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Original Article

Chronomodulated drug delivery system of Irbesartan: Formulation and development using Desing of Experiment (DoE)

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ABSTRACT

The work is based on pulsatile principles to deliver a programmed dose of Irbesartan, an angiotensin-II receptor antagonist for chronotherapy of hypertension induced by excessive secretion of aldosterone, thereby lower the blood pressure at early morning. Solid dispersion of Irbesartan, a BCS class II drug, was prepared by using Poloxamer-188 by melt method in ratio of 1:1 to increase the dissolution properties of drug. Compressed coated pulsatile tablets included a core layer consisting of Kyron T-134 as a super-disintegrant and pulsatile layer comprising of HPMC K4M and Eudragit RLPO. The prepared core tablets were evaluated for weight variation, hardness, thickness, friability, drug content, disintegration time and *In vitro* dissolution studies. Final core tablet (C8) was selected on the basis of disintegration time (23.33 ± 2.08 s). For optimization Face centred central composite design was employed to study the effect of independent variables viz. Weight ratio of HPMC K4M: Eudragit RLPO (X_1) and Total weight of coating (X_2) on dependent variables viz. Drug release lag time (Y_1) and Drug release after lag time within 15 min (D_{15}) (Y_2). Results revealed positive influence of independent factors on responses. The data were statistically analyzed using ANOVA and were found to be statistically significant ($P < .05$). Mathematical modeling for kinetic studies revealed that the release profile after lag time followed first order kinetics. Accelerated stability studies for one month at 40 ± 2 °C/75 ± 5% RH showed no remarkable changes concluding that a successful pulsatile drug delivery system of Irbesartan was developed.

1. Introduction

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions that demand release of drug after a lag time. i.e.; Pulsatile drug delivery system [1].

Pulsatile drug delivery system is time and site-specific drug delivery system, thereby providing special and temporal delivery and increasing patient compliance. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time [2]. Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form [3]. The principle rationale for the use of the pulsatile release of the drugs is where a constant drug release is not desired [4].

Hypertension is a disease which shows circadian rhythm in the pattern of two peaks, one in the evening at about 7 pm and other in the early morning between 4 and 8 a.m. The behaviour, physiology, and biochemistry of organisms changes rhythmically over 24 h. The rhythms are generated by “clock gene” encoded with genetic instruction which produce proteins whose level oscillates in the course of one day. Certain condition like day/night variation in asthmatic dyspnoea, secretion of acid in midnight, blood pressure attains peak maxima at early morning etc. result due to disturbance in circadian clock [5]. Conventional therapies are incapable to target those time points when actually the symptoms get worsened. To achieve drug release at those time points, chronomodulated delivery system may offer greater benefits [6].

Irbesartan is a non-peptide tetrazole derivative and an angiotensin-II antagonist which blocks the binding of angiotensin-II to the angiotensin-II AT1-receptor. Angiotensin II stimulates the adrenal cortex to synthesize and secrete aldosterone, which ultimately decreases the

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Table 1
Formulation of preliminary trial batch of Irbesartan pulsatile tablets for selection of polymers.

Ingredients		Formulation code with quantity in mg						
		P1	P2	P3	P4	P5	P6	P7
Core Tablet	Irbesartan: Poloxamer 188	150	150	150	150	150	150	150
	Kyron T-134	8	8	8	8	8	8	8
	Mannitol	26	26	26	26	26	26	26
	PVP K30	10	10	10	10	10	10	10
	Magnesium stearate	4	4	4	4	4	4	4
	Talc	2	2	2	2	2	2	2
Coating layer	Eudragit RLPO	150	–	–	–	150	–	–
	Carbopol P-934	–	150	–	–	–	150	–
	Ethyl cellulose	–	–	150	–	150	150	150
	Sodium CMC	–	–	–	150	–	–	150
	HPMC K4M	150	150	150	150	–	–	–
	Magnesium stearate	6	6	6	6	6	6	6
	Talc	4	4	4	4	4	4	4
Total		510	510	510	510	510	510	510

Table 2
Formulation of preliminary trial batch of Irbesartan PDDS for selection of ratio and amount of coating weight of polymer.

