Document heading doi: 10.21276/apjhs.2019.6.1.2 **Research Article**

Design, Development and optimization of chronomodulatedPulsincap delivery system of Valsartan

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Abstract

Aim of the present study was to formulate, evaluate and optimize the Pulsincap delivery system of valsartan used for treatment of hypertension, based on the chronotherapeutic approach. The prepared pulsincap system consist of immediate release tablet sealed inside formaldehyde treated insoluble capsule body by hydrogel plug composed of polymer HPMC K15M and guar gum. The formulation produced was targeted for the preparation of time controlling pulsatile formulation to delivery drug to site and time controlling for enhancing the bioavailability of drug, so preliminary batches were prepared to study the effect of concentration of HPMC K15M and guar gum on the lag time of the drug release. Optimization of hydrogel plug was carried out by employing 3^2 full factorial design using Design expert 7 Software.

Keywords: Chronothepary, Valsartan,hypertension , Pulsatile capsule, 3^2 Full factorial design.

Introduction

Pulsatile Drug Delivery System (PDDS) is a time-specific and site-specific drug delivery system, thereby it provides special and temporal delivery and increase patient compliance also. This system can be of great use for the drugs which do not require a constant drug release i.e. do not desire a Zero- order release.

PDDS can be defined as the rapid and transient release of certain number of molecules within a short–time immediately after a pre–determined off-release period, i.e. lag time. Lag time is defined as the time between the placement of dosage form into an aqueous environment and the time at which the active ingredient begins to get released from the dosage from. [1]

'Chrono pharmaceutics' is a word made after compiling two words, Chronobiology and Pharmaceutics.

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Chronobiology is the study of biological rhythms and their mechanisms. There are 3 types of mechanical rhythms in our body:

- **Circadian:** This word comes from Latin word 'circa' means about and 'dies' means day.
- **Ultradian:** Oscillations of shorter duration are termed as ultradian (more than 1 cycle 24 hrs) [4]
- **Infradian:** Oscillations that are longer than 24 hrs (less than one cycle per day) [2]

It is well- documented that majority of the body functions exhibit circadian rhythms e.g. heart rate, stroke volume, blood pressure, blood flow, body temperature, gastric pH etc. Moreover, in several organs their functions vary with the time of the day. [3]Cardiovascular disorders such as angina, heart attack, hypertension, stroke and sudden cardiac death. The differences in patterns of illness between day and night for these disorders have been documented. Dosing schedules have been made, medications have been formulated to provide appropriate concentration of a drug in body where drug is most needed. For example – blood pressure of a hypertensive patient increases rapidly after awakening and it peaks in the middle to late time of the day, decreases in the evening and it is lowest while the patient sleep at night [5].

In the present study, Valsartan was selected as the model drug. Valsartan blocks the actions of angiotensin II, which include constricting blood vessels and activating aldosterone, to reduce blood pressure. The drug binds to angiotensin type I receptors (AT1), working as an antagonist. This mechanism of action is different than the ACE inhibitor drugs, which block the conversion of angiotensin I to angiotensin II. Since valsartan acts at the receptor, it can provide more complete angiotensin II antagonism since angiotensin II is generated by other enzymes as well as ACE. Also, valsartan does not affect the metabolism of bradykinin like ACE inhibitors do. In order to obtain an appropriate formulation with minimum experiments, optimization method was adopted in the present study. A 3^2 full factorial design was chosen to optimize the variables. The search for the optimum was carried out using desirability function as this technique involves a way of overcoming difficulty of multiple, sometimes opposing responses.

MATERIALS AND METHOD

Materials

Valsartan, hydroxyl propyl methyl cellulose (HPMC K15M) and Avicel pH101 was obtained fromZydus Cadilla, Ahmedabad.Guar gum, sodium starch glycolate, talc and magnesium stearate were obtained from Nice Chemicals Pvt. Ltd. Kerala, IndiaEthyl cellulose and ac-di-sol was obtained from Optica Pharmaceuticals, Haryana, India.Ethanol was obtained from modi mill, Yamuna nagar, Haryana.

Drug-Excepient compatibility study by FTIR

The FTIR absorption spectra was performed for various physical mixtures of polymer and drug. The physical mixtures were then scanned at wavelength 4000 cm^{-1}- 400 cm^{-1}. The spectra were then studied for peaks obtained by comparing with the spectra of pure drug as seen in figure 1 and figure 2.

