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Formulation and Optimization of Compress Coated Pulsatile Tablet of Doxofylline for Chrono Pharmaceutical Approach for Treatment of Nocturnal Asthma

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ABSTRACT

Doxofylline, a new generation xanthine derivatives, is mainly used for treatment of asthma. The drug has less extra-respiratory effects than that of theophylline. The present investigation is aimed to formulate a pulsatile drug delivery system with time of administration between 9:30 to 10 p.m. with a lag time of about 6 hr. The developed formulation is expected to release the drug after 4 a.m. when symptoms of nocturnal asthma are exacerbates. Core tablet was prepared by direct compression method and sodium starch glycolate used as super disintegrant. The core tablet was compression coated with different ratio of HPMC K4M and HPMC E50LV. 32 Full factorial design was used for optimization of barrier layer. Total amount of polymer (X1) and % of HPMC K4M (X2) were selected as independent variables. The lag time (t10) and percentage drug release at 7th hour and time require for release 90 % of drug were selected as dependent variables. Tablets were evaluated for hardness, friability, weight variation, drug content and *in vitro* drug release. Formulation F6 containing 6 % sodium starch glycolate coated with 25 % of HPMC K4M with 150 mg coat weight was considered optimum because it showed desired lag time of 6 hours.

INTRODUCTION

Over recent years, controlled drug delivery systems have acquired very important role in pharmaceutical Research and Development (R&D) business, because these dosage forms offer many advantages over the conventional drug delivery systems; such as nearly constant level of drug at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency (1). However, there are certain disease conditions for which such a release pattern is not suitable. These conditions demand release of drug as a "pulse" after a predetermined lag time that ideally matches the biological requirement of given disease therapy. Such a release system is known as pulsatile drug delivery systems (2). Nowadays, pulsatile system is gaining a lot of interest as it is increasing patient compliance by means of providing time and site-specific drug delivery system, thus providing better and temporal delivery of drugs (3).

Through a number of clinical trials and epidemiological studies, it is well documented that the levels of disease activity of number of clinical disorders have a pattern associated with the circadian rhythm of the body. Circadian rhythm regulates many functions in human body like metabolism, physiology, behaviour, sleep pattern, hormone production. There are number of disease conditions which show circadian pattern and advantage of these conditions could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Diseases such as cardiovascular, asthma, peptic ulcer, arthritis etc. follow the body's circadian rhythm (4).

All these acted as push for the development of pulsatile drug delivery which release the drug after a predetermined lag time means during certain period of time there is no release of drug after that rapid and complete of drug that ideally match the circadian pathophysiology of particular disease (5).

Nocturnal asthma is a condition prevalent in two-thirds of the asthmatics. It is defined as a variable night time exacerbation of the symptoms like wheezing, shortness of breath, chest tightness, increased airway responsiveness and worsening of lung function. These symptoms typically occur between midnight and 8 am, especially around 4.00 am (6). It is inconvenient to take the medication at midnight because patient is sleeping. The maintenance of constant drug

level is not always desirable for the optimal therapy. A drug should be delivered only when and/or where it is needed at the minimum required dose (7).

Thus present study attempts to design & evaluate a chronomodulated drug delivery system of Doxofylline, a methylxanthines derivatives used for treatment of nocturnal asthma. It was aimed to have a lag time of 6 hours means if the system is taken at the bed time around 10 am then it is expected to release the drug after a period of 6 hours, at the 4 am when the asthma attacks are more exacerbates. Such time controlled pulsatile system can be formulated mainly with drug containing cores coated with various erodible polymers. Because coating of polymer to the core, it protect the core from the environment e.g. water, acidic pH and enzymes until the drug is released after a predetermined lag phase. The coatings can erode/dissolve rupture or alter their permeability at the required time (8).

Doxofylline is a next generation methylxanthine derivative with potent bronchodilator, mucosecretolytic and anti-inflammatory property. Doxofylline is chemically designated as 7-(1, 3-dioxolar-2-ylmethyl)-theophylline, a xanthine which has a dioxolone group in position 7.

Doxofylline has less affinity towards adenosine A1 and A2 receptors when compared with theophylline. Because of this Doxofylline has been shown to have better efficacy with fewer side effects than theophylline which shows a narrow therapeutic index, so it requires routine monitoring of blood levels whereas Doxofylline produces stable serum concentrations (9). Moreover, unlike theophylline, Doxofylline does not interfere with calcium influx into cells nor antagonizes the action of calcium channel blockers. Because of this, Doxofylline has less cardio-stimulant effects than Theophylline (10).