Ingredients		Formulation code with quantity in mg							
		T1	T2	T3	T4	T5	T6	T7	T8
Core Layer	Irbesartan: Poloxamer 188	150	150	150	150	150	150	150	150
	Kyron T-134	8	8	8	8	8	8	8	8
	Mannitol	26	26	26	26	26	26	26	26
	PVP K30	10	10	10	10	10	10	10	10
	Magnesium Stearate	4	4	4	4	4	4	4	4
	Talc	2	2	2	2	2	2	2	2
Coating Layer	HPMC K4M	150	75	175	87.5	200	100	225	112.5
	Eudragit RLPO	150	225	175	262.5	200	300	255	337.5
	Dicalcium phosphate	194	194	154	154	94	94	44	44
	Magnesium Stearate	4	4	4	4	4	4	4	4
	Talc	2	2	2	2	2	2	2	2
Total		700	700	700	700	700	700	700	700

Table 3
Dependent and independent variables.

Independent variables	Variable level		
	Low (–1)	Medium (0)	High (+1)
Translation of coded value in actual units			
Weight ratio of HPMC K4M:Eudragit RLPO (X_1)	1:1	1:2	1:3
Total weight of coating (X_2)	300	350	400
Dependent Variables			
Y_1	Drug release lag time (hrs)		
Y_2	D_{15} (drug release after lag time within 15 min) (%)		

excretion of sodium and increases the excretion of potassium. Angiotensin-II also acts as a vasoconstrictor in vascular smooth muscle. Irbesartan, by blocking the binding of angiotensin-II to the AT1 receptor, promotes vasodilation and decreases the effects of aldosterone and thus lower the blood pressure [7]. Majority of individuals suffer from increase in blood pressure especially at early morning in which the disease severity is maximum. Pulsatile drug delivery system being a delayed release dosage form, Irbesartan in a pulsatile drug delivery system gives highest concentration after a programmable lag phase at early morning when it is needed most [8].

2. Material and methods

2.1. Materials

Irbesartan was obtained a gift sample by Macleods Industries Limited, Daman, India. Kyron T-134 was obtained from Corel pharma, Ahmedabad, India. HPMC K4M was gifted by Colorcon, Goa, India. Eudragit RLPO was obtained from Evonik Industries, India. Poloxamer 188 was obtained from Analab Fine Chemical, Mumbai, India. Mannitol and PVP K30 were obtained from Ozone International, Mumbai, India. Methanol and other reagents used were of standard analytical grade. Double distilled water was used throughout the study.

2.2. Methods

2.2.1. Formulation of solid dispersion of Irbesartan

Irbesartan solid dispersion were prepared by melting method using carrier Poloxamer 188 and Irbesartan in proportions of 1:0.5, 1:1 and 1:2 drug to polymer ratios. The carrier was melted on water bath at 50 °C and then drug was mixed and allowed to dry at room temperature. The resultant solid dispersion was scraped, passed through 20# sieve and stored in desiccator until further use.

2.2.2. Formulation of rapid release core tablet (RRCT)

The core tablets containing Irbesartan solid dispersion (150 mg per tablet), Kyron T-134 (4% w/w), Mannitol (q.s), PVP K30 (5% w/w), Magnesium stearate (2% w/w) and Talc (1% w/w) were prepared by direct compression technique. Initially the powder blends of the core tablet ingredients were mixed in the mini double cone blender for 10 min. The core tablets (diameter, 8 mm; flat; average tablet weight, 200 mg) were compressed using the multi-station tablet compression machine (Hardik Engineering, Ahmedabad, India).

2.2.3. Formulation of pulsatile tablet

RRCT was taken as core part and the pulsatile tablet was prepared by press coating method. Dry coating of optimized RRCT was done by using different grades of various polymers at different concentrations (Tables 1and 2). Dry coated tablets were prepared by placing 50% of pulsatile release layer in die cavity of 10 mm, optimized RRCT was placed in the centre of it. Further remaining quantity of pulsatile release layer was added in cavity so as to cover the RRCT and finally compressed by using rotary compression tablet machine.

