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Development and Optimization of Pulsatile Release Formulation of Valsartan for Chronotherapy of Hypertension

Rajan Kalamkar[*1], Ashish Jain[1], Gangotri Yadav[1], Shailesh Wadher[2]

1.Shri D.D. Vispute College of Pharmacy & Research Center, Panvel

2.School of Pharmacy, SRTM University, Nanded

ABSTRACT

The aim of present work was to develop pulsatile release dosage form for chronotherapy of hypertension. Considering the biopharmaceutical, pharmacodynamics reasons of Valsartan and circadian rhythm of hypertension a time controlled rupturable tablet, which allowed the release of Valsartan in time controlled release manner was developed for treating early in the morning surge of blood pressure. Core tablet for formulation were prepared using direct compression technique and evaluated for various parameters like % drug content, hardness, thickness, friability and In-vitro disintegration time. To get desired lag time and release profile to achieve pulsatile delivery tablets were coated with ethyl cellulose: Eudragit L100 (3:1), containing dibutyl phthalate and magnesium stearate. Coated tablet was evaluated for in vitro dissolution study, Drug content and rupture time. Optimization was done by using 3^2 full factorial design by using conc. of croscarmellose in core and coating level as independent variables and rupture time or lag time as dependent variable. Formulation F-5 was found to optimized formulation containing 5% of superdisintegrant in core tablet and 5 % coating level. From the study it is also concluded that Increase in coating level increases lag time & increase in concentration of superdisintegrant decreases lag time.

Keywords: Pulsatile, Chronotherapy,Superdisintegrant, Optimization.

*Corresponding Author Email: rajankalamkar@gmail.com

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INTRODUCTION

Physiological processes and biological functions display constancy over time; much effort had been devoted in the past in developing the drug delivery systems that maintain a sustain plasma level for an extended period of time. However, chronobiological studies belie this concept. Along with many applications in local and systemic delivery of drugs, pulsatile release system is advantageous when a delay in absorption is desirable from a therapeutic point of view for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as nocturnal asthma, angina and rheumatoid arthritis. Pulsatile drug release system, which allows the release of active pharmaceutical material in single or successive pulses at precise and well controlled time periods, is a recently developed drug delivery system[1-3].Chronopharmaceutical drug delivery is the delivery of drugs in accordance with the circadian rhythms of the disease. It involves identification of a specific time dependent trigger, capable of provoking drug release from an oral formulation after a predetermined time interval. It is now recognized that episode of angina pectoris, asymptomatic ischemia, acute coronary syndrome, sudden death, ventricular ectopic activity and stroke exhibit an increased incidence in early mornings demanding a time scheduled drug release for effective drug action. This temporal pattern is dependent both on the staging of the specific circadian rhythms and the morning occurrence of triggers of the conditions[4-6]. Valsartan was used as a model drug due to its AT1 receptor antagonist action, fewer side effects and higher half life. Single oral dose results in peak plasma level of 2-3 h after ingestion, and the elimination half-life of 7-9 h demanding a single oral dose of a drug. Valsartan is a member of angeotensin 2 antagonist, used in the treatment of hypertension, angina pectoris, and some types of arrhythmia. Valsartan produces its antihypertensive effect primarily by working as AT1 receptor antagonist with a resultant decrease in peripheral vascular resistance[7,8]. The objective of the present study was to develop a novel system of "Time controlled rupturable polymer coated tablet" providing programmed delivery of Valsartan in pulsatile coated tablet dosage form for treatment of cardiovascular diseases. It provides an, bed time administration with early morning burst effect. So, peak plasma concentration is obtained at an optimal time and early morning hypertensive complications can be minimized. Modern optimization techniques based on experimental designs are helpful tool to the formulator, as they help in developing the best possible formulation under a given set of conditions, thus saving considerable time and money.

MATERIALS AND METHODS

Valsartan was obtained as gift sample from Zim Laboratories, Nagpur. Eudragit L100 is obtained

from Evonik industries. Cross povidone, Crasscormilise sodium & Sodium starch glycolate were obtained as gift sample from Concept Pharma, Aurangabad. All other chemicals are purchased from SD fine chemicals.

