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Formulation and Optimization of Chronotherapeutic Drug Delivery from Carvedilol Sulphate Compression Coated Tablets by using Design of Experiment Approach

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ABSTRACT

The aim of this present work was to develop and optimize compression coated tablet of carvedilol sulphate for chronotherapeutic application by response surface methodology based on 3^2 factorial designs. Compression coated tablet containing carvedilol phosphate in the core was formulated with an outer coat by eudragit L 100 and ethyl cellulose. The percentage weight ratio of ethyl cellulose to eudragit L 100 and coating level were selected as critical process parameters (CPPs), whereas critical quality attributes (CQAs) were lag time and cumulative percentage drug release at 8 hr in current study. For optimization, the effects of critical process parameters upon the critical quality attributes were modelled using the polynomial equations involving critical process parameters and their interactions for various critical quality attributes. A numerical optimization technique was adopted to achieve optimized formulation which was also used as the check point.The observed responses were closed well with the predicted values. The formulation exhibited pulsed release profile after a programmed lag time and thus suitable for chronotherapeutic delivery. The study demonstrated a successful optimized formulation followed by evaluation of compression coated tablet of carvedilol sulphate for chronotherapeutic drug delivery.

INTRODUCTION

During the past several decades, controlled release formulations have been developed for constant release rates to maintain drug concentrations in the human body, regardless of the patient's physiological condition. However, controlled-release preparations pose problems such as resistance, drug tolerance, and activation of the physiological system due to long-term constant drug concentrations in the blood and tissues. Numerous studies have been shown; safety and efficacy of drugs can be modified by the chronotherapeutic drug delivery with pulsatile release that matches the altered circadian rhythm resulting from a disease state (Hrushesky, 1994; Mastiholimath *et al.,* 2007; Lin and Kawashima, 2012; Bjorn, 1996)**.** Chronotherapeutic drug delivery systems (CDDS) are gaining importance, as these systems deliver the drug at specific time as per the pathophysiological need of the disease state, resulting in improved therapeutic efficacy and patient compliance. Diseases wherein CDDS are promising include nocturnal asthma, peptic ulcer, cardiovascular disease, arthritis and hypercholesterolemia. The pathophysiology of myocardial ischemia is at least two to three fold greater in between midnight and 9 a.m (Hausmann *et al.*, 1991; Mulcahy *et al.,* 1988; Rocco *et al.,* 1987). There are several approaches to develop chrono-therapeutic drug delivery system and among these methods compression coated tablets are the simplest to formulate which reduces the time and complicated coating or granulation process. Compression coated tablet may consist of immediate release core, coated by compression with polymeric barrier that slowly dissolve or disintegrates to make a lag time of drug release (Sunil *et al.,* 2011; Rane *et al.,* 2009). Carvedilol, a beta-adrenergic blocker without intrinsic sympathomimetic activity, that is safe and effective for treating hypertension, left ventricular dysfunction, and heart failure. The drug's half-life is 6–10 h and it is extensively metabolized by first-pass metabolism.

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Response surface methodology (RSM) is a collection of mathematical and statistical techniques useful for designing and optimising of pharmaceutical formulations, by minimum experimentation. Based on the principle of design of experiments (DoEs), the methodology objective is to optimize a *response* (output variable) which is influenced by several *independent variables* (input variables). The response surface methadology encompasses the use of various types of experimental designs, generation of polynomial equations and mapping of the response over the experimental domain to determine the optimum formulation

The purpose of this study was to develop pulsatile chronotherapeutic compression coated tablets containing carvedilol phosphate. Compression coated tablets containing carvedilol phosphate and other excepient in the core were formulated with an outer coat by Eudragit L 100 and ethyl cellulose. Eudragit L 100, an enteric polymer was selected for compression-coating because of its good flow properties, good compressibility and acid resistance. The problems of only enteric coated systems, such as a too short gastric resistance and premature release were improved by addition of water insoluble polymer ethyl cellulose(F. Lecomte *et al.*, 2003). Computer-aided optimization technique, using a 3^2 full factorial design, was employed to investigate the effect of 2 independent variables (percentage weight ratio of ethyl cellulose to eudragit L 100 and coating level) at three levels on lag time and drug release at 8 hour.