2.2.4. Drug-excipient compatibility study

The compatibility study of the drugs and excipients was checked out using the FTIR spectrophotometer. Sample compartment was purged with nitrogen gas before runs, and filled with dry desiccant to absorb any moisture present. Samples were prepared by physically mixing drug and different excipients separately in ratio of 1:1 and were kept for a month at 40 °C/75% RH. Then the mixture was mixed thoroughly with dry KBr (IR grade) in ratio of 1:5 and triturated in a small size mortar pestle. Then pellet of mixture was prepared by compressing the powder in a hydraulic press. Pure KBr powder was used as background, and for baseline correction. Samples were scanned in the region of 4000–450 cm^{-1} using a FT-IR spectrophotometer.

2.2.5. Dissolution studies of pulsatile tablets

2.2.5.1. Method A. In vitro drug release of Irbesartan was carried out by using USP dissolution Type II (Paddle apparatus).

2.2.5.2. Acid stage. 750 ml of 0.1 M HCl in the vessel was placed and

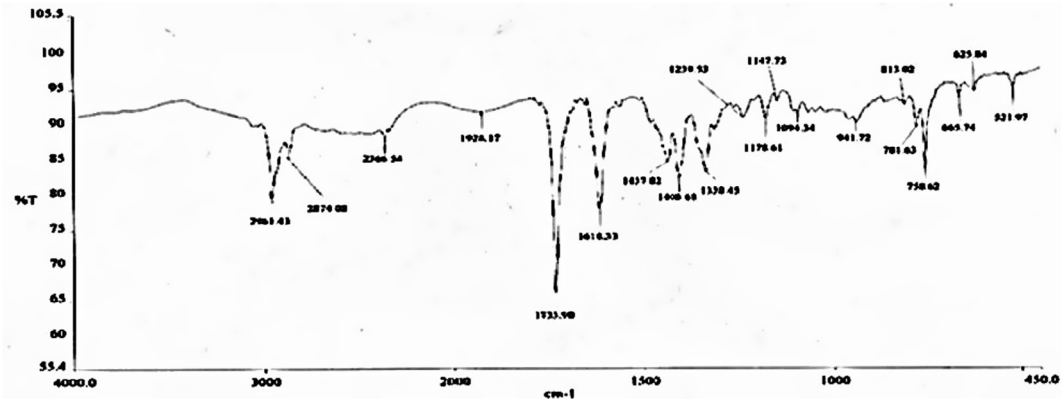

Fig. 1. FTIR spectra of Irbesartan.

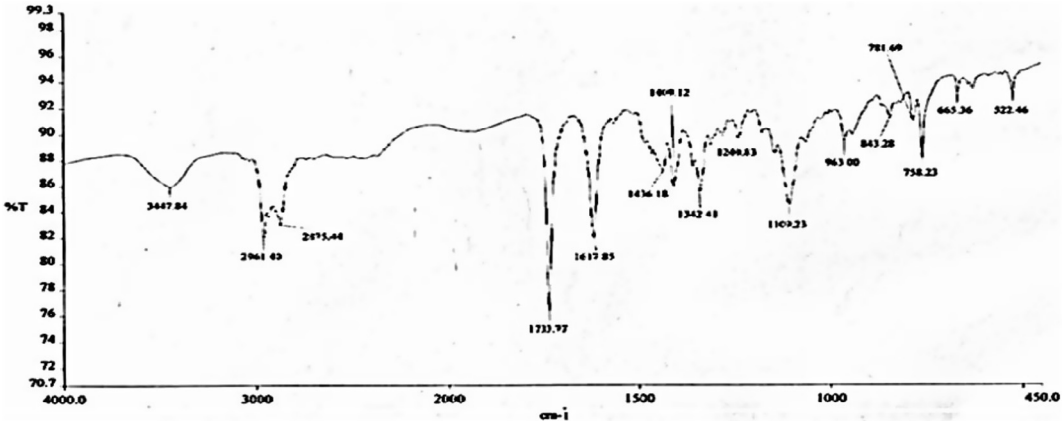

Fig. 2. FTIR spectra of Irbesartan with excipients.

Table 4
Pre-compression parameters of rapid release core tablet.

