single layer is immediate release as initial dose and the subsequent layer is the maintenance dose. Bilayer tablet remains enhanced favourable knowledge to overwhelmed the inadequacy of the single-layered tablet [4, 5].

Hypertension (HTN) otherwise similarly notorious as high blood pressure (BP), occasionally arterial hypertension, remains a chronic medicinal situation and that the BP in the arteries is upraised. This entails the heart to effort durable than regular to circulate blood over the blood vessels. The BP implicates two extents, systolic and diastolic, that are reliant on either the heart muscle remains constricting (systole) or relaxed (diastole) amid beats. Normal BP is at or beneath 120/80 mmHg. High BP is supposed to remain extant if it is obstinately at or beyond 140/90 mmHg [6, 7].

Losartan potassium (LSP) is a persuasive, vastly precise angiotensin II type 1 (AT1) receptor antagonist through anti-hypertensive action. It remains eagerly absorbed after the gastrointestinal tract through oral bioavailability of around 33% and a plasma elimination half-life extending after 1.5–2.5 h. Subsequent oral management, losartan is hastily absorbed, and formerly roughly 14% of a losartan dose remains metabolized into active carboxylic acid metabolite (E3174) by CYP2C9. E3174 is 10–40 fold further persuasive than owned parent composite, then the probable half-life sorts after 6–9h. Hydrochlorothiazide (HCT) is a thiazide diuretic and is adopted in the supervision of slight to modest hypertension. It remains precise marginally soluble in water holding a plasma half-life of 6h–14h and protein binding 67.9%. It remains variably absorbed from the gastrointestinal tract, eliminated rapidly by the kidney and primarily excreted in unchanged form in urine [8].

A fixed-dose combination of losartan potassium (LSP)/Hydrochlorothiazide (HCT) remedy might remain a consistent prime for anti-hypertensive management, comprising meant for preliminary remedy in patients with BP elevation >20/10 mmHg beyond management target. Particular adverse effects concomitant with HCT, comprising improved peril designed for new-onset diabetes mellitus, might be equipoise by losartan [8]. Losartan remained recurrently managed through HCT in the Losartan Intervention for Endpoint reduction in hypertension (LIFE) revision, in which there stood a 25% peril decline for stroke in the losartan-based paralleled through the atenolol-based supervision group. The efficiency, permissibility, and suitability of Losartan/HCT combination treatment might surge patient amenability and lessen peril for stroke, an unfortunate consequence in patients with hypertension [9].

The combinations of Losartan potassium and Hydrochlorothiazide obligate remain revealed to have an improver outcome on BP decline, reducing BP to a greater mark than either constituent alone. Several pharmacological interactions support the potential further anti-hypertensive benefits from combined therapy with the angiotensin-II receptor (type AT1) antagonist and diuretics. The combined drug is adopted as a fixed-dose permutation to diminish the quantity of medicines [10].

An experimental design stays a statistical strategy, which suggests or instructs a customary of permutation of variables. The numeral and outline of certain design facts inside the pilot section hinge on the quantity of issues such need to be probable. Provisional on the sum of aspects, their intensities, probable interfaces and directive of the exemplary, several experimental designs remain preferred. The most straightforward factorial design remains the two factorial design, in which two aspects are deliberated apiece at two levels, hints to four experiments that remain found in 2-dimensional factor space at the corners of a rectangle. The number of experiments is assumed by 2^n, where 'n' is the number of factors [11].

2. Materials and methods

LSP, HCT, HPMC K4M was obtained from SARC Research labs, Hyderabad. CrosPovidone, Indion 414 was procured from HIQ Labs, Hyderabad.

2.1. Compatibility studies of drug and polymers

2.1.1. Fourier transform infrared spectrometry (FTIR)

Approximately 300mg of KBr was weighed and grind to a fine powder, and then approximately 1mg of the Pure drug/combination of drug-excipients was added and grinded well to mix the sample with the KBr and then press this KBr mixer and made a palate by using IR press at the pressure of 8-tons [12].

2.1.2. Differential Scanning Calorimetry (DSC)

The DSC exploration confirmed physical stature of inherent medication esoteric the nanoparticles. The sample remains placed and wrapped typical aluminium pan and was perused between 25 °C to 300 °C with a heating rate of 10°C/minute beneath nitrogen atmosphere. A blank aluminium pan served as reference [13].

2.2. Preparation and optimization of bilayer floating tablets

2.2.1. Formulation of immediate-release tablets of HCT

The medication along with super disintegrants crospovidone/Indion 414, microcrystalline cellulose and lake sunset yellow were weighed and passed through sieve no 60 discretely as displayed in Table 1. The concentration of crospovidone and Indion 414 were 2, 3, 4, 5 % and 0.5, 1, 1.5, 2 % respectively. The admixture of powders remains swayed out by utilizing a pestle and mortar intended for 10 min. Finally, the prepared powder blend lubricated through magnesium stearate and colloidal silicon dioxide then further assorted in mortar pestle for 3 min. The prepared powder blend was manually fed into the 4 mm flat-faced punches and the tablets having a final weight of 50 mg remained primed by direct compression (DC) on ten stations rotary tablet machine (Rimek Mini Press-I) [14].

2.2.2. Preliminary trial batches (PTB) of controlled release floating tablet of losartan

The PTB remain primed by expending hydrophilic polymers HPMC K4M, effervescent agent (sodium bicarbonate) and buoyancy enhancer (ethylcellulose 4 cps) at different concentrations and % CDR, FLT and total floating duration remain patterned and on such premise stages of beyond constituents remain fixed as follows: HPMC K4M: 20 %–30 % w/

Table 1. Formulation Design of immediate-release tablets of HCT.

S.No	Ingredients in milligrams	A1	A2	A3	A4	A5	A6	A7	A8
1	HCT	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
2	Crospovidone	1	1.5	2	2.5	-	-	-	-
3	Indion 414	-	-	-	-	0.25	0.5	0.75	1
4	MCC (PH102)	35	35.85	34.25	33.5	36.25	36	35.75	35
5	Magnesium stearate	1	1	1	1	1	1	1	1
6	Colloidal silicon dioxide	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
7	Lake sunset yellow	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
	Total tablet weight	50	50	50	50	50	50	50	50

w, Sodium bicarbonate: 10 % to 15% w/w and Ethylcellulose (4 cps): 5 % to 10 w/w.

2.3. Optimization of LSP using 2^3 full factorial designs

By means of 3 factors at 2 levels, full-factorial trials entailing of 8 preparations, remain intended. ($2^3 = 8$) with one extra checkpoint formulation, as shown in Table 2 [15].