MATERIALS AND METHODS

Materials

Carvedilol was obtained as a gift from Cadila Pharmaceutical Ltd. Ahamadabad, India; Eudragit S 100 from Yarrow Chem Products, Mumbai, India; Ethyl cellulose (Ethocel 100) from Colorcon Asia Pvt.Ltd., Goa, India; Di calcium phosphate (DCP) from Signet Chemical Corporation, Mumbai, India); Sodium starch glycolate from Colorcon Asia Pvt.Ltd., Goa, India; Poly vinyl pyrrolidone (PVP K-30) from Loba Chemie Pvt. Ltd., Mumbai, India, and magnesium stearate from Loba Chemie Pvt. Ltd., Mumbai, India were received as a gift sample. The other materials were reagent grade bought from the market.

Experimental Design

3^2 (Two factor at three levels) full factorial design was used for optimization of pulsatile chronotherapeutic compression coated tablet containing carvedilol phosphate. Design-Expert 7.0.0 software (Stat-Ease Inc., USA) was used for mathematical modelling, evaluation of the ability to fit to the model and response surface modelling. Percentage weight ratio of ethyl cellulose to eudragit L 100 (X_1) and coating level (X_2) were selected as the independent variables whereas lag time (the time required for drug release up to 10%) (*Y*1) and cumulative percentage drug release incomplete 8 h (*Y*2).Levels for two factors are presented in Table 1.Table 1summarizes the matrix of the design.

Table. 1: Factorial design layout.

Formulation	Variables in coded Form		Lag time	Cumulative drug release at 8 hr
	X1(%)	X2(%)		
CCT 1	-1	-1	122	97.43
CCT 2	-1	0	148	97.12
CCT 3	-1	1	168	80.42
CCT 4	0	-1	181	97.1
CCT 5	0	0	206	96.05
CCT 6	0	1	232	57.3
CCT 7	1	-1	268	74.12
CCT 8	1	0	282	56.93
CCT 9	1	1	327	21.68
CCT 10	**19.34**	**31.03**	**263.50**	**75**
Coded Value	**Actual Value (%)**			
	X1		**X2**	
-1.000	**0**		**25**	
0.000	**10**		**50**	
1.000	**20**		**75**	

X1 indicates weight ratio of ethyl cellulose to eudragit L 100 (%); X2, coating level *(%w/w of core).*

Formulation of compression coated tablet

Preparation of core tablet

Carvedilol phosphate tablet core were prepared by direct compression. Carvedilol phosphate & excipients were weighed as per formulae given in Table 2 and then passed through a sieve No 120. Carvedilol phosphate, Di calcium phosphate, Sodium starch glycolate and Poly vinyl pyrrolidone were mixed in geometric proportion and blended for 30 minute. To this homogeneous blend, magnesium stearate (1% w/w) and talc (2% w/w) were added and blended for 10 minute. Core tablets (diameter, 6 mm; average tablet weight, 80mg) were compressed within 6 mm of punches on Cadmach 16 station compression machine under a common compression force of 3-4 Kg/cm^2.

Table. 2: Composition of core tablets of Carvedilol phosphate.

Ingredient	Quantity (mg)
Carvedilol phosphate	6.25
Di calcium phosphate	46.25
Poly vinyl pyrrolidone (PVP K-30)	10
Sodium starch glycolate	10
Talc	2.5
Magnesium stearate	5

Preparation of compression coated tablet

Six mm diameter drug cores were compression-coated into coated tablets with coating level 25 %, 50 % and 75 % based on the experimental design. The weight ratios of Eudagit L 100 to ethyl cellulose were 100:0%, 90:10% and 80:20% (w/w) based on the experimental design. Compression coated tablet were prepared by first filling half of the polymer blend in the die cavity, then centrally positioning the tablet core on the powder bed followed by filling the remaining half of the polymer blend on top. Then compressed Cadmach 16 station compression machine with a compression force to obtain tablets with hardness in the range of at 6-7 Kg/cm^2 (Sunil *et al.*, 2013, Rane *et al.*, 2009).