Formulation of Core Tablets[9]

The core tablet of Valsartan were prepared by direct compression technique. Valsartan 80mg with different quantity of superdisintegrant Croscarmellose Sodium were mixed properly. It was then mixed with directly compressible diluents microcrystalline cellulose and final weight was adjusted with appropriate quantity of lactose. This mixed blend was lubricated with magnesium stearate and talc. The compression of tablet was done by using 10mm biconcave punch.

Formulation of Film Coated Tablet

Coating trials[10]

Various coating composition were used for screening of polymer or polymer composition for coating of core tablets.

Table 1: Composition of coating trial

Sr.No	Ingredients	P-1	P-2	P-3	P-4	P-5
1	Polymer	2% Ethyl cellulose	2% ethyl cellulose : eudragit L100 – 3:1	2% ethyl cellulose : eudragit L100 - 1:1	2% cellulose acetate	2% ethyl cellulose : eudragit L100 – 3:1
2	Dibutyl pthalate	0.2ml	0.2ml	0.2ml	0.2ml	0.2ml
3	Magnesium stearate	200mg	200mg	200mg	200mg	-
4	Ethyl alcohol q.s to make	100ml	100ml	100ml	100ml	100ml

Optimization of Formulation[11]

Table 2: Composition formulation

Ingredients	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Drug	80	80	80	80	80	80	80	80	80
Microcrystalline cellulose	150	150	150	150	150	150	150	150	150
Lactose	52	49	46	52	49	46	52	49	46
Croscarmellose sodium	**12**	**15**	**18**	**12**	**15**	**18**	**12**	**15**	**18**
Mag. Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total weight in mg	300	300	300	300	300	300	300	300	300
Coating level : Ethyl cellulose: Eudragit L100 (3:1)	4%	4%	4%	5%	5%	5%	6%	6%	6%

According to the results obtained from dissolution profile of the preliminary trails, the batch that showed desired lag time was selected for factorial studies, to optimize the effect of variables on

formulation. There after further studies with 3^2 full factorial design were carried out using two factors namely conc. of superdisintegrant (croscarmellose sodium) and coating level. The nine optimization batches F-1 to F-9 were prepared in 3^2 factorial design as per table 2.

Full factorial design[11]

A 3^2 randomized full factorial design was used in this study. In this design two factors were evaluated, each at three levels and experimental trails were performed at 9 possible combinations. The conc. of croscarmellose sodium (A) and coating level (B) were selected as independent variables. The rupture time of film(lag time), % cumulative release at 5 hr and % cumulative release at 7.5 hr were selected as dependent variable.

Table 3: Factorial design layout and coded values

Batch No.	Independent variable	
	A	B
F-1	-1(4%)	-1(4%)
F-2.	0(5%)	-1(4%)
F-3	+1(6%)	-1(4%)
F-4.	-1(4%)	0(5%)
F-5.	0(5%)	0(5%)
F-6.	+1(6%)	0(5%)
F-7	-1(4%)	+1(6%)
F-8	0(5%)	+1(6%)
F-9	+1(6%)	+1(6%)

Evaluation of Valsartan Film Coated Pulsatile Release Tablet

Tablet Thickness and diameter[12]

Thickness and diameter of core tablets were important for uniformity of tablet size. Thickness and diameter was measured using vernier callipers.

Tablet Hardness[12]

The resistance of tablet to breakage under conditions of storage, during transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by pfizer hardness tester. The hardness was measured in terms of kg/cm^2.

Friability[12]

Friability is the measure of coated tablet strength. Roche type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined.

% loss = Initial wt. of tablets – Final wt. of tablets /Initial wt. of tablets X 100

Uniformity of content[12]

Tablets were crushed and powder equivalent to weight of tablet was dissolved in methanol. Then suitable dilutions were made and drug content was calculated using absorbance at wavelength 249.2 nm.

Rupture time[10,13]

Tablets were tested using a USP dissolution type II apparatus with paddle speed 50 rpm, in 900 mL of 0.1 N HCl for two hours followed by pH 6.8 phosphate buffer at 37^0C. Rupture was detected by visual observation. The lag time was defined as the time point, when the coating ruptured due to swelling (n=6).