Preparation of cross-linked gelatine capsules (Capsule no 1 plug 6 mm bound by EC mixture)

Formaldehyde treatment

Formalin treatment has been employed to modify the solubility of gelatine capsules. Exposure to formalin vapours results in an unpredictable decrease in solubility of gelatine owing to the cross linkage of the amino group in the gelatine molecular chain aldehyde group of formaldehyde by Schiff's base condensation.Fifty millilitres of 10% (v/v) formaldehyde was taken into desiccator and a pinch of potassium permanganate was added to it, to generate formalin vapours. The wire mesh containing the empty bodies of the 100 mg capacity hard gelatine (about 100 in number) capsule was then exposed to formaldehyde vapours. The caps were not exposed leaving them water-soluble. The desiccator was tightly closed. The reaction was carried out for 12 hrs after which the bodies were removed and dried at 50 °C for 30 min to ensure completion of reaction between gelatine and formaldehyde vapours. The bodies were then dried at room temperature to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated caps and stored in a polythene bag. [6,7]

Test for formaldehyde treated empty capsule bodies

Various physical tests, such as identification attributes, visual defects, changes in dimension were carried out.

Solubility studies for the treated capsules

When the capsules were subjected to solubility studies in different buffers for 24 hrs, the following observation were made a) In all the case of normal capsules, both cap and body dissolved within fifteen minutes. b) In the case of formaldehyde treated capsules, only the cap dissolved within 15 min, while the capsule remained intact for about 24 hrs.

Quantity test for free formaldehyde

The formaldehyde capsules were tested for the presence of free formaldehyde. Limit test for the presence of residual formaldehyde was carried. The sample solution was less intensively coloured when compared with standard inferring that less than 20 µg/ml of free formaldehyde is present in 25 capsules bodies) as per the I.P.[8]

Preparation of immediate release tablets

Immediate release coretablets were prepared by direct compression of a homogenous mixture of valsartan, Avicel PH-101, Ac-di-sol, Sodium starch glycolate, magnesium stearate & talc as given in Table 1. Weight variation, Hardness and Disintegration time were measured for the core tablets. Press coated tablets were formulated using different polymers as outer coating for core tablet including Ethyl Cellulose,HPMC K100, Guar Gum and Avicel.

Evaluation of immediate release tablets

The thickness and diameter of the tablets (n=10) were determined using micrometer [9]. The hardness of the tablets (n=10) was determined by using the pfizer hardness tester [10]Electrolab, Mumbai, India. The friability (%) of the tablets was determined by takingSample of whole tablets corresponding to about 6.5gm placed in the friabilator and were subjected to 100 revolutions [11]. The tablets were taken out, de dusted and reweighed to determine the friability of all the batches. Weight variation test of the tablets (n=20) was carried out as per the official method [12]. The disintegration time of core tablets was determined by the Disintegration tester USP [13] (ED-2AL, Electrolab, Mumbai, India). The drug content and uniformity of valsartan was determined using UV Spectrophotometer. The contents of 1 capsule transfer

to a 100 ml volumetric flask and dissolved in a suitable quantity of distilled water and sonicated for about 15 minutes. This solution adjusted with water to volume in 100 ml volumetric flask. The solution was used as stock solution and filtered using filter paper. Ten ml of sample was withdrawn from this solution and dilute up to 100 ml distilled water in 100 ml volumetric flask. The amount of drug was determined using UV spectrophotometer at 248 nm. The content of each batch was determined in replicates of three. [14]

Preparation of hydrogel plug

Hydrogel plugs (preliminary batches) were prepared by varying the concentration of polymer HPMC K15M and guar gum by direct compression technique using single punch tablet machine according to the formula mentioned in table 2. The average weight of hydrogel plug was found to be 100mg.

Evaluation of hydrogel plug

Hydrogel plug containing HPMC and guar gum were evaluated for weight variation, thickness and hardness.

Development of pulsincap system

One tablet from the optimized batch of core tablets was placed into the previously formaldehyde treated bodies by hand filling. The bodies containing the core tablet, were then plugged with hydrogel plug as shown in Table 4.8. Then the capsule body and cap were joined and sealed with a small amount of 5% ethyl cellulose ethanolic solution.

***In vitro* dissolution study of the capsule**

The dissolution testing of pulsed capsule was carried out using a USP Type II dissolution apparatus at 37±0.5 °C in 900 ml phosphate buffer pH 6.8 and a paddle speed of 75 rev./min. The *in vitro* dissolution study of pulsatile capsule device was carried out using USP Type II dissolution apparatus. The capsules were tied to circular wire mesh of diameter 2 cm and immersed in the dissolution medium. The study was carried out in 900 ml of 0.1 N HCl for the first 2 h, followed by 900 ml of phosphate buffer (pH 6.8). The dissolution medium was maintained at 37±0.5 °C. The paddle was lowered so that the lower end of the stirrer was 25mm above from the base of the beaker. The capsule assembly was tied to a wire mesh that was then introduced into the dissolution vessel and the paddle was rotated at 75 rpm. At different time intervals, 5 ml of sample was withdrawn and analyzed by UV–Visible spectrophotometer at 248 nm. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution vessel. [15]

Experimental design

A two factor, three level (3^2) FFD was used in the optimization of Hydrogel plug. The study design involved the investigation of the effect of independent variables viz concentration of HPMC (X_1) and concentration of guar gum (X_2) on the dependent variable lag time.