Drug Release Study

To verify how composition of the coat and core to coat ratio interfere drug release profile of tablet were studied using USP

XXXIII type II apparatus (Paddle apparatus TDL 08 L; Electrolab India Pvt. Ltd., Mumbai, India) in 900ml medium at 37±0.5 ^{0}C at a rotation speed of 100 rpm. With the medium change method, the release was performed in pH 1.2 for 2 h followed by pH 6.8 containing 1% sodium lauryl sulphate for 10 hr. Five millileter sample was withdrawn at pre determined time interval (1, 2, 3,4,5,6,8,10 and 12 hr) and replaced by the fresh dissolution medium. All the samples were filtered and analyzed by UV spectrophotometer (Shimadzu UV-2450, UV–Vis scanning spectrophotometer, Japan) at wavelengths of 241 nm The lag time was taken as the time of <10% drug released(Rane *et al.,* 2009).

Statistical analysis and validation of design

Statistical analysis and validation of model were performed using Design-Expert 7.0.0 software (Stat-Ease Inc., USA). The responses were analyzed using one way ANOVA, the individual response parameters were evaluated using F test and polynomial equation was generated for each response using multiple linear regression analysis (MLRA). 3D and contour response plots were constructed using Design-Expert software. By utilizing Design-Expert 7.0.0 software, one final formulation corresponding to the predicted optimum polymer and coating level were prepared to determine the validity of the model generated. afterward, the observed experimental data of the response properties were quantitatively compared with those of the predicted values.

RESULT AND DISCUSSION

The aim of present work is to design a new pulsatile, compression coated tablet, for the better treatment of cardiovascular disease. The system was formulated into two steps: first, core tablet was prepared containing carvedilol phosphate; second, core tablet were coated with polymer blend of eudragit L 100 (enteric polymer) and ethyl cellulose (water insoluble polymer).

3^2 factorial design experiments

To fabricate a system with time-lagged coating of enteric polymer with erodible polymer, coating level (Core to coat ratio) and composition of coating blend are critical process parameters (CPPs), whereas lag time and cumulative percentage drug release in 8 h are critical quality attributes (CQAs).

A 3^2 factorial design was used to found the optimum coating composition and coating level to achieve a pulsatile release pattern from a time-lagged compression coated tablet. A total of 9 trial formulations were proposed by 3^2 factorial design for two independent variables at three level (table 1). All the batches of compression coated pulsatile tablet were evaluated for drug release study (Figure 1).

Overview of the experimental trial and observed responses are presented in Table 1. The responses were analyzed using one way ANOVA and Polynomial models including interaction and quadratic terms were generated for each response variables using multiple linear regression analysis (MLRAs). The polynomial equation generated by this experimental design was as follows:

$$Yi = bo + b1X$$

$$Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where y_i is the dependent variable, b_0 is the arithmetic mean response of the 9 runs; and b_1 and b_2 are the estimated coefficients for the independent factors X_1 and X_2, respectively. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are including investigating nonlinearity. The result of the analysis of variance (ANOVA) for responses *Y*1 and *Y*2 ($P > 0.05$) were shown in table 3. The F value in the ANOVA table was the ratio of model mean square (MS) to the appropriate error (i.e. residual) mean square. The larger the F value and the more likely that the variance contributed by the model was significantly larger than random error. The model F-value and high R square values suggested that these models were significant.

Table 3 indicate that significant factors affecting the response lag time (*Y*1) were synergistic effect of the linear contribution of main effects *X*1 and *X*2 without producing any interaction. The response drug release in 8 hr (*Y*2) was significantly affected by the main effects (*X*1 & *X*2), quadratic contribution (X_1^2 and X_2^2) as well as cross-product contribution (interaction effects) of both the main effects *X*1 and *X*2.

Table. 3: Result of Analysis of variance (ANOVA).