2.3.1. Formulation of controlled release floating tablets of LSP

Tablets enclosing 50 mg of LSP was primed, conferring to the intention portrayed in Table 3, by DC. The corresponding powders, explicitly Losartan potassium, release-retarding polymer HPMC K4M, buoyancy enhancer ethyl cellulose (4cps) and gas generating agent $NaHCO_3$ remain conceded over sieve no. 60, distinctly as exhibited in Table 3. Mingling of powders remain conceded out expending a pestle and mortar meant for 10 min. Colloidal silicon dioxide and magnesium stearate remained, formerly auxiliary to the assorted powders. Admixture stood sustained intended for another 3 min. Lastly, 300 mg of respective mixture remain weighed and served physically into the die of a 10 station rotary tablet contrivance, fortified through flat-faced punches (9.5 mm), to result the preferred tablets [16].

2.4. Formulation of bilayer floating tablets

Optimized formulation from the immediate-release layer and controlled release layer was used to formulate bi-layer floating tablet of LSP and HCT. Accurately weighed 50 mg of immediate-release stratum powder blend then 300 mg of controlled-release floating layer powder blend separately. Lots of bilayer tablets remain primed by direct compression practice accordingly. Initially controlled release powder composite served physically into the dies of 10 stations rotary tablet contrivance and formerly compacted at low compression force to the designed uniform layer of powder. Consequently, immediate-release layer's powder blend of HCT was added over pre-compressed immediate-release layer then improved compression force and then compressed by tablet punching contrivance through by means of 9.5 mm flat-faced punch [17].

2.5. Characterization parameters

Appearance: The appearance was acknowledged visually through proving the colour variance.

Hardness: It was measured using Monsanto hardness tester.

Thickness: A Mitutoyo Digital Vernier calliper stood adopted to regulate the thickness of ten arbitrarily designated tablets [18].

Friability: 10 tablets remained arbitrarily designated and employed in the drum of tablet friability check equipment then stood familiar to revolve 100 intervals in 4 min. The tablets remained impassive then precisely balanced. The % weight loss stood ascertained [19].

$$\% F = \{1 - (W_t / W)\} \times 100$$

where, % F = Friability in %, W = Initial wt of tablets, Wt = Wt of tablets after revolution.

Weight variation: 20 tablets remain randomly designated, the average weight stood ascertained, and then they remain weighed individually to calculate the standard deviation.

Drug content: 20 tablets remain balanced and crumpled. An extent of powder corresponding to the quantity of single tablet (50 mg) stood accurately weighed and reassigned to 100ml volumetric flask. Volume was prepared up to the streak through methanol in a 100ml volumetric flask then Sonicated intended for 10–15 min. The drug content remain indomitable by UV spectroscopy at a wavelength of 270nm for HCT; 234nm for Losartan potassium [20].

2.5.1. Tablet floating behaviour

Cconcisely, tablets remain allocated in a glass beaker, carrying 200 mL of 0.1 N HCl, asserted in a water bath at 37 ± 0.5 °C. The floating lag time remains notorious as the time inside tablet prologue and its buoyancy. The entire floating extent the time through that tablet remnant buoyancy remains reported.

2.5.2. Swelling index

The water uptake revision of the tablet stood prepared expending USP dissolution apparatus II. The vehicle adopted remains distilled water, 900 ml revolved at 50 rpm. The vehicle stay retained at 37 ± 0.5 °C through

Table 2. Factorial Design Batches of LSP floating tablet.

Variables	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	C1 (Check point)
$\mathbf{X_1}$	-1	+1	-1	-1	+1	+1	- 1	+1	0
$\mathbf{X_2}$	-1	-1	+1	+1	+1	-1	-1	+1	0
$\mathbf{X_3}$	-1	+1	+1	-1	+1	-1	+1	-1	0

Where $\mathbf{X_1}$ = Conc. of HPMC K4M (%), $\mathbf{X_2}$ = Conc. of $NaHCO_3$ (%) and $\mathbf{X_3}$ = Conc. of Ethyl cellulose (%).
Coded and actual values of X_1: -1 = 20, +1 = 30, 0 = 25.
Coded and actual values of X_2: -1 = 10, +1 = 15, 0 = 12.5.
Coded and actual values of X_3: -1 = 5, +1 = 10, 0 = 7.5.

Table 3. Composition for the controlled release floating tablets of Losartan potassium.

S.No.	Ingredients in mg	F1	F2	F3	F4	F5	F6	F7	F8	C1
1	Losartan potassium	50	50	50	50	50	50	50	50	50
2	HPMC K4M	60	90	60	60	90	90	60	90	75
3	Ethyl cellulose (4cps)	15	30	30	15	30	15	30	15	22.5
4	Sodium bicarbonate	30	30	45	45	45	30	30	45	37.5
5	Microcrytalline cellulose (PH 102)	137.5	92.5	107.5	122.5	77.5	107.5	122.5	92.5	107.5
6	Colloidal silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
7	Magnesium stearate	6	6	6	6	6	6	6	6	6
	Total tablet weight	300	300	300	300	300	300	300	300	300

the revision [21]. Subsequently a designated period interval, the tablets remained introvert, marked to take away surplus water then balanced. Swelling individualities of the tablets remain uttered in rapports of water uptake (WU) as:

$$\mathrm{WU}(\%) = \frac{\text{Weight of the swollen tablet} - \text{initial weight of the tablet}}{\text{Initial weight of the tablet}}$$

2.5.3. In vitro disintegration test for immediate release HCT tablets

Arbitrarily 6 tablets stood designated from the respective lot for disintegration test. Disintegration test remain accomplished deprived of the disc in simulated gastric fluid ($37 + 0.5^0$c) expending disintegration apparatus.

2.6. In vitro dissolution studies [22]

2.6.1. Immediate release HCT tablets

It stood conceded out on type II apparatus exhausting the paddle. 500 ml of pH 1.2 buffer (0.1N HCl) as dissolution medium at 37 ± 0.5 °C through the rotational speediness of 50 rpm. The illustrations remain introvert at a determined time interim up to 40 min and analyzed on UV spectrophotometer at 270 nm.

2.6.2. Controlled-release floating tablets of losartan potassium

It remains conceded out on type II apparatus expending the paddle. 900 ml of pH 1.2 buffer (0.1N HCl) as dissolution medium at 37 ± 0.5 °C through a rotational speediness of 50 rpm. The sample stood introvert at scheduled period interval adequate 12h and explored on UV spectrophotometer at 234 nm.

2.6.3. Floating bi-layer tablet of losartan and HCT

Dissolution of the bilayer tablets remain conceded out on type II apparatus using a paddle. 900 ml of pH 1.2 buffer (0.1N HCl) as dissolution medium at 37 ± 0.50C with a rotational speediness of 50 rpm. The sample stood introvert at scheduled period interval up to 12h and evaluated on UV spectrophotometer by simultaneous estimation method [23].

2.7. Statistical analysis of responses

The Surface response plot, Contour plots were drawn using Design Expert Software v 8.0.6.1 (STATEASE).