Thus, this study focus on the development of press coated pulsatile tablet of Doxofylline for providing the relief from nocturnal asthma. For optimization of the formulation 32 full factorial design were employed to investigate the effect of two factors which is total amount of coating and % of HPMC K4M because they affect the lag time and cumulative release of pulsatile drug delivery system.

MATERIALS AND METHODS

Materials

Doxofylline IP was gifted by Trio pharmaceutical Pvt. Ltd, Ahmadabad, India. HPMC K4M and HPMC E50LV were obtained from Coral Chemical, New Delhi, India. Microcrystalline cellulose and Sodium starch glucolate were procured from Molychem, Mumbai, India.

Methods

Identification of drug

Identification of Doxofylline was carried out by Infra-Red Absorption Spectroscopy (FT-IR) and compared with standard IR spectrum of Doxofylline

Preformulation studies

Bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose were performed for core powder blend (11).

Drug – excipients compatibility studies

Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product.

A) Fourier Transform Infra-red Spectroscopy (FTIR)

FT-IR spectra (400-4000cm^{-1}) of Doxofylline, other excipients used in formulations and physical mixture were obtained on a Thermo scientific FT-IR spectrophotometer. Samples were prepared by KBr pellet technique by mixing weighed amount of drug (3 mg) with 100 mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and subjected to compress under 10 ton pressure in a hydraulic press to form a transparent pellet. Similar procedure is followed for all other excipients and physical mixture used (12).

B) Differential Scanning Calorimeter (DSC)

Differential scanning calorimetry study was carried out using Differential Scanning Calorimeter (Shimadzu DSC- 60). Samples were heated in an aluminium sample pans at a rate of 10°C/min over a temperature range of 35 to 350 °C under a nitrogen flow of 50 ml/min.

Formulation of press coated tablet

Formulation of core tablet by direct compression method

Core tablet of Doxofylline was prepared by direct compression method using the composition as shown in below table.

Table 1: Composition of core tablet

Ingredients(mg)	Batch code		
	C1	C2	C3
Doxofylline	400	400	400
Sodium starch glycolate	9	18	27
Microcrystalline cellulose	36.5	27.5	18.5
Magnesium stearate	2.25	2.25	2.25
Talc	2.25	2.25	2.25
Total	450	450	450

All ingredients used in formulation including Doxofylline, SSG and MCC were passed through a #40 sieve and dry blended for 15 minutes. Pre-lubricated this dry mixed blend with pre-sifted talc through #40 sieve and mixed for 5 minutes. Lubricated this blend with pre sifted magnesium stearate through #60 sieve and mixed for 3 minutes.

Final lubricated blend was directly compressed using 9.5 mm round, concave punch by using rotary tablet compression machine (Hardik Eng. Pvt. Ltd, Ahmadabad, India) (13,14).

Development of Press-coated tablets

The core tablet was compression coated with different quantities of coating material containing different ratio of HPMC K4M and HPMC E50LV. Powder blend for press-coated tablet was prepared by dry blending together different compositions of the HPMC.

Half the quantity of the coating polymer was placed in the die cavity; the core tablet was carefully placed in the centre of the die cavity and filled with the other half quantity of the coating polymer. The coating material was compressed using 11 mm flat punch by using rotary tablet compression machine (Hardik Eng. Pvt. Ltd, Ahmadabad, India) (12,15,16).

Table 2: Compression coat formula for different tablet batches

Ingredients*	Core tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet	450	450	450	450	450	450	450	450	450	450
HPMC E50 LV	-	25	50	75	37.5	75	112.5	50	100	150
HPMC K4M	-	75	50	25	112.5	75	37.5	150	100	50
Total	450	550	550	550	600	600	600	650	650	650

Formulation optimization

In this study, a 32 full factorial design was used for the optimization by using STATISTICA® 7 (StatSoft® Inc.) software. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations (17). Two independent variables i.e. X_1: Total amount of polymer and X_2: % of HPMC K4M were selected against three dependent variable Y_1: Lag time (t_{10}), Y_2: Drug release at 7^{th} hour, Y_3: Times require for 90 % drug release for optimization.

Table 3: Formulation Design layout for 32 full factorial design

Batch code	Coded value		Actual value	
	X_1	X_2	Total amount of polymer (mg) X_1	% of HPMC K4M X_2
F1	-1	+1	100	75
F2	-1	0	100	50
F3	-1	-1	100	25
F4	0	+1	150	75
F5	0	0	150	50
F6	0	-1	150	25
F7	+1	+1	200	75
F8	+1	0	200	50
F9	+1	-1	200	25

Evaluation of compress coated tablets

Core and compress coated tablets were evaluated for post compression parameters such as weight variation, thickness, hardness, friability test, content uniformity test and *in vitro* drug release study (18,19).