For lag time					
Regression	**Df**	**SS**	**MS**	**F**	**R^2**
	2	36176.17	18088.08	201.46	0.9965
Residual					
	6	538.72	89.79		
For Cumulative drug release at 8 hr					
	5	5380.40	1076.08	58.27	0.9898
Residual					
	3	55.40	18.47		

DF indicates: degrees of freedom; SS, sum of squares; MS, mean of squares; F, ischer's ratio; R^2 , regression coefficient..

Table. 4: Summary of results of regression analysis.

For lag time						
Response	**b_0**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
	203.44	73.17	26.00	3.25	12.83	4.33
P value		0.0001	0.0023	0.3955	0.0700	0.4198
For Cumulative drug release at 8 hr						
	91.50	-20.37	-18.21	-8.86	-12.20	-12.02
P value	-	0.0014	0.0019	0.0259	0.0277	0.0288

The results of multiple linear regression analysis (table 4) reveal that both the coefficient b_1 and b_2 bear a positive sign for lag time (Y1). Therefore, increasing the ethyl cellulose content and coating level was expected to prolong lag time. For response drug release at 8 hr (Y2), both the coefficient b_1 and b_2 bear a negative sign; indicate antagonistic effect of both independent variables (X1

& X 2). Therefore, an increase in ethyl cellulose content and coating level leads to decrease in cumulative drug release in 8 hr. The polynomial equation for each response variable was as follow:

$$Y_1 = 214.89 + 73.17X_1 + 26.00X_2$$

$$Y_2 = 91.50 - 20.37X_1 - 18.21X_2 - 8.86X_1X_2 - 12.20X_1^2 - 12.02X_2^2$$

Three-dimensional response surface plots and corresponding contour plots to study the effects of the two factors on lag time and cumulative drug release at the end of 8 hr were presented in Figure 2 and 3. Fig. 2 indicates a linear synergistic relationship between the two factors on response lag time (*Y*1) as was also observable from the one way ANOVA (*p*-values) listed in Table 3.The addition of ethyl cellulose prolong the lag time because ethyl cellulose significantly retarded the erosion of the Eudragit L 100 coating and decrease in solvent uptake. Results of the mathematical model indicate that the effect of weight ratio of ethyl cellulose to eudragit L 100 (X_1) was more significant than coating level (X_2). Fig. 3 showed curvilinear relationship for cumulative drug release at the end of 8 hr (Y 2) with 'a region of maxima' lying between the lower to intermediate to levels of both the factors. This was attributed to the occurrence of interaction between two independent variable (factor) as was also shown by the one way ANOVA result (table 3). Result of equation indicates the effect of *X*1 (weight ratio of ethyl cellulose to eudragit L 100) was slightly more significant than *X*2 (coating level), Moreover, both factor have a negative effect on cumulative drug release at the end of 8 hr (Y 2).As ethyl cellulose content increases, decrease in medium uptake of the coating membrane with less pores for the effective drug diffusion. Decrease in dissolution rate due to less porous diffusion path length while increase in coating level. To develop an optimized formulation a numerical optimization technique based on the desirability approach was adopted. In this study optimization was performed with constraints for responses and factors as shown in Table 5 and figure 4. The optimal calculated parameters were independent variable X_1 (weight ratio of ethyl cellulose to eudragit L 100) and X_2 (coating level) for formulation of optimize formulation were 19.34% & 31.03% respectively (Table 1&5). The observed value of Y1 (lag time) and Y2 (cumulative drug release at the end of 8 hr) of check point batch/optimize formulation were in close agreement with the value predicated by model.

Table. 5: Optimization of Compression coated tablet.

Constraints				
Name		**Goal**	**Lower limit**	**Upper Limit**
Weight ratio of ethyl cellulose to eudragit L 100		In range	0	20
Coating Level		In range	25	75
Lag time (min)		In range	210	270
Cumulative drug release at 8 hr (%)		Target ≥ 75	21.68	97.43
EM (Mpa)		minimize	0.34	1.0
SOLUTION (CCT 10)				
Weight ratio of ethyl cellulose	**Coating Level**	**Lag time (min)**	**Cumulative drug release at 8 hr (%)**	**Desirability**
19.34	31.03	263.50	75	1.00

CCT 10 used as checks point and optimized batch.