Batch	Angle of repose (°)	Carr's index (%)	Hausner's ratio
C1	26.85	14.98	1.20
C2	29.88	14.02	1.17
C3	25.24	16.00	1.16
C4	27.10	18.03	1.21
C5	24.22	17.43	1.19
C6	25.69	16.24	1.18
C7	28.95	17.22	1.16
C8	24.65	15.15	1.15

the apparatus was assembled. The tablet was placed in the vessel and the apparatus was operated. After 2 h, 5 ml of sample was withdrawn and replaced with 5 ml of fresh medium, sample withdrawn was filtered through whatman filter paper. Appropriate dilutions were made to get the absorbance in linearity range of medium. The absorbance of the samples was determined at wavelength of 244 nm by using UV-Visible spectrophotometer (Shimadzu, 1800, Japan).

2.2.5.3. Buffer stage. With the apparatus operating, in the vessel 250 ml of 0.2 M, pH 6.8 solution of trisodium phosphate dodecahydrate was added. A sample of 5 ml was withdrawn at predetermined time interval and replaced with 5 ml of fresh medium, sample withdrawn was filtered through whatman filter paper. Appropriate dilutions were made to get the absorbance in linearity range of medium. The absorbance of the samples was determined at wavelength of 244 nm by using UV-Visible spectrophotometer.

2.2.6. Optimization by using Face centred central composite design

Traditionally pharmaceutical formulations developed by changing one variable at a time by trial and error method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique

Table 5
Post compression parameters of rapid release core tablets.

Batch	Weight (mg)	Drug content (%)	Hardness (kp/cm^2)	DT (sec)	Thickness (mm)	Friability (%)
C1	198.66 ± 0.57	98.95 ± 0.71	3.12 ± 0.230	63.00 ± 2.64	2.2 ± 0.40	0.77
C2	198.17 ± 0.16	99.21 ± 0.38	3.33 ± 0.15	54.33 ± 0.57	2.10 ± 0.10	0.74
C3	199.55 ± 0.50	99.88 ± 0.12	3.10 ± 0.10	61.33 ± 1.52	2.20 ± 0.20	0.80
C4	197.52 ± 0.50	98.36 ± 0.25	3.15 ± 0.25	48.66 ± 3.51	2.10 ± 0.10	0.86
C5	199.40 ± 0.75	98.52 ± 0.23	3.26 ± 0.25	52.33 ± 2.51	2.14 ± 0.11	0.71
C6	197.66 ± 0.57	98.99 ± 0.67	3.23 ± 0.20	48.00 ± 1.73	2.13 ± 0.25	0.84
C7	198.66 ± 0.57	98.77 ± 0.39	3.06 ± 0.15	36.33 ± 0.57	2.26 ± 0.15	0.81
C8	199.07 ± 0.13	99.18 ± 0.28	3.10 ± 0.26	23.33 ± 2.08	2.16 ± 0.20	0.79

*All values are ± SD which are mean of 3 determinations.

Table 6
Evaluation of preliminary trial batch of pulsatile drug delivery system for selection of polymers.

Trials	Polymer	Ratio of Polymer	Lag time (hrs)
P1	HPMC K4M:Ethyl cellulose	1:1	4.9
P2	HPMC K4M:Carbopol P934	1:1	3.2
P3	HPMC K4M:Sodium CMC	1:1	4.3
P4	HPMC K4M:Eudragit RLPO	1:1	5.5
P5	Ethyl cellulose:Eudragit RLPO	1:1	5.0
P6	Ethyl cellulose:Carbopol 934	1:1	3.5
P7	Ethyl cellulose:Sodium CMC	1:1	4.1

Table 7
Evaluation of preliminary trial batch of Irbesartan pulsatile tablet for selection of ratio and amount of coating weight.

Trials	Weight (mg)	Hardness (kg/cm^2)	Lag time (hrs)
T1	699.95 ± 0.85	6.13 ± 0.57	5.5
T2	698.87 ± 0.54	6.04 ± 0.52	6.0
T3	699.38 ± 0.53	6.03 ± 0.64	5.6
T4	698.87 ± 0.82	6.19 ± 0.30	6.3
T5	697.93 ± 0.71	6.26 ± 0.28	6.0
T6	697.62 ± 0.60	6.36 ± 0.25	6.5
T7	698.88 ± 0.82	6.02 ± 0.20	7.0
T8	699.77 ± 0.43	6.26 ± 0.20	7.2