2.8. Release kinetics

In edict to apprehend the contrivance and kinetics of drug discharge, the outcomes of the *in vitro* drug discharge revision stood fitted through innumerable kinetic reckonings namely zero-order (% release vs time), first-order (log% unreleased vs time), and Higuchi matrix (% release vs square root of time). To delineate a exemplary that resolve epitomize a restored fit designed for the preparation, drug release statistics advance considered by Peppas equation, $Mt/M\infty = ktn$, where Mt is the quantity of drug released at time t and M∞ is the quantity released at the time ∞, the Mt/M∞ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent, a degree of the principal contrivance of drug discharge. Regression coefficient (r^2) values remain contrived for the linear curves acquired by regression exploration of the beyond plots [24].

2.9. Stability studies

Stability application of the enhanced preparation remains conceded out as conferring to the ICH recommendations, at 40 ± 2 °C/75 ± 5% RH by adopting Thermolab TH 90S stability chamber for 3 months. The carried remain observed for drug content, floating behaviour and *in vitro* drug release profile [25].

3. Results & discussion

3.1. Compatibility studies of drug and polymers

3.1.1. Fourier transform infrared spectrometry (FTIR)

It was found that there was no possible interaction in between drug and super disintegrants in their original form and mixture form as displayed in Figure 1.

3.1.2. Differential Scanning Calorimetry (DSC)

Compatibility examinations stood similarly conceded by using DSC, which is a qualitative analytical tool for assessing the interactions. The thermograms indicated no significant change in drug endotherm peaks in mixture samples, as shown in Figure 2.

3.2. Preparation and optimization of bilayer floating tablets

The contemporary concerns was carried out to advance a bilayer floating drug release practice of LSP and HCT to augment absorption and bioavailability through amassed the gastric retention period of the drug. In apprehension towards this method, the crucial requisite remains to float the tablet in a gastric environs and further proceedings for the development of floating bilayer tablets.

Preformulation study remain toted out expending different concentration level of HPMC K4M, Sodium bicarbonate and Ethylcellulose (4cps) for floating layer and Crospovidone and Indion 414 for immediate release layer to optimize the formulations. The criteria for selection of optimum immediate-release tablet were *in vitro* disintegration period and *in vitro* drug delivery. Eight formulations remain prepared using different concentration of Crospovidone (A1-A4) and Indion-414 (A5-A8). Formulation A8 containing 2% of Indion 414 was optimized formulation.

3.3. Optimization of LSP using 2^3 full factorial design

A full factorial $2^3 = 8$ experiments were designed with one extra checkpoint formulation. Optimization of the HBS system was made based on 3 dependent variables viz: i) Drug release at 12h ii) time required to 50% of drug discharge iii) Floating lag time. The preparations were

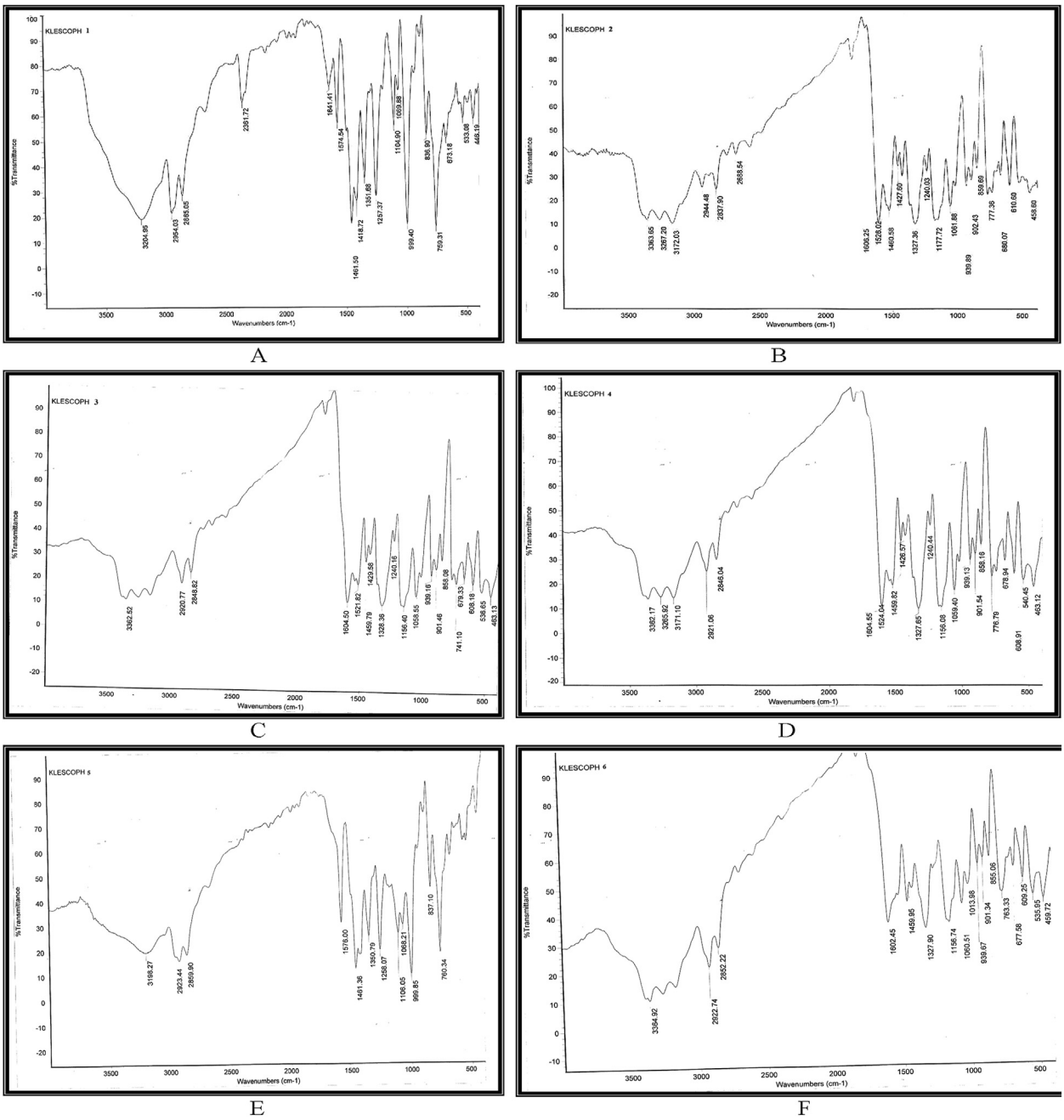

Figure 1. FTIR spectrum of (a) pure LSP (b) pure HCT (c) HCT + Crospovidone + MCC + Magnesium stearate + Colloidal silicon dioxide + Lake sunset yellow (D) HCT + Indion 414 + MCC + Magnesium stearate + Colloidal silicon dioxide + Lake sunset yellow (E)Losartan Potassium + HPMC K4M + Ethyl cellulose + Sodium bicarbonate + MCC + Magnesium stearate + Colloidal silicon dioxide (F) LSP + HCT + HPMC K4M + Ethyl cellulose + Sod bicarbonate + Indion 414 + MCC + Magnesium stearate + Colloidal silicon dioxide + Lake sunset yellow.

studied for the effect of concentration of swelling agent (HPMC K4M), the concentration of gas spawning agent (Sodium bicarbonate) and buoyancy enhancer (ethylcellulose 4cps) on the dependent variables (response). To know the effect of each variable on the responses, the variables and responses were selected for the Analysis of Variance (ANOVA) and multiple linear regression analysis. Formulation F4 containing 20% of HPMC K4M, 15% sodium bicarbonate and 5% of ethyl cellulose was optimized formulation.