The levels of the factors studied were chosen based on results of preliminary studies, so that their relative difference was adequate to have a measurable effect on the response, along with the information that the selected levels are within practical use. After developing the experimental design nine batches of hydrogel plug were formulated. Nine formulations (Table 3) were prepared according to the experimental design.

The factorial design is a simplified representation in analytical form of a given reality. In this mathematical approach, each experimental response Y can be represented by a quadratic equation of the response surface: $Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2 + \beta_4 X_1^2 + \beta_5 X_2^2$, in which Y is the measured response associated with each factor-level combination; X1 and X2 are the factors studied; B0 is an intercept; B1– B5 are the regression coefficients. The equation enabled the study of the effects of each factor and their interaction over the considered responses.

Optimization of hydrogel plug

The optimization process was used to obtain a model equation that provides a means of evaluating changes in response due to changes in the independent variable levels. After application of full factorial design and with help of polynomial terms the optimized pulsincap system (PCZ1) was produced. Pulsincap formulation was prepared as per the composition given in Table4. This batch targeted to lag time 360 min.

Stability studies

In order to assess stability, the optimum pulsincap of Valsartan were packed in an amber colored air tight vial and stored at (40 ± 2 °C and 75 ± 5% RH) for a period of 6 months. The formulations were withdrawn after a period, analyzed for physical appearance, weight, drug content, and lag time. At this point, the data was statistically analyzed using ANOVA to test the significance of difference at the level of significance 0.05.

RESULTS AND DISCUSSION

Preformulation studies

Drug and excipient studies were performed and FTIR studies revealed that there is no incompatibility between drug and excipients used in the study. The IR spectrum of valsartan exhibits characteristic peaks at 3304 cm1 (N–H functional group), 2960 cm1 (C–H group stretching vibration), 1728 cm1 (carboxyl carbonyl), 1598 cm1 (amide carbonyl group). The peak at 1467 cm1 indicates the presence of CQC aromatic group. Appearance of these peaks in the physical mixture and liquisolid

formulation indicate the absence of chemical interaction between the drug and excipients.

Physical test

It was found that after formaldehyde treatmentthe length and dimension of capsule bodies were decreased

Disintegration test of capsules

It was found that the untreated capsules and the caps of treated capsules were disintegrated within 20 min. whereas the treated capsules remained intact for 24 hours

Formaldehyde treatment of empty gelatin capsule

Formalin treatment has been employed to modify the solubility of the gelatin capsules. Exposure to formalin vapors results in an unpredictable decrease in solubility of gelatin owing to the cross-linkage of the amino groups in the gelatin molecular chain with aldehyde groups of formaldehyde by Schiff's base condensation. The solubility tests were carried out for untreated capsules and formaldehyde treated capsules for 24 h. It was observed that in all untreated capsules, both cap and body dissolved within 30 min, whereas in formaldehyde-treated capsules, only the cap dissolved within 30 min, while the capsule body remained intact for about 24 h and hence indicates the suitability for colon targeting. The formaldehyde capsules were tested for the presence of free formaldehyde. The sample solution was not more intensely colored than the standard solution, inferring that less than 0.8 mg of free formaldehyde per capsule was present as residual amount.

Evaluation of prepared powder blend

Prepared powder blend of immediate release core tablet and hydrogel plug was subjected to evaluate various micromeritic properties. It was found that the powder exhibit good flow property as evident from the table 5 and 6

Evaluation of prepared immediate release tablet

Prepared immediate release tablets were subjected to check various physico-chemical properties and the values were found within the limits. Results are depicted in table 7

Evaluation of compressed hydrogel plug and pulsincap system

After formulating preliminary batches of hydrogel plugs, the evaluation study of hydrogel plugs was carried out, and the results obtained are represented in Table 8. It was found that all the formulations exhibited uniform weight with low standard deviation values, indicating the uniformity of the weight in hydrogel plugs prepared by direct compression method. The weight of the hydrogel plug varied between 101.73 mg and 98.42 mg. Range of hydrogel plug thickness was found to be between 6.245mm – 6.52mm.Hardness of hydrogel plug was determined by Pfizer hardness tester taking average of ten hydrogel plugs. It was found that with the increase in concentration of polymer there was an increase in the hardness value of plug. Range of hardness for hydrogel plug was in between 2.47 kg/cm^2 – 4.37 kg/cm^2 with minimum standard deviation.

***In vitro* dissolution studies**

In vitro drug release from pulsincap delivery system containing hydrogel plug with varying polymer concentration is depicted fig 3. each formulation released the drug after a certain lag time and the lag time attained was dependant on type and concentration of polymer. It was found that maximium lag time (440 min) was shown by the formulation PP1containing 45mg of HPMC k15and minimum lag time (300 min) was shown by formulation PP4 containing 35mg of HPMC k15. Based onpreliminary studies, it was found that with increase in the concentration of the polymer the lag time of drug release was also increased. Based on values of hardness obtained it was observed that with decreasing the concentration of polymer value of hardness also decreased. Based on these findings combination of polymer was selected for further studies.