Weight variation

Weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meet USP-XXIX test if no tablet differs by more than two times of percentage deviation.

Hardness and Thickness

For each formulation, the hardness of 10 tablets was determined using Monsanto hardness tester and thickness of 5 tablets was determined using vernier caliper.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula, % Friability=Initial weight−Final weight Initial weight X 100

Drug content

10 tablet of Doxofylline were taken and crushed. Amount of the powder equivalent to 10 mg of Doxofylline was dissolved in 100 ml of distilled water, filtered, diluted suitably and analysed for drug content at 273 nm using UV-spectrophotometer (20).

***In vitro* dissolution study**

In vitro dissolution study was performed using USP Type I dissolution apparatus (Basket type) at speed of 100 rpm. 0.1 N HCl of pH 1.2 was first used for 2 hr, which was then replaced with phosphate buffer pH 6.8 and kept up to 12 hr. Aliquot of dissolution medium (5 ml) were withdrawn at specific time intervals of 1 hr and filtered each with Whatman filter paper. Equal amount of fresh dissolution medium was replaced immediately after each withdrawal. The amount of drug present in each sample was determined by UV-spectrophotometer at 273 nm.

RESULTS AND DISCUSSION

An absorption maximum was determined by scanning different concentration of solution of Doxofylline. It was found to be 273 nm and method obeys Beer's law in concentration range 5 to 25 µg/ml, R2 was found to be 0.998.

Pre-compression evaluation like angle of repose, bulk density, tapped density; % compressibility and Hausner's ratio of core powder blend are shown in below table

Table 4: Pre-compression parameters of core powder blend

Parameters	Observation (n = 3)
Angle of repose (radian)	30±1.032
Bulk density (gm/ml)	0.685±0.004
Tapped density(gm/ml)	0.806±0.009
Carr's index	15±0.025
Hausner's ratio	1.17±0.125

The values of pre-compression parameters of core powder blend were within prescribed limit as per USP XXVII and indicate good flow properties.

FT-IR spectra of Doxofylline, other excipients used in formulations and physical mixture are shown in below Figure 1. The DSC thermo grams of pure drug and final formulation are shown in below Figure 2.

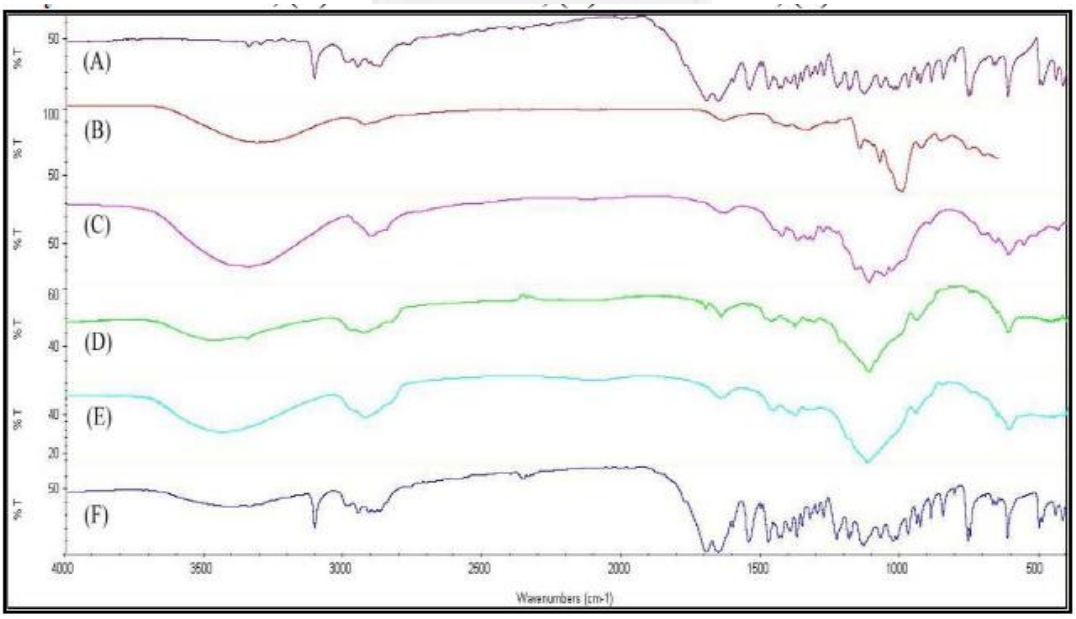

Figure 1: FT-IR spectra of (A) Doxofylline, (B) Sodium starch glycolate, (C) Microcrystalline cellulose, (D) HPMC E50 LV, (E) HPMC K4M, (F) Final formulation