3.4. Formulation of bilayer floating tablets

Optimized formulation A8 from the immediate-release layer and F4 from the floating layer was used for the formulation of the bilayer tablet. Direct compression method employed for all formulations was found to be satisfactory for instance the physicochemical evaluation constraints remained inside the permissible limits.

3.5. Characterization parameters

3.5.1. Characterization parameters for immediate release tablets of HCT

The thickness of the prepared tablet is in the range of 2.523 ± 0.036 to 2.736 ± 0.019mm. The hardness of the formulated tablets remain institute in the array of 3.4–3.8 kg/cm^2. The friability of all the tablets remain institute to be less than 1%, i.e. in the array of 0.231%–0.426% as displayed in Table 4. The formulation A8 shows lowest disintegration time 11.27 s because of its swelling tendency on wetting.

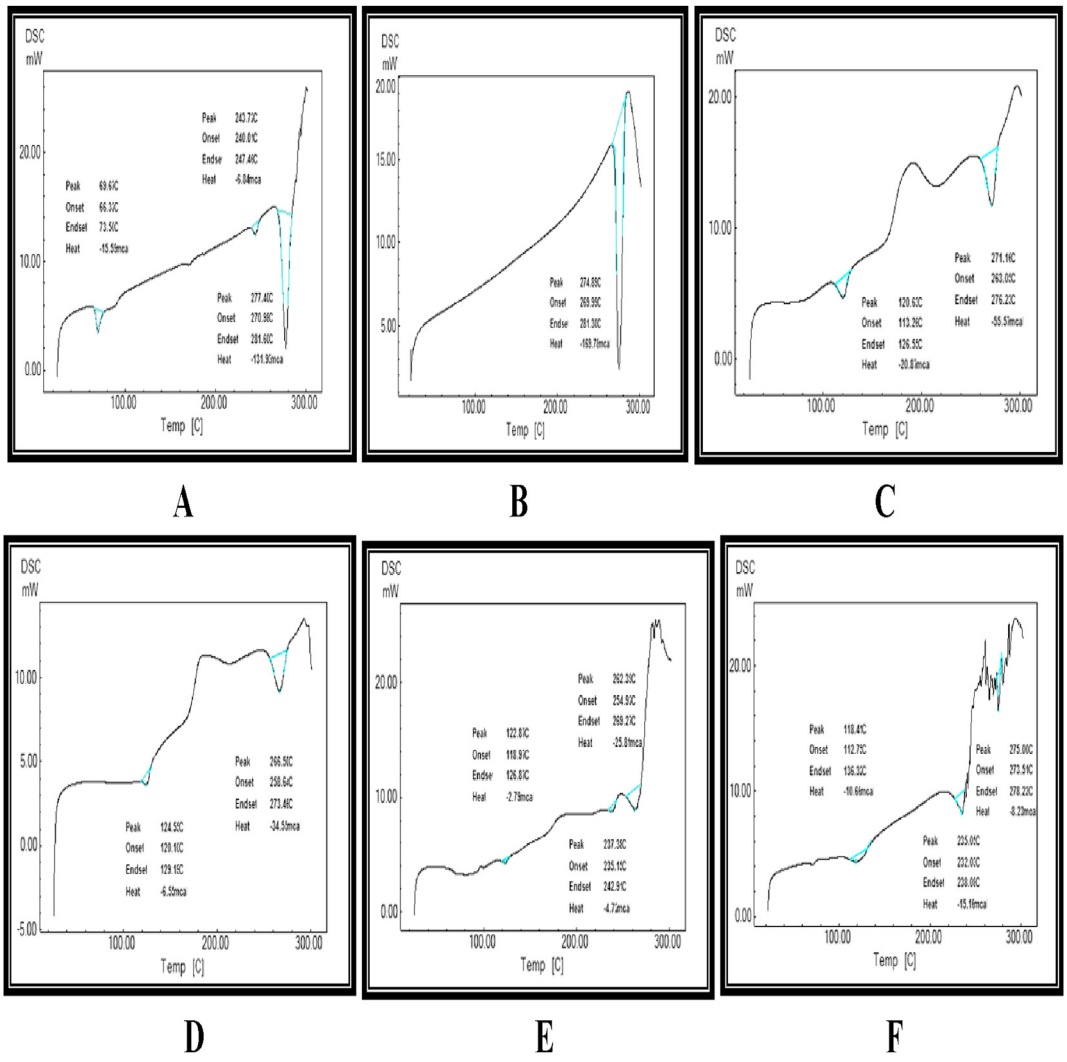

Figure 2. Differential Scanning Calorimetry (DSC) spectrum of (a) Pure LSP (b) pure HCT (C)HCT + Crosspovidone + MCC + Magnesium stearate + Colloidal silicon dioxide (D) HCT + Indion 414 + MCC + Magnesium stearate + Colloidal silicon dioxide (E) LSP + HPMC K4M + Ethyl cellulose + Sodium bicarbonate + MCC + Magnesium stearate + Colloidal silicon dioxide (F) LSP + HCT + HPMC K4M + Ethyl cellulose + Sodium bicarbonate + MCC + Indion 414 + Magnesium stearate + Colloidal silicon dioxide + Lake sunset yellow.

Table 4. Evaluation parameters for immediate release tablets of HCT.

Formulation code	Evaluation parameters					
	Thickness± S.D. (mm) (n = 10)	Hardness ± S.D.(kg/cm^2) (n = 5)	Friability (%) (n = 10)	Avg. weight variation (n = 20)	Drug content (%)	Disintegration time (in sec) (n = 6)
A1	2.544 ± 0.064	3.5 ± 0.2	0.412 ± 0.7	48.6 ± 2.065	99.24	25.24 ± 1.96
A2	2.586 ± 0.016	3.4 ± 0.3	0.231 ± 0.3	49.1 ± 1.48	98.42	20.16 ± 2.03
A3	2.661 ± 0.054	3.8 ± 0.2	0.425 ± 0.5	51.23 ± 2.54	99.34	17.36 ± 1.89
A4	2.523 ± 0.040	3.8 ± 0.1	0.323 ± 0.6	50.69 ± 1.64	97.22	13.41 ± 2.66
A5	2.731 ± 0.036	3.7 ± 0.2	0.351 ± 0.7	51.06 ± 2.70	99.13	22.38 ± 2.21
A6	2.677 ± 0.012	3.6 ± 0.4	0.411 ± 0.4	49.95 ± 2.70	99.65	18.52 ± 2.33
A7	2.736 ± 0.019	3.5 ± 0.3	0.365 ± 0.3	51.63 ± 2.70	98.23	14.39 ± 2.065
A8	2.523 ± 0.036	3.5 ± 0.5	0.426 ± 0.6	47.96 ± 2.70	98.59	11.27 ± 2.12

3.5.2. Characterization parameters for floating tablets of LSP

The thickness of the prepared tablet remains in the range of 3.908 + 0.046 to 3.988 + 0.051mm. The hardness of the formulated GRDDS of Losartan remains institute in the array of 5.2–5.6 kg/cm^2. The friability of entire tablets remain institute to be less than 1%, i.e. in the array of 0.205%–0.419% as displayed in Table 5.