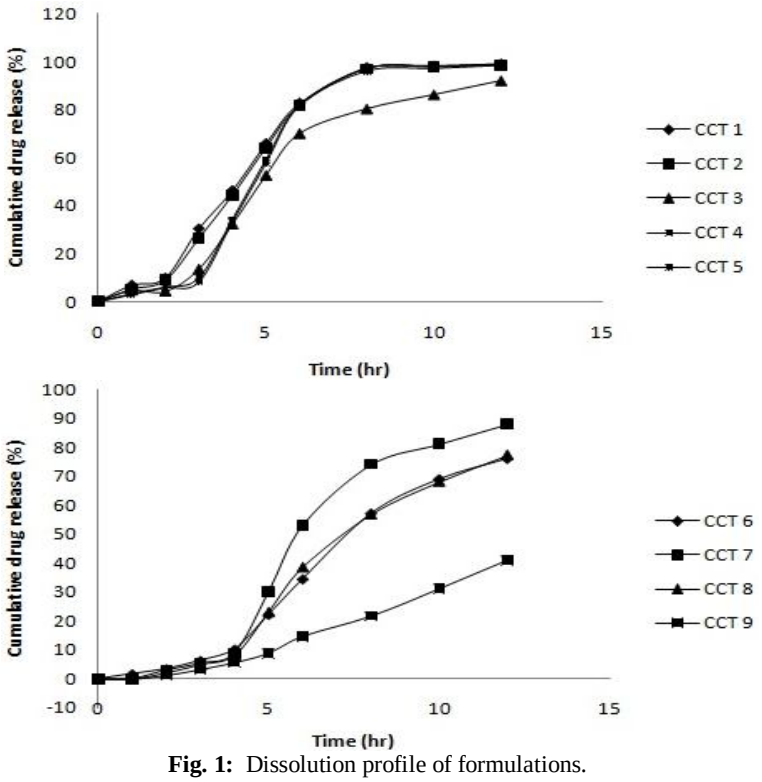

Fig. 1: Dissolution profile of formulations.

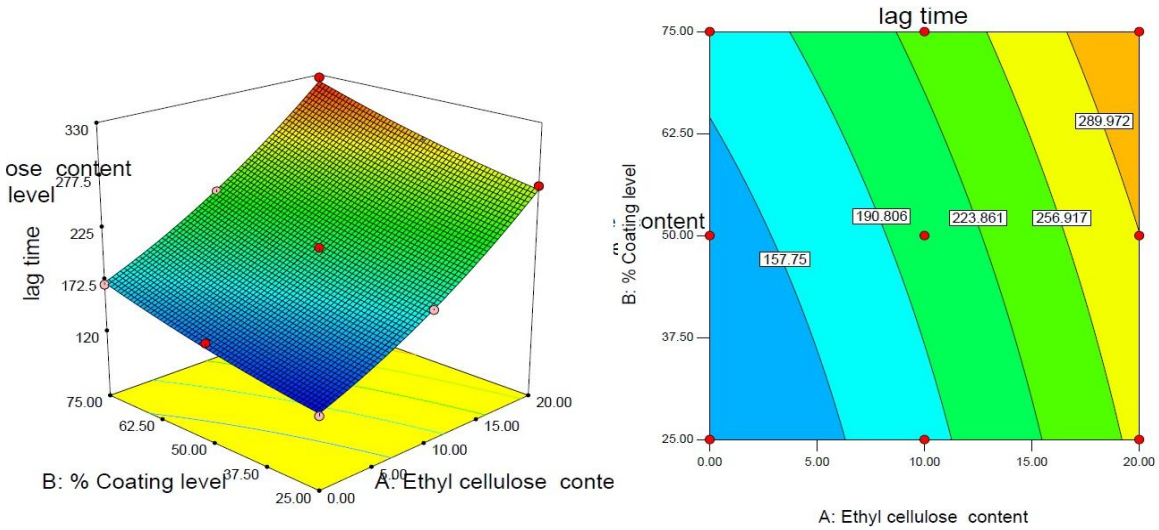

Fig. 2: Response surface plot showing the influence of percentage weight ratio of ethyl cellulose to eudragit L 100 and coating level on lag time and corresponding contour plot showing the relationship between various levels of 2 critical process parameters (CPPs).