since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established tools such as central composite design. In addition to the art of formulation, the technique of central composite design is an effective method of indicating the relative significance of a number of variables and their interactions. Central composite design requires two independent factors that should have three levels respectively. Every experimental point has factor levels of two at their low or high extreme and one at its middle. The number of experimental runs (N) required for implementation of central composite design is $N = (2^k + 2k) + Co$; where k is the number of factors and Co is the central points [9]. Face centred central composite experimental design was employed to evaluate main effects and interaction effects of independent variables on the various responses of Irbesartan time controlled tablet in order to optimize the formulation. The non-linear quadratic model generated by the design is as follows:

$$\mathbf{Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}\,X_1X_2 + b_{11}\,X_1^2 + b_{22}\,X_2^2} \quad (1)$$

Where, Y_i is dependent variable, b_0 is arithmetic mean response of 9 runs and b_i is the estimated coefficient for factor X_i. The main effects (X_1 and X_2) signify average result of altering one factor at a time from its lowest to highest value. The interaction terms (X_1X_2) prompt change in responses when two factors are simultaneously altered. The polynomial terms (X_1^2 and X_2^2) are added to investigate non-linearity of the model. A two-factor, three-level Face centred central composite design was generated by an experimental design-expert software version 8.0.4 (Stat Ease, Inc). Based on preliminary trials, levels of independent variables viz. Weight ratio of HPMC K4M: Eudragit RLPO (X_1) and Total weight of coating (X_2) were determined. The coded levels for each independent and dependent variables are summarized in Table 3. All the formulations were evaluated for responses like Drug release lag time (Y_1) and Drug release after lag time within 15 min; D_{15} (Y_2).

Table 8
Face centred central composite design layout with respective observed response.

Factorial batches	Weight ratio of polymer (X_1)	Total weight of coating (X_2)	Drug release lag time (hrs) (Y_1)	D_{15} (drug release after lag time within 15 min) (Y_2)
F1	−1	−1	5.5	70
F2	1	−1	5.6	63
F3	−1	1	6.1	50
F4	1	1	6.4	42
F5	−1	0	5.8	58
F6	1	0	6.0	54
F7	0	−1	5.5	66
F8	0	1	6.2	45
F9	0	0	5.9	56

2.2.7. Differential scanning calorimetry studies

The sample of Solid dispersion of Irbesartan and pure drug were subjected to differential scanning calorimeter which was previously calibrated with indium standard. Sample (5 mg) was sealed in an aluminium crucible and subjected to a purging of nitrogen gas at a flow rate of 50 mL/min. The heating was done in between 50 and 300 °C temperature a rate of 10 °C/min.

2.2.8. Accelerated stability studies

The accelerated stability study of the optimized formulation was carried out. The sample of tablets were wrapped in the laminated aluminum foil and placed in the stability chamber at 40 ± 2 °C/75 ± 5% RH for a period of one month. Sampling was done at a predetermined time intervals of 0, 15 and 30 days. The tablets were evaluated for different physicochemical parameters.

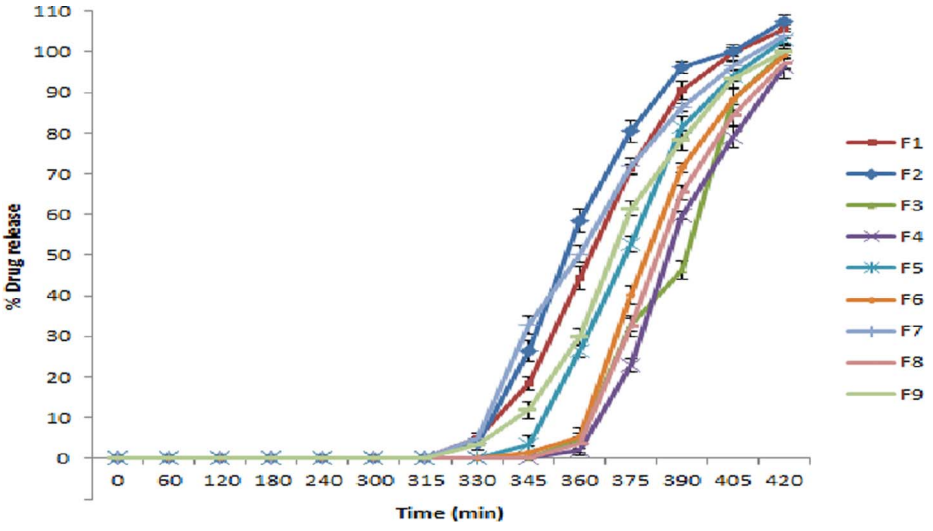

Fig. 3. *In vitro* drug release profile of Irbesartan Pulsatile tablets of experimental design batches.