Statistical and response surface analysis of models for lag time

Statistical analysis

It was investigated, lag time showed a wide variation with change in concentration of two factors. Table 9 describes effect of HPMC and guar gum. It was found that with increase in concentration of HPMC and guar gum lag time for drug release also increased. According to dissolution profile it was found that lag time PP1-PP9 (fig. 4) varied between 300-440 min. Formulation PP2 released drug after a lag time of 370 min. and the percentage of drug released from the formulation was found to be 97.98%.

Optimization

Optimization was done employing a 3^2 FFD. The dependent and independent variables were related using quadratic equations obtained with the Design Expert software (Design Expert 7) ANOVA was performed to identify insignificant factors. Model selection was based on lower p values than assigned significance level, high F value i.e.65.72, absence of lack of fit, highest level of adjusted R^2 and predicted R^2, low standard deviation and lower PRESS value. All values are represented in Table 10. All values implythat the model is significant. High value of R^2 for dependent variable was obtained, which indicate a good fit. Value of p less than 0.05 indicated that model terms are significant.

Response surface analysis

Response surface plot was generated for response to study the behavior of the system. Response surface plot for hardness in fig.5 and fig.6 shows that with the increase in the concentration of HPMC lag time of drug increases in linear manner and with increase in concentration in guar gum the lag time value of the hydrogel plug also increases in a curvilinear manner.

Table 1: Composition obtained for optimized batch

Ingredients	Fast release core tablet
Valsartan	80
Acdisol	4.32
Sodium starch glycolate	4.36
Avicel PH 101	67.32
Magnesium Stearate	2
Talc	2

Table 2:Formulation of trial batch of Pulsed capsule

Batch	PG1	PG2	PG3	PG4	PG5	PG6	PG7	PG8	PG9
HPMC K15M	30	40	50	0	0	0	30	40	50
Guar Gum	0	0	0	20	30	40	40	30	20
Avicel pH101	66	56	46	76	66	56	26	26	26
Mg Stearate	2	2	2	2	2	2	2	2	2
talc	2	2	2	2	2	2	2	2	2

Table 3:Formulation of the Pulsed capsule with Immediate release core tablet

Formulation code	Immediate release tablet (mg)	Hydrogel composition (mg)			
		HPMC K15M	Guar gum	Avicel pH101	Magnesium stearate
PP1	150	45	30	24	1
PP2	150	40	25	34	1
PP3	150	45	25	29	1
PP4	150	35	25	39	1
PP5	150	35	30	34	1
PP6	150	45	35	19	1
PP7	150	40	35	24	1
PP8	150	35	35	29	1
PP9	150	40	30	29	1

Table 4: Composition obtained for optimized batch of Pulsed Capsule

Ingredients	**Pulsed Capsule (PCZ1)**
Core Tablet	150
HPMC K15m	38.3
Guar Gum	29.85
Avicelph 101	27.85
Mg stearate	2
Talc	2

Table 5: Characterization of powder blends of core tablets

Parameters	**Bulk density (gm/cm3)**	**Tapped density (gm/cm3)**	**Compressibility index (%)**	**Hausner's Ratio**	**Angle of repose (º)**
CT1	0.365± 0.016	0.406± 0.022	10.056± 1.062	1.112± 0.013	27.683± 0.229
CT2	0.377± 0.019	0.421± 0.018	10.618± 0.623	1.119± 0.008	28.33± 0.46
CT3	0.364± 0.019	0.409± 0.019	11.018± 0.709	1.124± 0.009	28.018± 0.346
CT4	0.367± 0.009	0.413± 0.011	11.122± 0.632	1.125± 0.008	28.798± 1.014
CT5	0.39± 0.008	0.436± 0.013	10.541± 0.902	1.118± 0.011	27.256± 0.885
CT6	0.382± 0.016	0.424± 0.019	9.743± 1.07	1.108± 0.013	27.822± 0.528
CT7	0.361± 0.021	0.399± 0.022	9.617± 1.187	1.107± 0.014	26.867± 0.33
CT8	0.375± 0.01	0.412± 0.011	8.9± 0.895	1.098± 0.011	27.839± 0.605
CT9	0.346± 0.015	0.375± 0.013	7.583± 0.928	1.082± 0.011	26.338± 0.307
CT10	0.396± 0.014	0.425± 0.011	6.988± 0.903	1.075± 0.01	25.249± 0.107
CT11	0.38± 0.016	0.411± 0.015	7.634± 1.06	1.083± 0.012	26.916± 0.396
CT12	0.382± 0.014	0.418± 0.012	8.544± 1.241	1.094± 0.015	26.648± 0.278

* n=3; ** Calculated from average values of tapped density and bulk density.