3.5.2.1. Tablet floating behaviour. The exploration discloses that entire preparations retain good floating effects. The order of floating lag period remains institute to be: F3<F4<F7<F1<F5<C1<F8<F2<F6.

3.5.2.2. Swelling index. The swelling index remains extending in amid 50.59 %–79.13 % as displayed in Table 6. High level of HPMC K4M

Table 5. Evaluation parameters for floating tablets of Losartan Potassium.

Formulation code	Evaluation parameters				
	Thickness ±S.D. (mm) (n = 10)	Hardness ± S.D (kg/cm^2) (n = 5)	Friability (%) (n = 10)	Avg. weight variation (n = 20)	Drug content (%)
F1	3.942 ± 0.093	5.2 ± 0.4	0.291 ± 0.5	302 ± 0.011	97.29
F2	3.908 ± 0.046	5.4 ± 0.2	0.308 ± 0.4	298 ± 0.010	98.41
F3	3.934 ± 0.035	5.3 ± 0.2	0.410 ± 0.6	305 ± 0.018	97.16
F4	3.941 ± 0.023	5.6 ± 0.1	0.152 ± 0.7	304 ± 0.013	99.63
F5	3.962 ± 0.048	5.5 ± 0.6	0.419 ± 0.6	295 ± 0.014	98.17
F6	3.956 ± 0.039	5.5 ± 0.3	0.244 ± 0.5	304 ± 0.009	97.24
F7	3.988 ± 0.051	5.2 ± 0.2	0.298 ± 0.3	299 ± 0.021	99.92
F8	3.928 ± 0.025	5.5 ± 0.3	0.205 ± 0.5	308 ± 0.011	99.52
C1	3.964 ± 0.058	5.4 ± 0.4	0.393 ± 0.4	304 ± 0.015	98.64
Bilayer FT	4.62 ± 0.055	5.4 ± 0.2	0.244 ± 0.5	348 + 0.009	98.23 (LSTN) 99.48 (HCT)

Table 6. Results of the floating property of the losartan floating tablets.

F. Code	Floating lag time (sec)	Total floating time (Hr)	% Swelling Index	T 50% (Hr)
F1	30.32 ± 0.8	>12	46.57 ± 0.012	6.214
F2	58.25 ± 0.9	>12	63.1 ± 0.018	9.286
F3	13.64 ± 0.5	>12	59.52 ± 0.014	4.315
F4	20.15 ± 0.4	>12	63.54 ± 0.021	4.169
F5	48.31 ± 0.5	>12	79.13 ± 0.0135	7.296
F6	66.39 ± 0.4	>12	67.21 ± 0. 04	7.539
F7	23.54 ± 0.6	>12	50.59 ± 0.036	7.124
F8	56.81 ± 0.5	>12	74.92 ± 0.0163	7.164
C1	49.26 ± 0.4	>12	62.85 ± 0.0132	6.638
Bilayer FT	24.26 ± 0.5	>12	–	–

exhibited maximum water uptake, indicated the extreme swelling property. The concentration of $NaHCO_3$ improved commencing 10%–15% swelling index remain amplified owing to an upsurge in degree of pore development then subsequently, swift hydration of the tablet milieus.

3.6. In vitro dissolution studies

The dissolution contour of the preparations containing both the disintegrants was compared. Therefore, formulation A8 having disintegrant Indion 414 in the concentration of 2% remain designated as per the optimized formulation by way of it disintegrates very swiftly in 11.27 s and releases more than 99% drug in 35 min as exhibited in Table 7 and Figure 3A. Thus batch A8 of an immediate-release layer and batch F4 of the floating layer was used to formulate bilayer floating tablets of LSP and HCT.

Formulae F4 containing the highest gas-forming agent concentrations and lowest HPMC K4M concentration showed the highest drug release, as shown in Table 8 and Figure 3B. These release revisions exposed that the imperative of release remained institute to exist F4>F3>F1>C1>F7>F8>F5>F6>F2.

3.7. Statistical analysis of responses

Multiple linear regression analysis was performed for dependent variables Q12, FLT and T50% as shown in Figure 4. The most significant coefficient means the causal factor has a more potent influence on the response. The values of the correlation coefficient for Q12, FLT and T50% are 0.9996, 0.9995 and 0.9189, respectively. The above concentration of ingredients was almost the same as the value of factorial batch F4 formulation. Consequently, batch F4 remained desirable by means of the optimized batch, as shown in Figure 5.

Table 7. In vitro drug release study for HCT immediate-release tablets.

Time (min)	A1	A2	A3	A4	A5	A6	A7	A8
3	10.906	20.555	24.356	27.280	21.140	39.859	42.743	55.935
5	37.296	34.659	46.965	51.066	35.538	42.570	65.422	59.856
10	44.621	45.50018	63.958	66.594	40.226	47.844	69.524	63.372
15	48.137	57.512	73.040	76.556	58.684	63.372	71.575	77.435
20	57.512	78.900	79.779	82.708	61.321	65.715	75.677	81.244
25	70.696	85.638	87.396	89.154	64.837	67.766	78.021	90.619
30	75.970	89.447	90.912	92.670	67.180	71.282	80.951	95.307
35	79.486	90.033	92.963	96.772	70.989	78.021	83.880	99.701
40	87.689	90.619	96.479	98.822	75.091	83.880	90.619	–
45	96.479	98.530	98.237	99.547	84.759	90.619	98.822	–