Table 9
ANOVA for dependent variables.

Sources	Sum of squares	Degrees of freedom	Mean square	F Value	P Value	R^2	Adjusted R^2
For Y_1 = Drug release lag time							
Regression	0.83	5	0.17	63.86	.0030	0.9907	0.9752
Residual	0.0077	3	0.0025				
Total	0.84	8					
For $Y_2 = D_{15}$ (drug release after lag time within 15 min)							
Regression	701.58	5	140.32	95.31	.0017	0.9937	0.9833
Residual	4.42	3	1.47				
Total	706.00	8					

Table 10
Summary of results of multiple regression analysis for Y_1, Y_2.

Dependent variables	Drug release lag time (Y_1)		D_{15} (drug release after lag time within 15 min) (Y_2)	
	Coefficients	P value	Coefficients	P value
Intercept	5.86	.0030	55.67	.0017
X_1	0.12	.0112	−3.17	.0078
X_2	0.35	.0005	−10.33	.0002
X_1X_2	0.050	.0144	−0.25	.0480
X_1^2	0.017	.6749	0.50	.6010
X_2^2	0.017	.6749	0.0	1.000

3. Results and discussion

3.1. Drug excipient compatibility studies

IR spectra of Irbesartan and drug with excipients are shown in Figs. 1 and 2. It confirms the purity of drug and showed that no remarkable changes in peaks of drug in presence of excipients were observed when compared to spectra of pure Irbesartan, indicating absence of any major interaction.

3.2. Preliminary trial batches of core tablets

Core tablets of Irbesartan were characterized for pre- and post-compression parameters and the results are tabulated in Tables 4 and 5. Results indicated that powder blend had good flow property with good compressibility and was suitable for direct compression method. From the preliminary trials it was found that C8 batch containing Kyron T-134 in concentration of 4% w/w had ability to disintegrate rapidly (23.33 ± 2.08 s) which fulfilled the requirements for the burst release.

3.3. Preliminary trial batches of pulsatile tablets

Pulsatile tablets were evaluated for post compression parameters and the results are shown in Tables 6 and 7. Lag time is most important parameter in pulsatile drug delivery system. From the trial batches of pulsatile tablet as shown in Table 6, it was found that when Ethyl cellulose was used in 1:1 ratio with polymers like HPMC K4M, Eudragit RLPO, Carbopol P-934 and Sodium CMC for pulsatile coating it gave drug release lag time which could not satisfy the requirement of predetermined (5.5–6.0 h) lag time [10]. When HPMC K4M was used in 1:1 ratio with polymers like Ethyl cellulose, Carbopol P934, Sodium CMC,

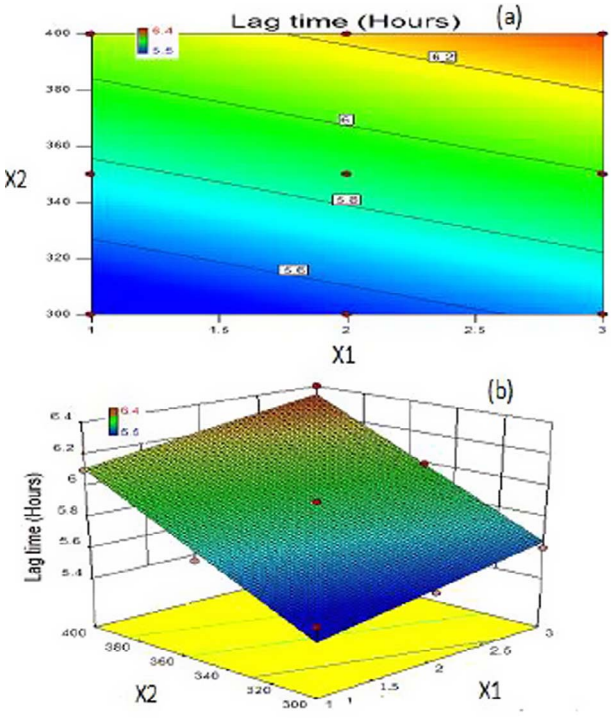

Fig. 4. Response surface graph (a) Contour plot and (b) 3d graph of influence of X_1 and X_2 on Y_1.