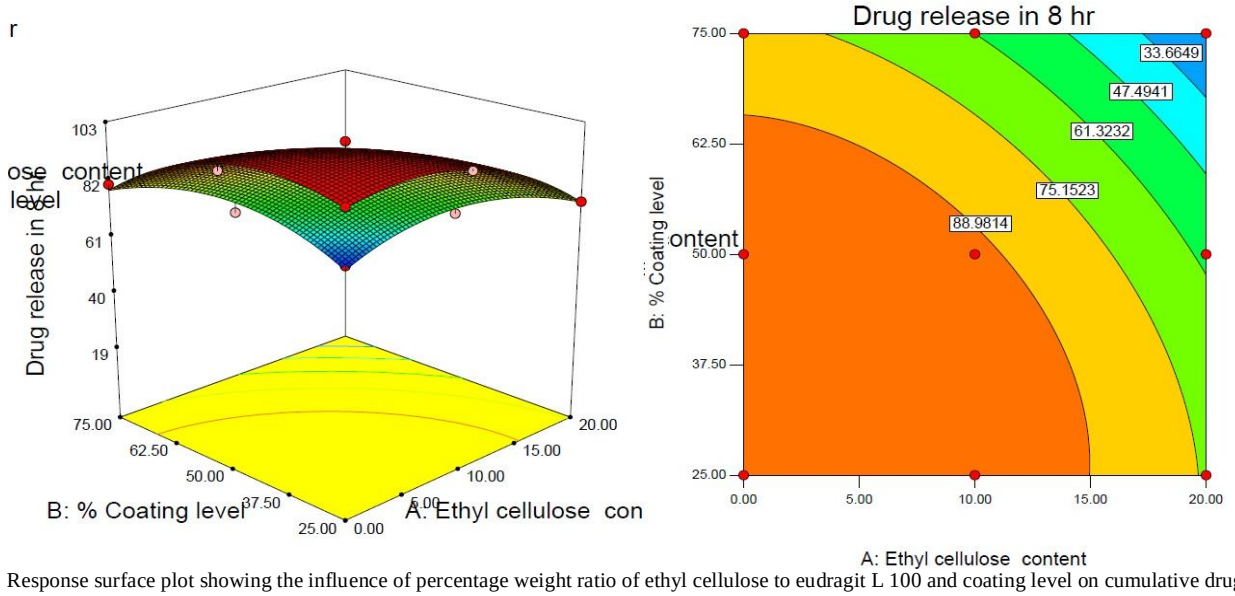

Fig. 3: Response surface plot showing the influence of percentage weight ratio of ethyl cellulose to eudragit L 100 and coating level on cumulative drug release at 8 hr and corresponding contour plot showing the relationship between various levels of 2 critical process parameters (CPPs).