In the FT-IR spectrum of Doxofylline the characteristic peaks corresponding to an amide C=O stretching (1658 cm^{-1}), N-H stretching (3109 cm^{-1}), C-N stretching (1027 cm^{-1}), Ketone group (1698 cm^{-1}) were identified, which were same in all drug and final formulation. Thus there was no any interaction between drug and excipients.

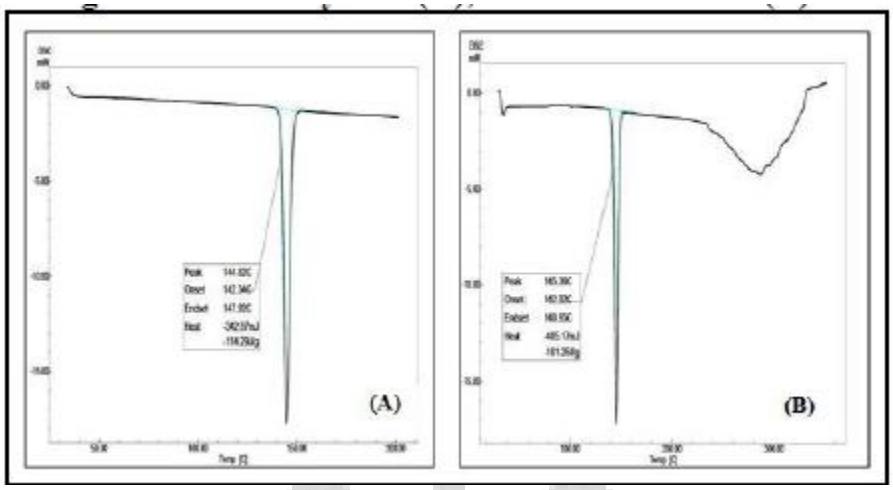

Figure 2: DSC thermograms of Doxofylline (A), final formulation (B)

In DSC thermogram, Doxofylline showed a melting peak at 144.8^{0}C with an enthalpy of fusion (ΔH) of -342.87 mJ. Negative values of enthalpy indicated that the process was endothermic. This characteristic peak of Doxofylline was also observed in final formulation indicate that there was no interaction of drug with the excipients.

Core tablet (C1- C3) was characterized for post compression parameters like weight variation, thickness, hardness, friability, drug content and *in vitro* disintegration time.

Table 5: Post-compression parameters of core tablet

Batch code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability	Drug content	*In vitro* disintegration time (sec)
C1	452 ± 2.15	5.69±0.4	3.3±0.67	0.45±0.07	97.3± 1.24	30±2.98
C2	448 ± 2.47	5.64±0.35	3.4±0.84	0.47±0.05	96.8± 1.87	24±2.87
C3	453 ± 2.34	5.65±0.23	3.1±0.42	0.49±0.04	98.4± 1.4	18±2.94

From the result of post compression parameters of core tablet, deviation in weight is less than 5 % indicated that there was no significant weight variation in the core tablets. Hence, all the tablet formulations passed the USP-XXIX weight variation test. The hardness test indicates good mechanical strength. Friability of all formulation was less than 1 %, which indicates the tablets had good mechanical resistance. Drug content was found to be uniform in all formulations. From the result of *in vitro* disintegration time of core tablet it was found that as the percentage of super disintegrants increased (2 to 6 %), the disintegration time decreased. Minimum disintegration time (18 ±2.94 sec) was observed with formulation C3 containing 6 % sodium starch glycolate. So the formulation C3 containing 6 % sodium starch glycolate is selected as optimized core tablet for further preparation of compress coated tablet.