Water Uptake of Pulsed Tablet Measurements[10,13]

Water uptake by tablets was determined using the same conditions for rupture test. At predetermined time intervals, tablets were removed from the medium and weighed with an analytical balance after carefully removing the excess water on the surface of tablets with paper tissue. The %water uptake was calculated as follows:

$$\%\text{Water uptake} = (W_t - W_0)/ W_0 \times 100$$

Where W_t is weight of wet tablet at time t and W_0 is weight of dry tablet.

Scanning electron microscopy

The surface and cross-section of the pulsatile release film coated tablet was observed under scanning electron microscope to confirm the absence of any cracks on the surface and uniformity of coating.

In vitro dissolution study

The dissolution studies were performed according to the USP II, paddle, 75 RPM (elecrolab, model TDT-06PL) using 900ml of 0.1 N HCl at 37 ± 0.5 ^{0}C for first two hours. The same tablets were removed and placed in 900ml of phosphate buffer pH 6.8, at 37^0C ± 0.5 ^{0}C for further 6 hours. The samples were withdrawn at every 1,2 ,3 ,4 , 5, 6, 6.5, 7, 7.5 and 8 hours, properly diluted and filtered through whatman filter paper and analyzed UV spectrophotrometer at 250nm. An equal volume of fresh dissolution medium maintained at the same temperature was added after withdrawing each sample to maintain the volume.

RESULTS AND DISCUSSION

Evaluation of preliminary coating trail batches

The preliminary trail batches P-1 to P-5 were evaluated for the in vitro dissolution study, to study the effect of different polymer and polymer ratio on drug release profile. The core formulation containing 5 % superdisintegrant was used for preliminary trails

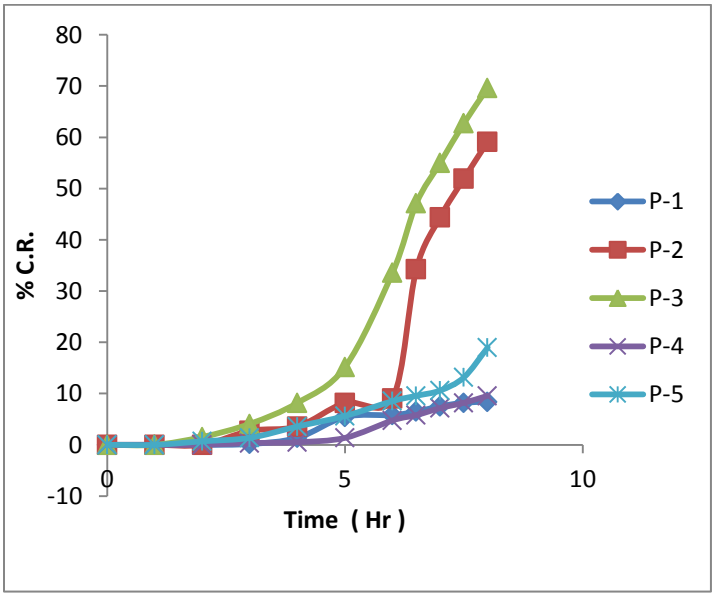

Figure 1: In- vitro release study of coating trail

From the above results it is observed that formulation coated with only ethyl cellulose shows longer lag time which was not desirable. If Eudragit L100 was used with ethyl cellulose in combination then it maintains desirable lag time (P-2). As Eudragit L100 is soluble at intestinal pH 6.8 it slowly get dissolves in intestinal media and forms the pores in the thick, strong film of ethyl cellulose. In the case when Eudragit L100 concentration is increase in combination with ethyl cellulose (P-3) the drug release before lag time was found to be more as drug release occurs due to diffusion as well as erosion, hence desired pulsatile effect was not observed in this case. Cellulose acetate was too rigid and also couldn't provide pulsatile release. A high sensitivity of the lag time on the ethyl cellulose coating level was observed. It would be desirable to develop a less sensitive or more robust system. Adding magnesium stearate to the ethylcellulose coating decreased the mechanical properties of cast films in the dry and wet state. Hence proper lag time is maintained in coating solution with magnesium stearate.