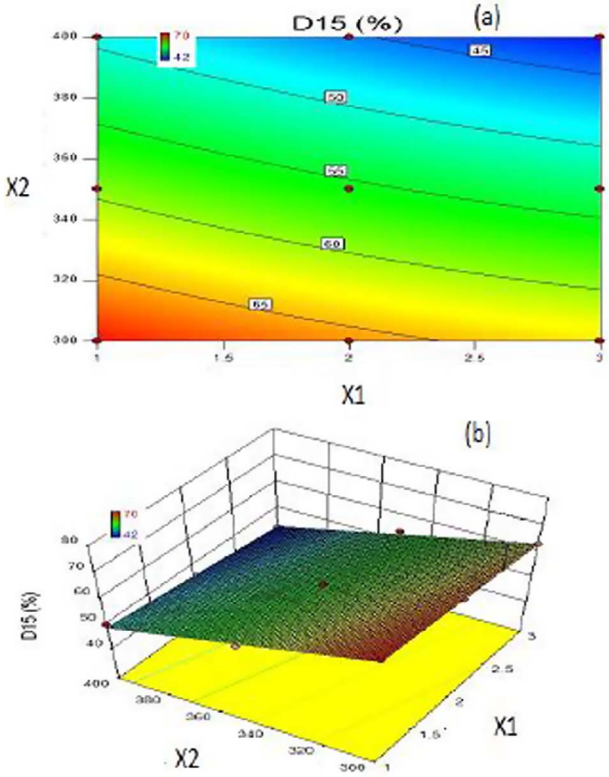

Fig. 5. Response surface graph (a) Contour plot and (b) 3d graph of influence of X_1 and X_2 on Y_2.

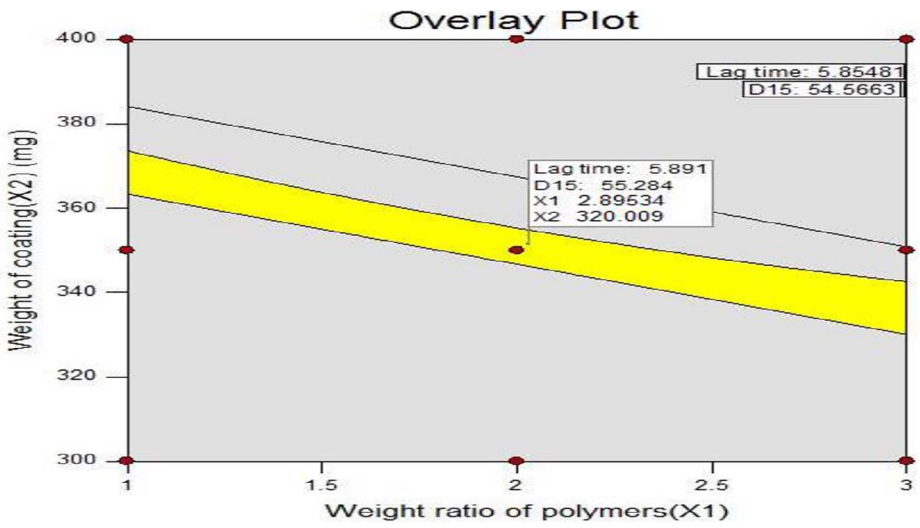

Fig. 6. Overlay plot showing optimized region of pulsatile tablet of Irbesartan.

Table 11
Comparison of experimental value of optimized-check point batch with theoretical value.

Response variables	Optimized batch		
	Theoretical value	Experimental value	% Relative error
Drug release lag time (Y_1)	5.89	5.91 ± 0.51	0.33
D_{15} (drug release after lag time within 15 min) (Y_2)	55.28	54.97 ± 0.23	0.56

Table 12
Summary of kinetic models of optimized batch.