Table 6: Characterization of powder blends trial batch

Formula final	bulk density	tapped density	Compressibility index(%)	Hausner's Ratio	Angle of repose (º)
PG1	0.374 ± 0.001	0.462 ± 0.009	18.901 ± 1.759	1.234 ± 0.027	25.414 ± 0.549
PG2	0.373 ± 0.004	0.457 ± 0.011	18.264 ± 2.746	1.225 ± 0.041	25.226 ± 0.835
PG3	0.383 ± 0.004	0.456 ± 0.004	15.94 ± 1.528	1.19 ± 0.021	24.51 ± 0.439
PG4	0.394 ± 0.005	0.462 ± 0.019	14.654 ± 4.183	1.174 ± 0.058	24.18 ± 1.197
PG5	0.392 ± 0.002	0.469 ± 0.013	16.321 ± 2.709	1.196 ± 0.04	24.633 ± 0.814
PG6	0.388 ± 0.004	0.459 ± 0.005	15.509 ± 1.495	1.184 ± 0.021	24.39 ± 0.437
PG7	0.381 ± 0.004	0.463 ± 0.009	17.572 ± 1.305	1.214 ± 0.02	24.999 ± 0.404

PG8	0.394 ± 0.002	0.466 ± 0.002	15.514 ± 0.401	1.184 ± 0.006	24.38 ± 0.117
PG9	0.397 ± 0.007	0.465 ± 0.004	14.756 ± 1.238	1.173 ± 0.017	24.168 ± 0.345

* n=3; ** Calculated from average values of tapped density and bulk density

Table 7: Post Compression parameters of core tablet

Hardness (kg/cm2)	Friability (%)	DT (sec)
2.98 ± 0.13	0.82 ± 0.07	29 ± 1

Table 8:Post Compression parameters of hydrogel plug

Parameters	Hardness	friability
PG1	3.87±0.06	0.767 ± 0.153
PG2	4.13±0.06	0.6 ± 0.1
PG3	4.37±0.06	0.467 ± 0.153
PG4	2.47±0.4	0.567 ± 0.153
PG5	2.87±0.06	0.633 ± 0.208
PG6	3.17±0.06	0.6 ± 0.173
PG7	3.57±0.29	0.333 ± 0.208
PG8	3.9±0.17	0.733 ± 0.058
PG9	4.07±0.12	0.567 ± 0.153

Table 9:Lag time of Experimental batch

Formulation code	**Immediate release tablet (mg)**	**Hydrogel composition (mg)**				**Lag Time(min)**
		HPMC K15M	**Guar gum**	**Avicel pH101**	**Magnesium stearate**	
PP1	150	45	30	24	1	410
PP2	150	40	25	34	1	370
PP3	150	45	25	29	1	400
PP4	150	35	25	39	1	300
PP5	150	35	30	34	1	320
PP6	150	45	35	19	1	440
PP7	150	40	35	24	1	390
PP8	150	35	35	29	1	330
PP9	150	40	30	29	1	380

* n=3

Table 10:ANOVA results of the model

Std. Dev.	Mean	R-Squared	Adj R-Squared	C.V. %	PRESS	Pred R-Squared	Adeq Precision
7.136240321	371.1111111	0.990953947	0.975877193	1.922939009	1849.362245	0.890498288	22.31102459

SS- sum of squares, DF- degree of freedom, MS- Mean square, SD- Standard deviation