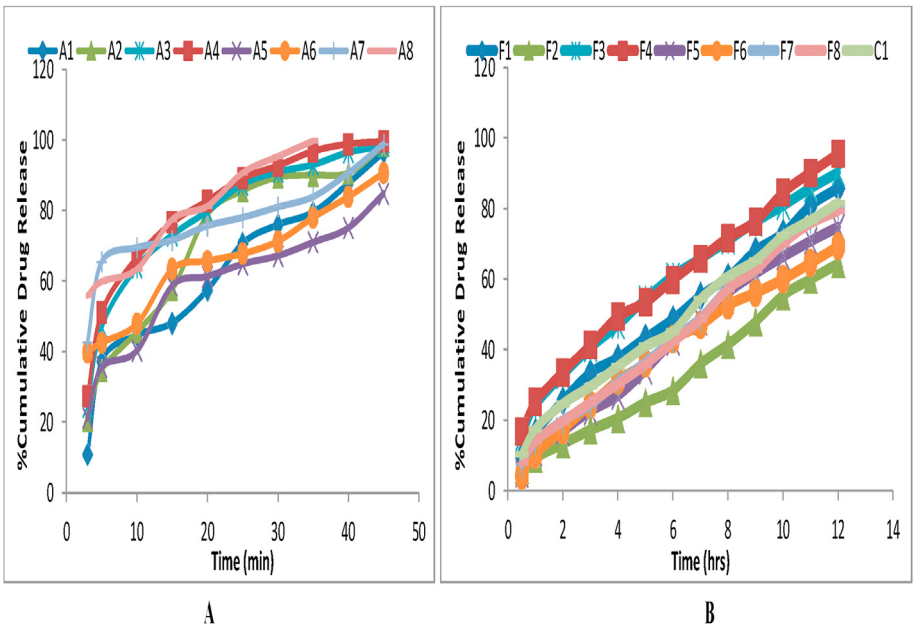

Figure 3. *In vitro* drug release study for A) HCT tablets B) Losartan floating tablets.

Table 8. *In-vitro* drug release study for Losartan floating tablets.

Time (Hr)	F1	F2	F3	F4	F5	F6	F7	F8	C1
0.5	9.75	5.908	15.054	16.701	4.993	4.335	7.554	8.103	10.298
1	16.353	9.394	24.044	25.143	10.859	10.310	13.844	14.155	17.452
2	25.510	13.331	32.835	33.567	16.902	17.269	19.832	19.649	24.594
3	33.384	17.234	40.526	41.259	22.579	24.411	24.411	24.960	29.538
4	37.596	20.565	46.936	49.316	26.975	31.187	30.820	30.271	35.215
5	43.273	24.960	54.261	53.345	34.117	36.131	36.314	35.765	40.892
6	48.584	28.440	60.854	59.755	42.357	42.907	42.907	42.174	45.104
7	55.177	35.9483	65.798	65.798	48.218	46.936	48.950	48.584	54.261
8	60.487	41.442	70.926	71.658	56.092	52.613	57.374	57.191	60.671
9	67.992	47.851	76.237	76.237	61.586	56.092	63.234	62.502	65.249
10	72.941	55.360	80.815	84.477	66.348	59.938	70.743	70.010	72.208
11	80.815	59.938	85.759	90.154	70.743	64.516	76.603	75.870	76.603
12	85.759	64.334	90.154	95.465	74.772	69.278	80.449	79.350	81.547

A checkpoint lot remains primed at X1 = 0 level, X2 = 0 level and X3 = 0 level as displayed in Table 9, indicates the results of checkpoint batch. From the equation generated from regression analysis by putting the values of X1, X2 and X3 in percentage it remains probable such the significance of Q12 of the checkpoint batch ought to be 79.88 %, the value of FLT of the checkpoint batch ought to be 39.66 s and T 50% of checkpoint batch ought be 6.629h. The outcomes achieved with checkpoint batch are precise adjacent to expected values. Consequently, we can accomplish which the statistical exemplary remains mathematically expedient.

3.8. For floating bilayer tablets

Composition of bilayer floating tablet includes an immediate-release layer (A8 Batch) and controlled release floating layer (F4 Batch) as exhibited in Table 10. The average weight, thickness and hardness of primed tablet remain institute to exist 348mg, 4.62 mm and 5.4 kg/cm^2 correspondingly. The drug content of the primed bilayer tablets remain establish to be 98.23 (LSP) and 99.48 (HCT). The *In vitro* drug release of the primed bilayer tablets remains institute to stay 97.32% (LSP for 12h) and 98.56% (HCT in 35 min).

3.9. Release kinetics

The results ascertained such the release mechanism for LSP floating tablets remained by diffusion and swelling controlled mechanism, i.e. Non-fickian/anomalous transport where n value lies amid 0.45 to 0.89 for entire preparations as displayed in Table 11. From the 'n' value of optimized formulation (0.560) acquired it can remain assumed that the diffusion charted Non-fickian mechanism and from regression coefficient value (0.9851) it can be said that it follows Peppas model for drug release.

3.10. Stability studies

Stability study was performed for optimized floating bilayer tablet formulation at 40 ± 10C and RH 75% for 3 months. The illustrations remain examined for hardness, percent drug content, floating behaviour