Models	R	R^2
Zero order	0.7045	0.4963
First order	0.8804	0.7751
Hixon Crowell	0.8201	0.6726
Koresmeyer Peppas	−0.2254	0.0508
Higuchi	0.6262	0.3922

it showed similar results. The study conducted that HPMC K4M and Eudragit RLPO in 1:1 can fulfil the criteria of pulsatile drug delivery which showed lag time of 5.5 h. Further as shown in Table 7, it was found that coating weight ratio influenced the release characteristics of drug from the pulsatile preparation.

3.4. Evaluation of experimental design batches

On the basis of preliminary studies, levels of independent variables were selected. A face centred central composite design was applied to study the relationship between independent variables and dependent variables using software Design Expert 8.0.4. Fig. 3 shows the release profiles of the 9 experimental runs performed in accordance with Table 3. Results shown in Table 8 demonstrated responses of all the 9 design batches: response Y_1 (Drug release lag time, hrs) and response Y_2 (drug release after lag time within 15 min%). The data indicated that X_1 (Weight ratio of HPMC K4M:Eudragit RLPO) and X_2 (Total weight of coating) influences the selected responses; Y_1 and Y_2.

Table 9 exhibited the results of analysis of variance (ANOVA). P value of the applied quadratic model was below 0.05, thus suggested that the applied model was significant and hence further reduced model was not generated [11,12]. The individual parameters were evaluated and mathematical relationship was generated between dependent variables and independent factors using multiple linear regression analysis, for determining the optimum levels to yield desired response. The fitted polynomial equation relating the responses; Y_1 and Y_2 to the transformed factors, and the associated p-values are presented in Table 10. Results depicted that significant factors affecting the response Y_1 were synergistic with linear contribution of main effects of X_1 and X_2 respectively, without producing any interaction. The response Y_2 was significantly affected by antagonistic effect of linear contribution of X_1 and X_2, respectively. The relationship between the dependent and independent variables was further elucidated by constructing contour plots, 3D surface plots and overlay plot based on central composite design shown in Figs. 4–6 and .

The results obtained with optimized batch were very close to predicted values as shown in Table 11. Lower value of% relative error suggested that there was no significant difference between theoretical and experimental value. Thus, we had concluded that the statistical model was mathematically valid.

Dissolution profiles of optimized batch were fitted to various models and release data were analysed for Koresmeyer Peppas, Zero order, First order, Hixon Crowell and Higuchi kinetics. Results as depicted in Table 12, concluded that R value and R^2 value was found to be higher

Table 13
Results of stability study of optimized-check point batch.

Condition	Hardness (kg/cm^2)	Drug release lag time (hrs)	% Drug Content (%)	% Drug release after 15 min
Initial	6.10 ± 0.32	5.91 ± 0.51	99.20 ± 0.25	54.97 ± 0.23
After 15 days 40 ± 2 °C/75 ± 5% RH	6.08 ± 0.84	5.87 ± 0.99	99.12 ± 0.65	54.80 ± 0.71
After 30 days 40 ± 2 °C/75 ± 5% RH	6.07 ± 0.59	5.87 ± 0.91	99.19 ± 0.82	54.72 ± 0.93

*All values are ± SD which are mean of 3 determinations.

for First order release as compared to other models [13].

Optimized batch was investigated for one month stability studies in accelerated conditions at 40 ± 2 °C/75 ± 5% RH. Results as shown in Table 13 revealed no significant difference in physicochemical parameters like hardness, drug release lag time, drug content and% drug release after 15 min.

4. Conclusion

The present study demonstrates the successful preparation of chronomodulated drug delivery system of Irbesartan with an aim to lower the blood pressure in the early morning. The formulation is to be taken after dinner at around 22:00 h in night. This will provide an ideal therapeutic regimen with enhanced patient compliance. Experimental design applied to the manipulation of formulation parameters provided optimum levels of independent variables to formulate an optimal batch. The optimized formulation exhibited release profile closed to the predicted profile. Thus, the developed formulation can be considered as one of the promising preparation for the relief of early morning surge in blood pressure.

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The authors report no conflicts of interest.

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