Evaluation of optimized batches

The batches developed as per 3^2 factorial design were evaluated for hardness, friability, weight variation, drug content , rupture time of film, SEM photographs and water uptake study.

Evaluation parameters for batches developed as per 3^2 factorial design is shown in table below.

Table 4: Evaluation of optimized batches F-1 to F-9

Formulation	Hardness(kg/cm^2)	Thickness (mm)	Diameter (mm)	Drug content (%)	Rupture time(min)
F-1	6.46 ± 0.057	4.42 ± 0	10.90 ± 0.005	98.95 ± 0.17	282
F-2	6.66 ± 0.152	4.41 ± 0.005	10.90 ± 0.005	99.16 ± 0.18	220
F-3	6.53 ± 0.057	4.41 ± 0.005	10.91 ± 0.01	99.27 ± 0.18	210
F-4	6.66 ± 0.057	4.43 ± 0.005	10.91 ± 0.005	98.64 ± 0.35	385
F-5	6.73 ± 0.057	4.43 ± 0.005	10.92 ± 0	98.95 ± 0.17	340
F-6	6.66 ± 0.057	4.44 ± 0.005	10.92 ± 0.005	98.74 ± 0.31	320
F-7	6.76 ± 0.057	4.48 ± 0.01	10.93 ± 0.005	98.22 ± 0.18	405
F-8	6.9 ± 0.1	4.47 ± 0.005	10.93 ± 0.015	98.75 ± 0.62	375
F-9	6.96 ± 0.057	4.48 ± 0	10.94 ± 0.005	98.85 ± 0.47	370

From the results it is observed that, the lag time of formulation which depends on rupture time of film, increases with increasing the conc. of croscarmellose sodium in the core tablet. Also the lag time increases with increases in coating level. The formulation F-5 showed the desired lag time of nearly six hours (n=6).

In vitro drug release study

The results shows that very less%, or no drug was released in first two hours in 0.1 N HCl. Valsartan was weakly acidic drug with pKa 3.9 to 4.7 as a result it is practically insoluble in acidic conditions. As pH increases from 4 above the solubility of Valsartan increases. In vitro release study reveals that, as the proportion of superdisintegrant croscarmellose sodium in core tablet was increased from 4% to 6% there was change in the rupture time in turn lag time of formulation from F-1 to F-9.It is observed that as the medium reaches core, crosscarmellose sodium get swelled and generates a pressure on the outer polymeric film of ethyl cellulose to rupture the film. The lag time was also controlled by coating level, as the coating level increases, lag time increases, as more pressure is needed to rupture the thicker film. The direct relation was found from optimization study applying 3^2 factorial design between the amount of croscarmellose sodium in core tablet and the coating level.

Table 5: *In vitro* drug release of batches F-1 to F-9

Time (Hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	0	0.26±0.19	0.47±0.14	0	0	0.098±0.07	0	0	0
3	2.10±0.0	4.31±0.26	4.65±0.19	1.305±0.26	2.84±0.17	3.91±0.17	0	1.07±0.17	1.13±0.09
4	3.23±0.34	46.59±0.19	53.07±0.09	2.32±0.09	4.94±0.170	5.34±0.09	1.35±0.17	2.55±0.17	2.89±0.17
5	44.49±0.5	61.81±0.2	64.55±0.19	3.922±0.17	7.50±0.26	44.44±0.09	2.83±0.19	3.58±0.19	5.68±0.19
6	54.08±0.3	71.82±0.19	71.10±0.09	5.404±0.35	52.40±0.19	55.85±0.09	4.14±0.09	8.75±0.09	45.±0.17
6.5	64.37±0.2	80.43±0.09	78.68±0.09	47.68±0.19	61.49±0.35	64.89±0.17	5.45±0.17	49.73±0.26	55.39±0.19
7	71.20±0.0	87.50±0.34	87.46±0.09	55.23±0.35	72.01±0.26	72.12±0.17	46.48±0.19	56.94±0.26	65.40±0.17
7.5	79.35±0.1	92.26±0.17	93.41±0.09	62.11±0.09	81.92±0.35	79.76±0.09	49.09±0.25	63.99±0.17	73.37±0.35
8	88.08±0.09	96.28±0.37	96.97±0.17	71.38±0.35	91.27±0.12	89.50±0.17	60.34±0.09	80.14±0.09	82.37±0.09