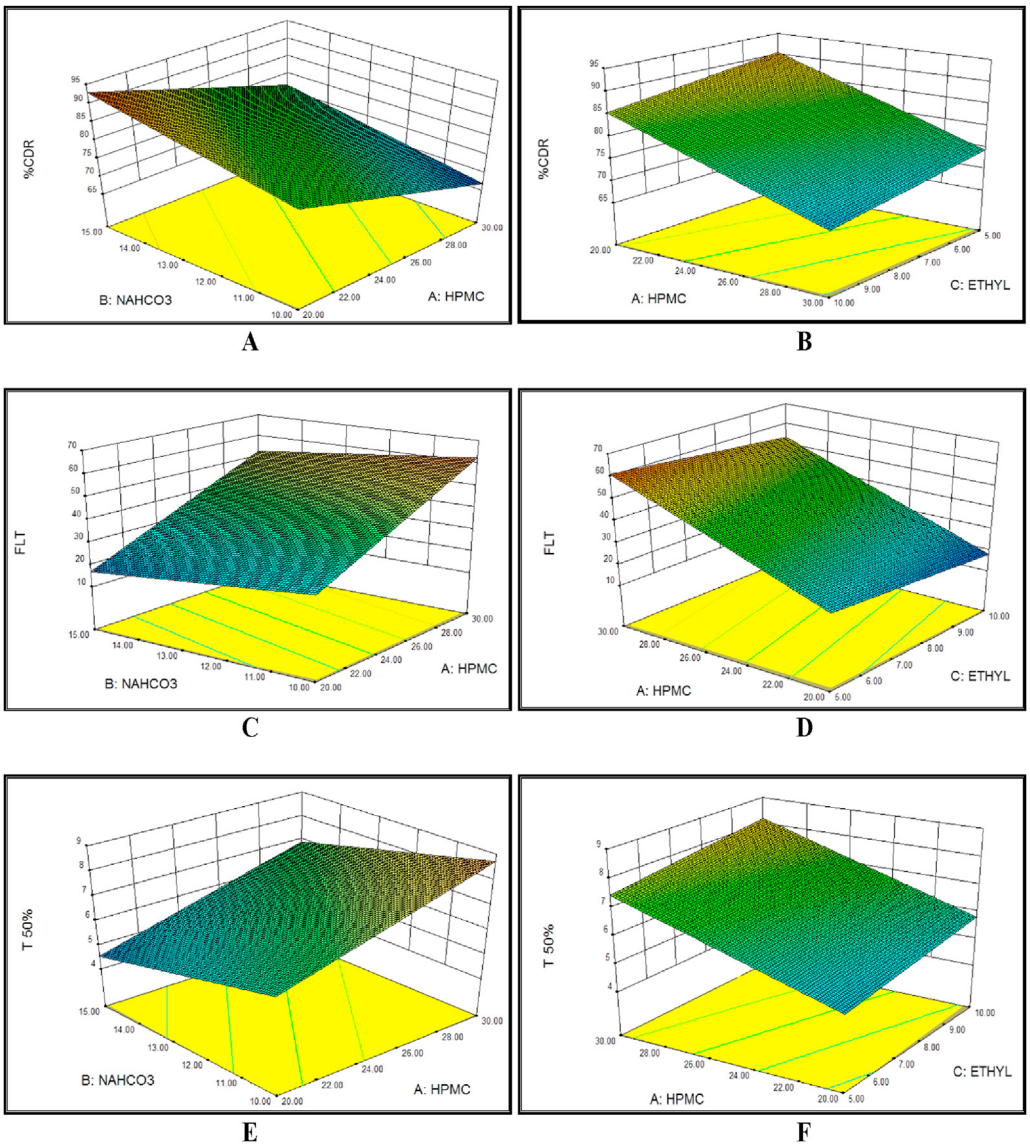

Figure 4. 3D Response Surface plot showing the effect of factorial variables on: A, B-% CDR at 12h; C, D- Floating lag time; E, F- T 50%.

and *in-vitro* drug release revisions. The results are given in Table 12. No substantial variance was perceived for the beyond parameters.

4. Discussion

An effort remained thru to upsurge the oral bioavailability of Losartan and Hydrochlorothiazide fixed-dose combination through retentive the dosage form in the stomach intended for a more extended epoch. This remains accomplished by evolving a gastroretentive floating drug delivery system. The precise tablets remain primed to surge the bioavailability of the medications by employing the medications to a complete degree evading avoidable incidence of dosing and consequently the first-pass metabolism.

Losartan and Hydrochlorothiazide combination indicated for hypertension with left ventricular hypertrophy adults. Losartan was having a plasma elimination half-life extending after 1.5–2.5h with oral bioavailability of about 33% needs gastro-retention to improve bioavailability and to evade the first-pass consequence, on the other hand, Hydrochlorothiazide having a half-life of 8 h–14 h with 67.9 % protein binding needs immediate release. To achieve patient compliance by controlling blood pressure for an extended duration of time, a floating bilayer tablet of this fixed-dose combination was suggested.

For the formulation of bilayer floating tablets floating as well as immediate release layers were optimized separately. Crospovidone and Indion 414 were used as super disintegrants. HPMC K4M stood practiced as matrix creating gelling agent. Ethylcellulose adopted as a buoyancy enhancer and release retardant. Other excipients used were MCC (Diluent), $NaHCO_3$ (gas generating agent), Magnesium stearate (lubricant) and colloidal silicon dioxide (glidant).

FTIR and DSC thermograms inveterate the nonappearance of any drug/polymers/excipients interfaces. A physical mixture of medication and polymer were considered by FTIR spectral exploration designed for every physical along with chemical disparity of the medication. From the outcomes, it remain determined that there existed no interfering in the functional groups as the principal peaks of the Losartan and Hydrochlorothiazide remain institute to be intact, designating they stood compatible chemically. Compatibility studies were also carried by using DSC, which is a qualitative analytical tool for assessing the interactions. The thermograms indicated no substantial amendment in drug endotherm peaks in mixture samples. However, the change in shape and alterations in drugs mixture peak was related to the absorbed moisture by the samples.

Direct compression practice remains engaged to articulate the tablets, since of its cost-clout and owing to reducing the sum of developed strides.

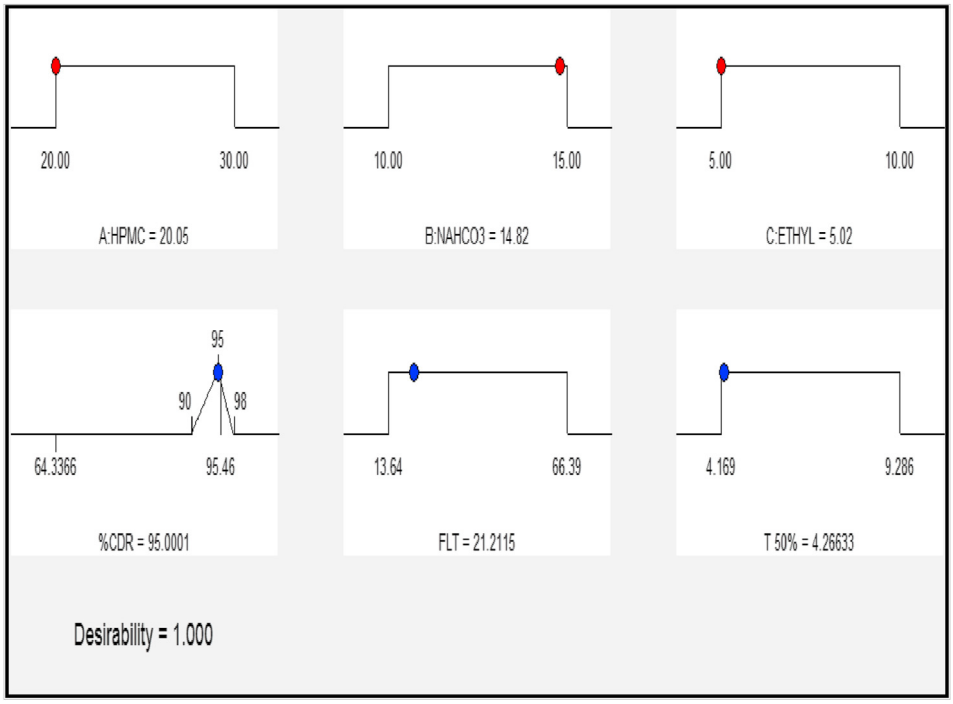

Figure 5. Numerical optimization Solution Tool Ramps.

Table 9. Dissolution Parameters for 2^3 Full Factorial Design formulations.

Formulation code	Variable levels in coded form			$T_{50\%}$ (Hours)	% CDR in 12h (Q12)	Floating Lag time (Sec)
	X1	X2	X3			
F1	-1	-1	-1	6.214	85.75	21.26
F2	+1	-1	+1	9.286	64.33	34.32
F3	-1	+1	+1	4.315	90.15	9.62
F4	-1	+1	-1	4.169	95.46	14.56
F5	+1	+1	+1	7.226	74.77	27.13
F6	+1	-1	-1	7.539	69.27	39.65
F7	-1	-1	+1	7.124	80.44	16.23
F8	+1	+1	-1	7.164	79.35	35.89
C1	0	0	0	6.638	81.54	41.24

Table 10. Comparison of the observed value and predicted value for checkpoint formulation C1 and optimized formulation F4.