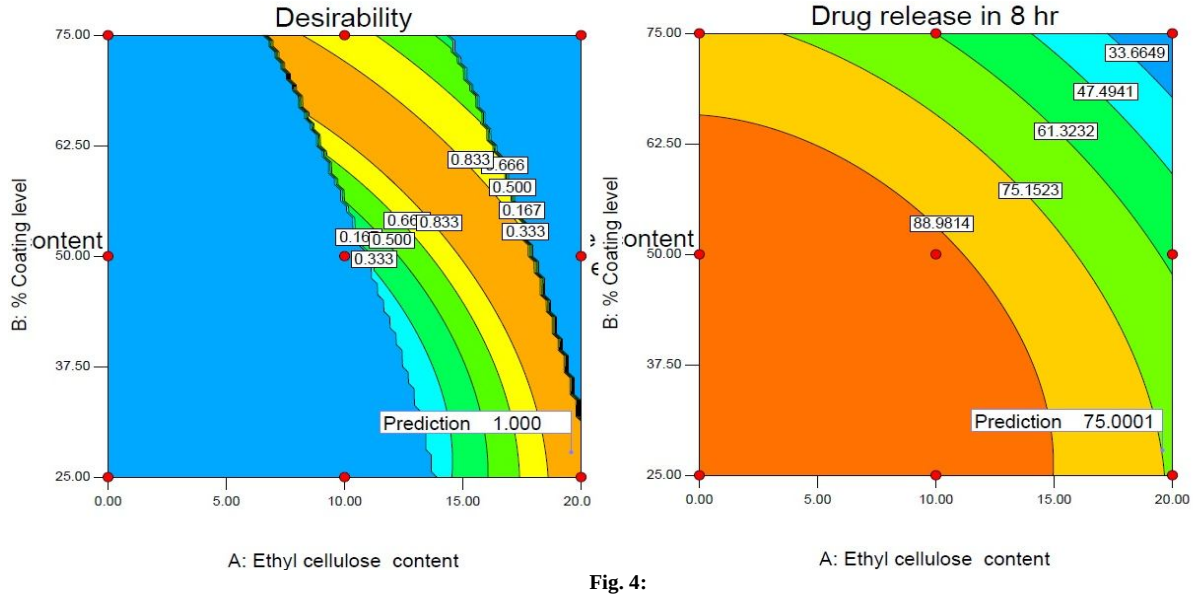

Fig. 4:

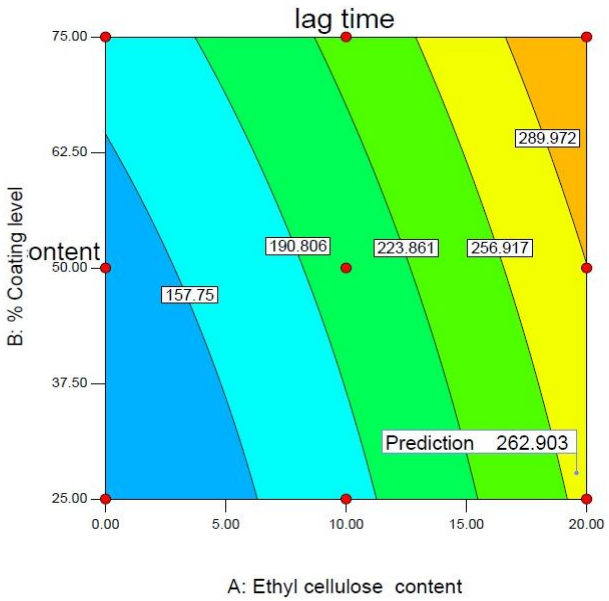

Fig. 4: Response surface predication plot Desirability, lag time and cumulative drug release at 8 hr.

CONCLUSION

The use of blend of water insoluble and enteric polymeric barriers with erodible characteristics in the dry coating of cores allows the production of 'chronotheraputic' pharmaceutical dosage forms. Compression coated tablet proved to be successful to provide the desired pulsed release profile after a programmed lag time. The 3^2 factorial design was used to optimize the formulation. The three-dimensional response surface plots and corresponding contour plots relating *Y* 1(lag time) and Y 2 (cumulative percentage drug release at 8 hr) indicated the synergistic effect on *Y* 1(lag time) and antagonistic effect on Y 2 (cumulative percentage drug release at 8 hr) with the increase in X 1 (weight ratio of ethyl cellulose to eudragit L 100) value and X 2 (coating level) value. The optimized formulation with 19.34 % ratio of ethyl cellulose with eudragit L 100 at 31.03 % coating level showed 267 minute lag time (Y1) and 76.2 % cumulative drug release after 8 hr (Y 2). Thus the formulation can be considered as one of the promising tool for chronotherapeutic management of cardiovascular diseases with improved patient compliance.

Declaration of Interest

The authors declared that there is no conflict of interest in the manuscript

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