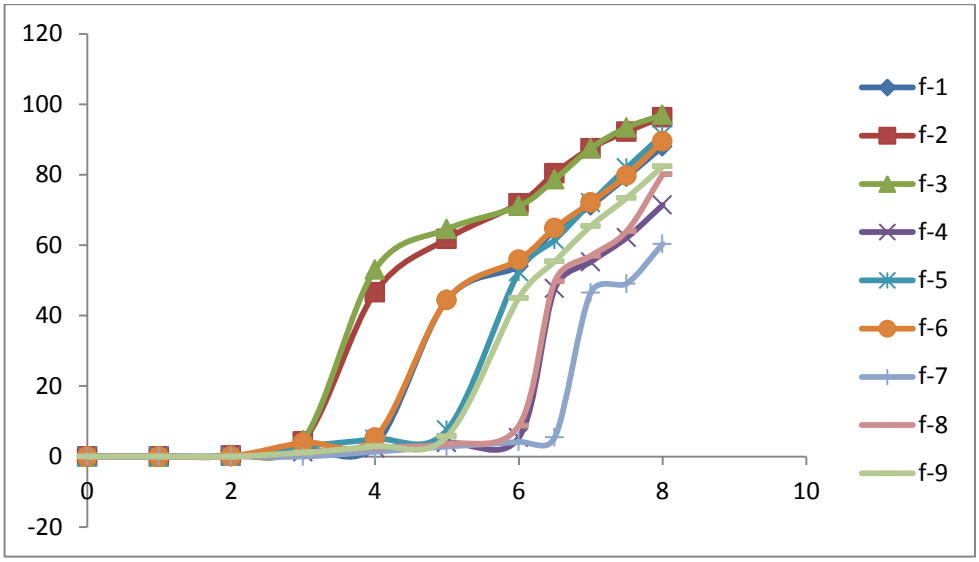

Figure. 2: In vitro release study of optimized formulations F-1 to F-9

Factorial Design

A 3^2 full factorial design was constructed to study the effect of conc. Croscarmellose sodium in core tablet (A) and ratio of coating level (B) on the rupture time or lag time of formulation, % C. R. at 5 hour and % C.R. at 7.5 hour. The three dependent variable rupture time of film which indicates the lag time and % C. R. at 5 hour which should be minimum and C. R. at 7.5 hour which should be maximum for pulsatile system were selected as dependent variable. The results were compiled in the table below.

Table 6: Factors and the response observed under study

Run	Factor 1 A: conc. of CCS (%)	Factor 2 B: coating level (%)	Response 1 Rupture time (min)	Response 2 % C. R. at 5 hr	Response 3 % C.R. at 7.5 hr
1	4	4	282	44.49	79.35
2	5	4	220	61.81	92.26
3	6	4	201	64.55	93.41
4	4	5	385	3.92	62.11
5	5	5	340	7.5	81.92
6	6	5	315	44.44	79.76
7	4	6	405	2.83	49.09
8	5	6	375	3.58	63.99
9	6	6	370	5.68	73.37

Various computations for the current optimization study were performed using, design expert® software. A two factor, three level full factorial design was used for systemic study of combination of conc. of croscarmellose sodium and coating level. A 3^2 full factorial design was constructed where the conc. of croscarmellose sodium (A) and coating level (B) were selected as

independent variable, i,e, factor. The level of these factor were selected on the basis of initial studies and observations. All the other formulation aspect and processing variables were kept invariant through the study period. Statistical validity of the polynomials was established on the basis of analysis of variance (ANOVA) provision in the design expert software. Level of significance was considered significant at $p< 0.005$. The best- fitting mathematical model was selected based on the comparison of several statistical parameters including the coefficient of variation (CV), the multiple correlation coefficient (R^2), the adjusted multiple correlation coefficient (adjusted R^2) and the predicted residual sum of square (PRESS) provided by the software. PRESS indicates how well the model fits the data and for the chosen model it should be small relative to the other models under consideration. The 3-D response surface graph and the 2-D contour plots were also generated by design expert software. These plots are very useful to see interaction effects of the factors on the response.