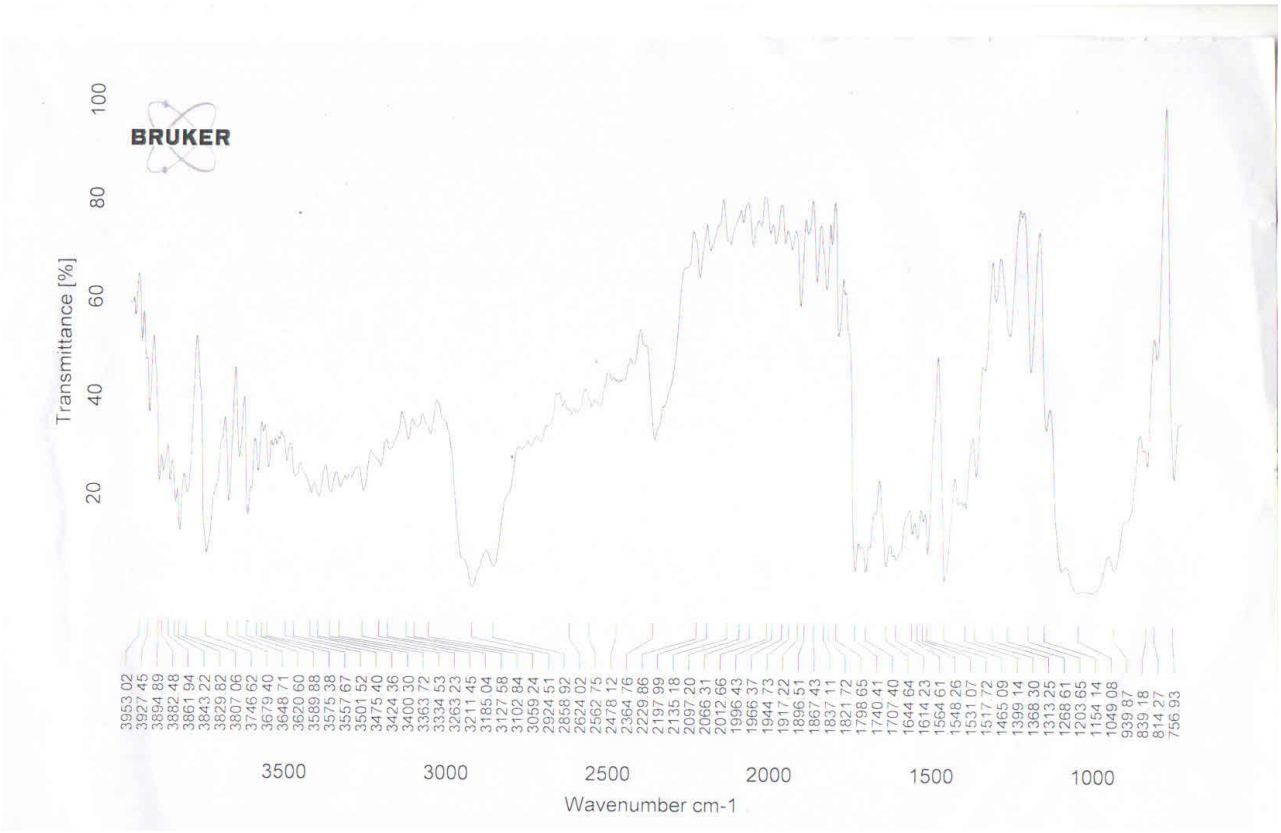

Figure 1: FTIR of drug with HPMC K15M

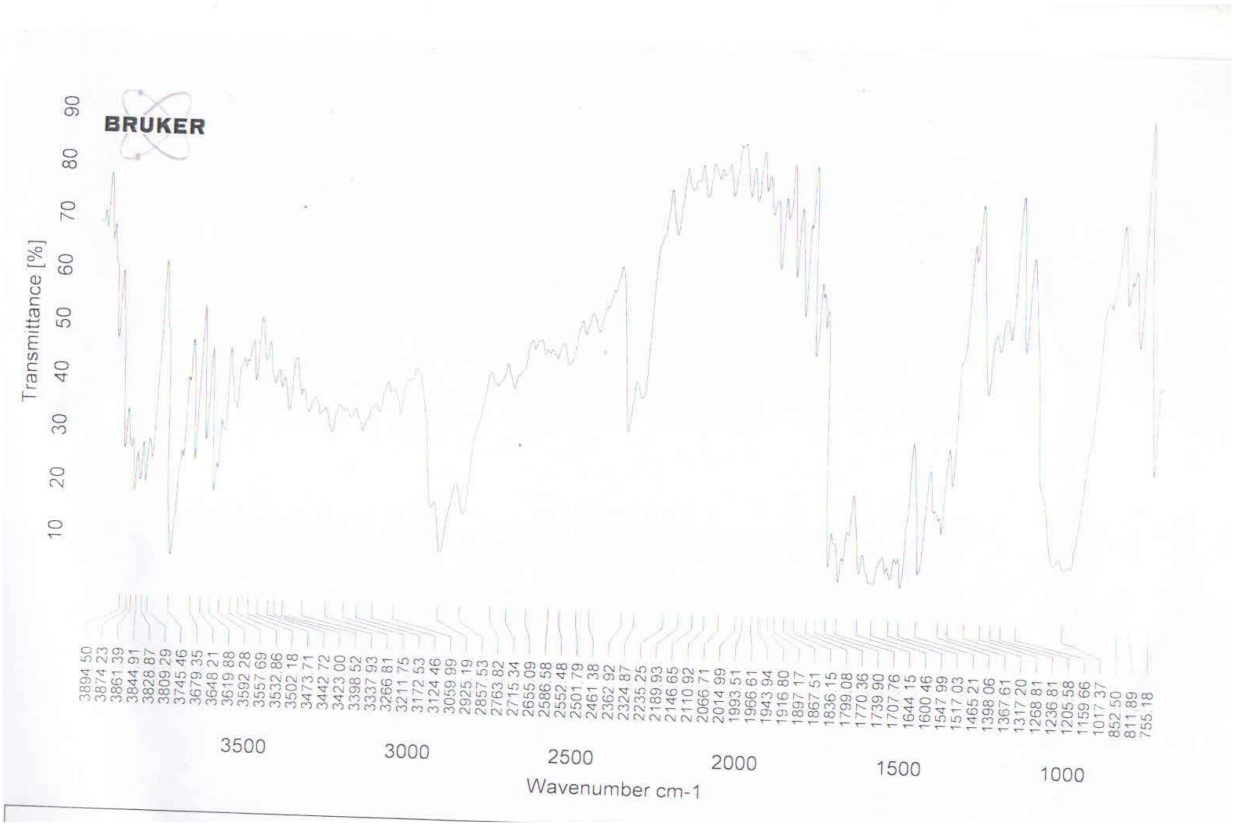

Figure 2: FTIR of drug with GUAR GUM

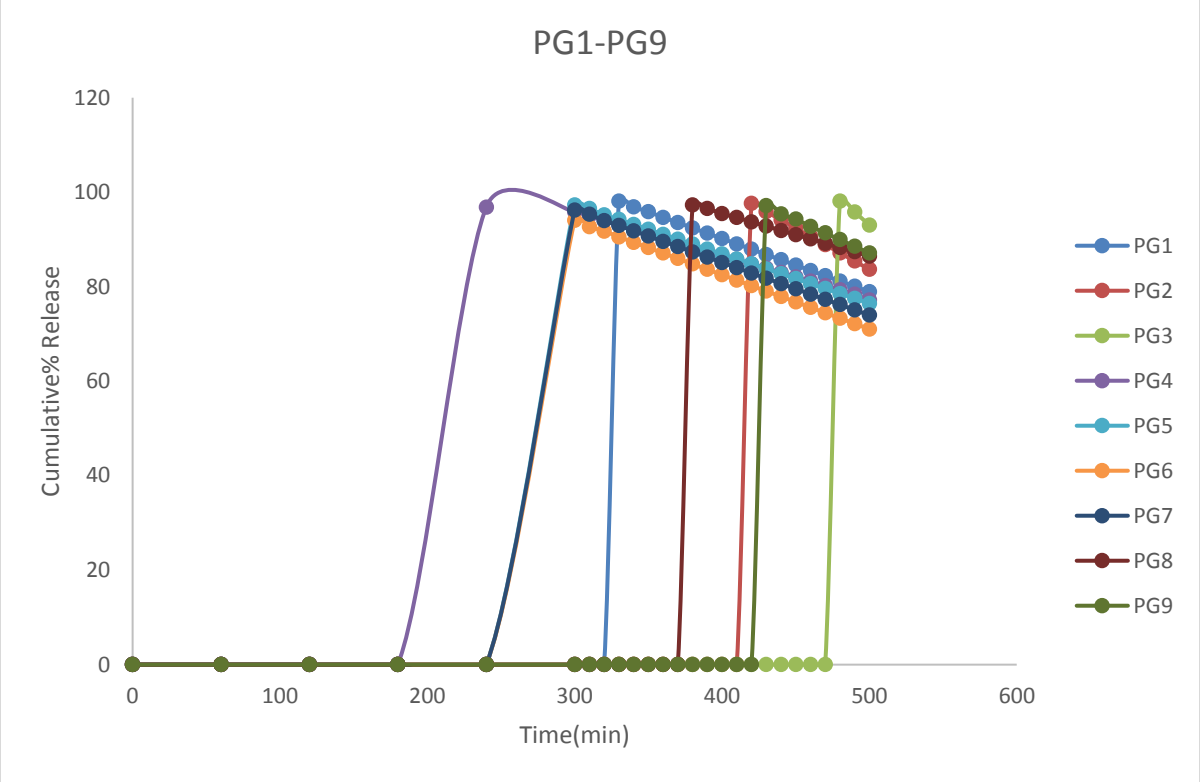

Figure 3: In-vitro release profile of pulsed capsule PG1-PG9

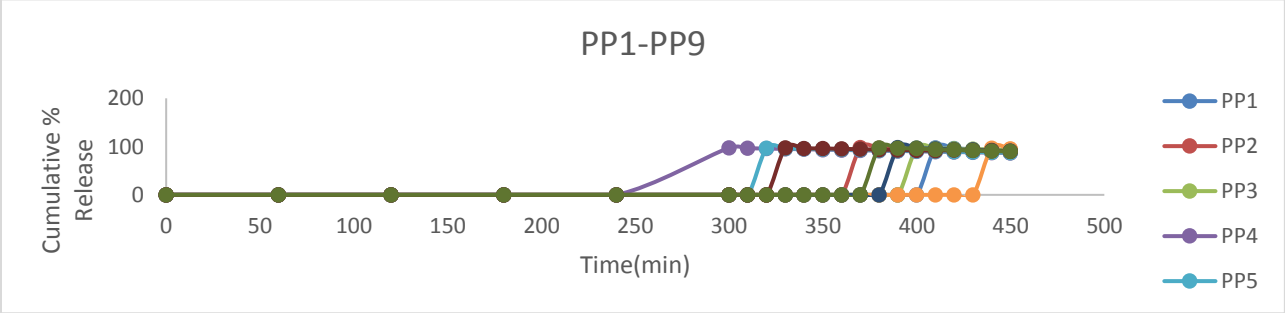

Figure 4: In-vitro release profile of pulsed capsule PP1-PP9

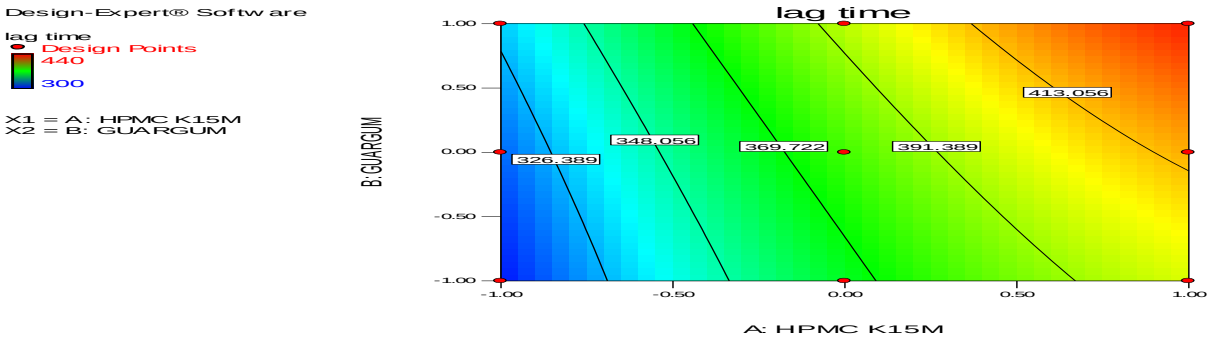

Figure 5:Contour plot showing the influence of X1 and X2 on the lag time of pulsatile capsules of Valsartan

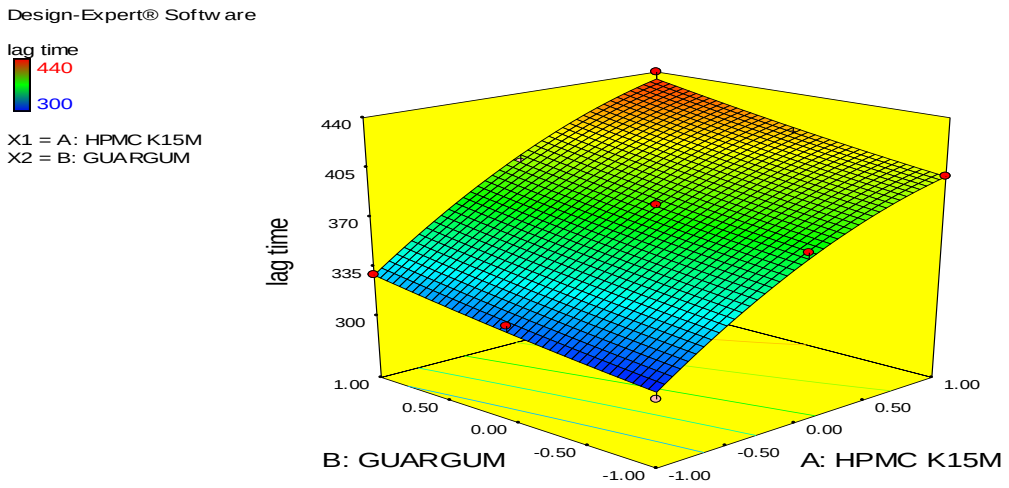

Figure 6: Surface response graph showing the influence of X1 and X2 on the lag time of pulsatile capsules of Valsartan

Accelerated stability studies

Accelerated stability studies on the optimized promising formulation ofpulsincap (PCZ1) was carried out by storing the formulations (in amber colored rubber stoppered vials) at 40±2^{0}C and 75±5% RH for 6 months. At regular intervals the formulation was characterized for different parameters. It is shown that there was no change in physical appearance, weight, hardness, drug content during the study period and at the end of the six months. Also, no significant change was shown in the percent drug release, before and after storage. Thus, results imply good stability of the formulation on six-month storage. Since the accelerated data showed little or no change over time and little variability, a statistical analysis was considered unnecessary.

Conclusion

It was concluded that, implementation of a suitable experimental design results in achievement of an appropriate formulation, in the shortest time with minimum efforts. Pulsincap formulation of valsartan prepared by using polymer HPMC and guar gum was found to be better alternative for the patients having rheumatoid arthritis that follows the circadian pattern because the prepared formulation released the drug according to the need of disease. Lag time for the release of drug from the optimized formulation was found to be 360 which was the desired value. Thus, it can be said that our prepared formulation might be beneficial in a diseased state to provide relief at its worst condition.

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