Responses	Predicted value		Observed value		% Deviation	
	C1	F4	C1	F4	C1	F4
Q12	79.88	95.001	81.54	95.46	0.96	0.459
FLT	39.66	21.2115	41.24	20.15	1.58	0.0615
T50%	6.629	4.266	6.638	4.169	0.009	0.097

The prepared floating tablet, immediate-release tablet and bilayer tablets remain assessed for hardness, weight variation, thickness, friability, drug content uniformity, *in vitro* disintegration time, buoyancy lag time, total floating time, water uptake (swelling index), *in-vitro* dissolution studies. The order of floating lag time remain found to be F3<F4<F7<F1<F5<C1<F8<F2<F6. The above results showed such upsurge in the concentration of HPMC K4M upsurges of floating lag time because at high-level HPMC K4M intend perhaps prevent the admittance of medium under the tablet matrix and persist the floating lag period. As proportions of $NaHCO_3$ upsurges, the floating lag period declines. This spectacle influence is owing to the bearing of more massive extents of effervescence through greater $NaHCO_3$ proportions. This intend prime to an upsurge in the degree of pore development then subsequently, swift hydration of the tablets matrices. The above order of results showed such upsurge in the concentration of ethyl cellulose results in a decline of floating lag period since of its little bulk density.

The swelling index showed the utmost water uptake, revealed the extreme swelling property. The capacity of hydrogels to engross water is owing to the existence of hydrophilic groups. The hydration of the particular functional groups outcomes in water admittance towards the polymer matrix prominent to extension then subsequently an assembling of the polymer chains.

Entire preparations remain imperilled to five diverse models viz. Zero-order, First order, Higuchi matrix, Peppas model and Hixson-Crowell equations and all the formulations followed Peppas model. The curve fitting consequences of discharge degree contours for the

Table 11. Kinetic data of various models for release study.

F. code	Zero order		First order		Matrix		Peppas			Hixon Crowell		Best fitting model
	R	k	R	k	R	k	R	k	n	R	k	
F1	0.9802	0.0183	0.9803	0.0002	0.9737	0.0526	0.9982	0.0349	0.6986	0.9802	0.0001	Peppas
F2	0.9953	0.0127	0.9953	0.0001	0.9217	0.0356	0.9893	0.0179	0.8161	0.9953	0.0000	Zero order
F3	0.9336	0.0207	0.9338	0.0002	0.9953	0.0603	0.9990	0.0517	0.5756	0.9337	0.0001	Peppas
F4	0.9516	0.0211	0.9518	0.0002	0.9818	0.0611	0.9851	0.0532	0.5600	0.9517	0.0001	Peppas
F5	0.9965	0.0159	0.9965	0.0002	0.9467	0.0451	0.9966	0.0196	0.9054	0.9965	0.0001	Peppas
F6	0.9871	0.0150	0.9871	0.0001	0.9664	0.0429	0.9924	0.0188	0.9125	0.9871	0.0000	Peppas
F7	0.9952	0.0169	0.9953	0.0002	0.9506	0.0479	0.9955	0.0266	0.7792	0.9952	0.0001	Peppas
F8	0.9943	0.0167	0.9943	0.0002	0.9516	0.0474	0.9946	0.0275	0.7557	0.9943	0.0001	Peppas
C1	0.9807	0.0176	0.9807	0.0002	0.9722	0.0505	0.9956	0.0353	0.6698	0.9807	0.0001	Peppas

Table 12. Results for stability studies of optimized formulation.

Time (Month)	Evaluation parameters						
	Hardness (kg/cm^2)	Drug content (%)		Floating behaviour		CDR (%)	
		LSP	HCT	FLT (sec)	TFT(h)	LSP	HCT
0	5.4	98.23	99.48	24.26	>12	97.32	98.56
1	5.3	97.76	99.12	26.34	>12	97.13	98.23
2	5.3	97.29	98.86	27.23	>12	96.96	98.16
3	5.2	97.25	98.49	28.68	>12	96.84	98.09

premeditated preparations remain imperilled for data exploration expending PCP-V2 dissolution software. It remains institute that entire the preparations stood fitted into Korsemeyers-Peppas model, which remains the best-fitted model.

The floating, immediate and bilayer tablets were compressed using 9.5mm, 4mm, 9.5mm circular flat-faced punches using RIMEK I multi-station rotary punching machine. Floating property revision exposes that all formulations had suitable floating property. All the formulation floats for more than 12h because the gel layers, designed through the probed polymers, facilitated proficient entrapment of the engendered gas bubbles. Upsurge in concentration of HPMC K4M results in the rise of floating lag time because at high-level HPMC K4M exert probably prevent the access of ways towards the tablet matrix then extend the floating lag period.

As the percentage of $NaHCO_3$ upsurges, the floating lag time declines. This spectacle potency is owing to the procreation of more significant extents of effervescence through advanced $NaHCO_3$ proportions. This prime effect to an upsurge in proportion of aperture development then subsequently, swift hydration of the tablets matrices. The above order of results revealed that upsurge in the concentration of ethyl cellulose results in the decline of floating lag period since of its low bulk density. The capacity of hydrogels to captivate water remains owing to the existence of hydrophilic groups. The hydration of the particular functional group outcomes in water admittance towards the polymer complex prominent to extension then accordingly an assembling of the polymer chains.

Based on various evaluation parameters formulation, F4 and A8 were selected as a composition for bilayer floating tablet and was further subjected to *in vitro* release revision, and stability study. The optimized bilayer floating tablet indicated good stability and values remain inside permitted limits.

5. Conclusion

The strategy of two diverse release phases keep is certainly familiar in together delivery degree and the proportion of the dosage fractions, bestowing to the pharmacokinetics and therapeutic prerequisites. In the immediate-release layer, Indion 414 has a potent effect on *in vitro* disintegration and *in vitro* drug discharge. The result of 2^3 full factorial design discovered such as the HPMC K4M, $NaHCO_3$ and ethyl cellulose concentrations alluringly distress the responses, % CDR, FLT, % Swelling index and T 50%. From the result, it was determined that through assuming a systematic preparation advent, conveyance of two drugs out of a distinct dosage practice could be acquired that might expand bioavailability, patient compliance then provide restored disease supervision.

Declarations

Author contribution statement

P. Kesharwani: Analyzed and interpreted the data; Wrote the paper.

B. Maddiboyina and M. Hanumanaik: Conceived and designed the experiments; Performed the experiments.

R.K. Nakkala and V. Jhawat: Performed the experiments.

A. Alam, A.I. Foudah and P. Rawat: Analyzed and interpreted the data.

M.M. Alrobaian: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

R. Shukla: Performed the experiments; Contributed reagents, materials, analysis tools or data.

S. Singh: Performed the experiments; Wrote the paper.

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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