Full and reduced model assessment for the dependent variable

a) Full model for rupture time of film (lag time)

Full model equation is,

lag time = +336.89 -31.00 * A + 74.50 * B + 11.50 * A * B + 14.67 * A^2 - 37.83 * B^2

The Model F-value implies the model is significant.Values of "Prob > F" less than 0.0500 indicate model terms are significant.

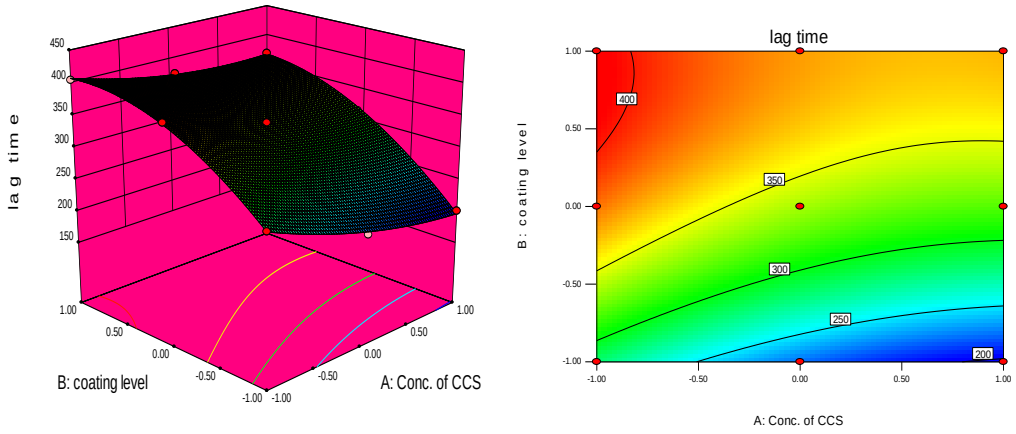

Figure. 3 :3D response curve & Counter plotof rupture time (lag time)

From the figure of the response curve of rupture time (lag time) for pulsatile system, it was observed that as the conc. of croscarmellose sodium increases from -1 level to 0 and +1 level, rupture time in turn lag time of valsartan pulsatile release tablet decreases significantly. Also as the coating level increases from -1 to 0 and +1 level , lag time increases significantly.

b)Full model for % cumulative release at 5 hour:

Full model equation is,

% CR at 5 hr = +16.38 +10.57 * A - 26.46 * B - 4.30 * A * B + 3.36 * A^2 + 11.87 *B^2

Values of "Prob > F" less than 0.0500 indicate model terms are significant.

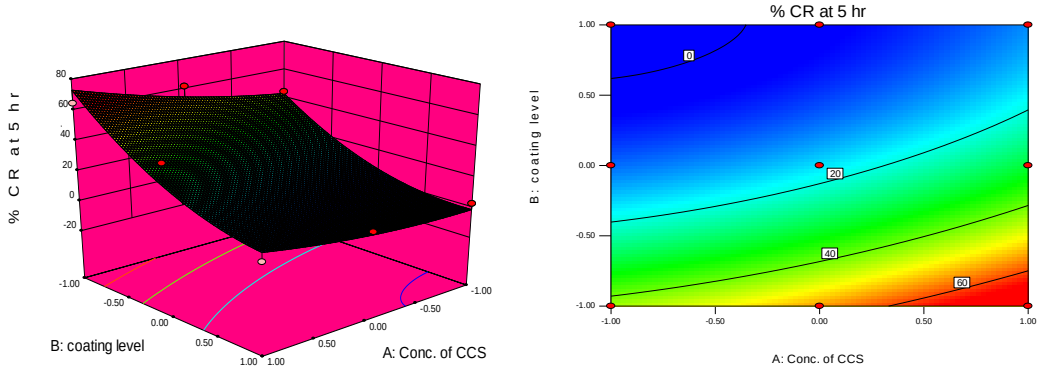

Figure.4 : D surface & 2D counter graph for response of % C.R. at 5 hour

From the figure of the response curve of % C.R. at 5 hr for pulsatile system, it was observed that as the conc. of croscarmellose sodium increases from -1 level to 0 and +1 level, % C. R. at 5 hr of valsartan pulsatile release tablet increases significantly. Also as the coating level increases from -1 to 0 and +1 level , % C.R. at 5 hr decreases significantly.But in this model response of % C.R. at 5 hr the independent variables were found to be not showing significant effect on dependent variable. Therefore model terms are insignificant in this case.

c)Full model for response % cumulative release at 7.5 hour:

Full model equation is,

% CR at 7.5 hr =+8.88 +0.56 * A -0.77 * B +0.20 * A * B -0.39 * A^2 + 4.086E-003 * B^2

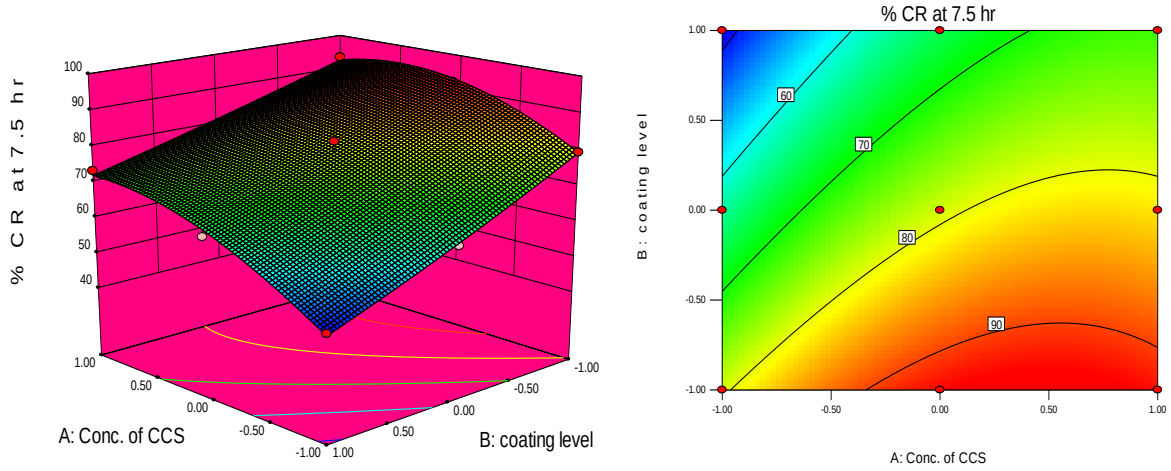

Figure 5: 3 D surface & 2 D counter graph for response for % C.R. at 7.5 hr

Validation of optimum formulation

In the results of comparison between the observed and predicted values of the different response, it can be seen that in all cases there was a reasonable agreement between the predicted and experimental values as % prediction error was found to be between 2.395 and – 2.654%. for this reason it can be concluded that the equation describe adequately the influence of the selected independent variables on the response under study. This indicates that the optimization technique was appropriate for optimizing pulsatile drug delivery formulation.

CONCLUSION

A satisfactory attempt was made to develop new pulsatile release enteric coated tablet of Valsartan using time and pH dependent polymer (ethyl cellulose and eudragit L100) and evaluated for in vitro characterization studies. From the results obtained from the experimental work it can be concluded that to achieve desired lag time & release profile coating was done by using time & pH dependent polymers like ethyl cellulose & Eudragit L100 in combination of 3:1. Appropriate factorial design and optimization technique can be successfully used in the development of pulsatile formulation based on conc. of super disintegrant in the core and coating level to achieve desired lag time. Factorial design concludes the adequate influence of selected independent variables on response under study. The formulation F-5 containing 5% of croscarmellose sodium in core tablet and 5% coating level of ethyl cellulose : eudragit L100 (3:1) was found to be showed desired lag time and drug release profile to achieve chronotherapy of hypertention.

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