Compress coated tablet (F1- F9) was characterized for weight variation, thickness, hardness and friability. Results are shown in below table

Table 6: Post compression parameters of press coated tablet

Formulation	Weight variation(mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability
F1	551.66±2.95	5.52±0.32	6.8±0.68	0.32±0.05
F2	552.25±3.05	5.7±0.07	6.9±0.84	0.39±0.08
F3	548.59±2.87	5.72±0.17	6.8±0.26	0.34±0.09
F4	603.27±2.54	6.06±0.16	7.3±0.37	0.45±0.05
F5	605.2±3.48	6.12±0.12	7.4±0.72	0.38±0.06
F6	601.45±2.97	6.19±0.09	7.2±0.89	0.47±0.07
F7	648.75±3.24	6.76±0.04	7.5±0.41	0.49±0.04
F8	653.2±2.84	6.75±0.02	7.6±0.34	0.41±0.06
F9	650.87±2.74	6.68±0.09	7.64±0.29	0.43±0.07

From the result of post compression parameters of core tablet, Deviation in weight is less than 5 % indicated that there was no significant weight variation in the core tablets. Hence, all the tablet formulations passed the USP-XXIX weight variation test. The percentage friability was less than 1 % in all the formulations, indicating that the friability is within the prescribed limits. The hardness test indicates good mechanical strength. The tablet thickness was found to be 5.52 to 6.76 mm.

In vitro drug release profile of all nine formulations was found typical sigmoidal curves with a distinct lag time. It showed that lag time increased with increasing concentration of HPMC K4M.

This might be due to the greater degree of hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway.

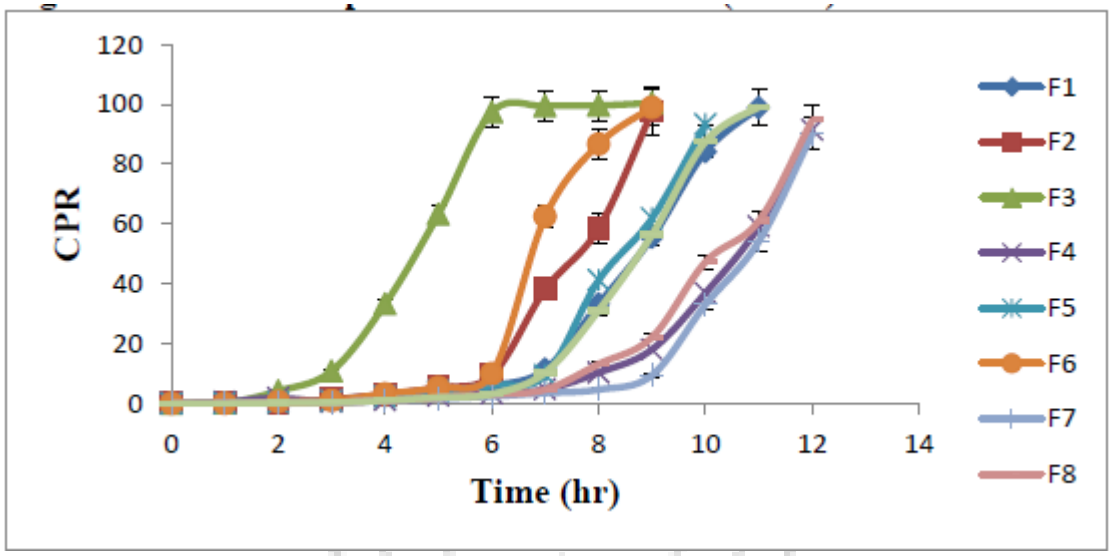

Figure 3: Dissolution profiles of final batches (F1-F9)

It was observed that the higher amount of drug was released from batches containing lower level of polymer weight in coating layer. From release profile of all nine batches it was observed that drug release from tablet was inversely proportional to coat weight. Drug release rate was highly retarded in formulation F7, F8 and F9 which contain a higher level of coat weight (200 mg).

From all the batches, formulation F3 showed >90 % of drug released before the lag time of 6 hours. The intermediate drug release retardation was observed from the batches F1 and F5 while significant retardation was observed from the batches F4, F7, F8 and F9 containing higher amount of HPMC K4M in the outer shell. Formulation F2 and F6 show less lag time of 6 hours and nearer 99 % of drug release at the end of 9 hours.

Rupture sequence of pulsatile release tablet showed that at 0 hr coating of HPMC layer was intact, after 2 hrs there slightly swelling of HPMC coating was observed. After 6 hrs there was start of rupture of HPMC occurred. When rupturing of HPMC layer was occurred, fluid

penetrates into inner core of tablet. Because of penetration of fluid swelling of sodium starch glycolate causes burst release of drugs and complete release of drug observed within 9 hrs.

Result of dependent variable of 32 full factorial design (Table 7) showed that batch F2 and F6 have lag time 6 hours and time requires for release 90 % of drug are 8-9 hours. But batch F6 showed much more drug release as compared to batch F2 at 7^{th} hour. So, based on the all dependant variables batch F6 was selected as optimized batch.

Table 7: Results of dependent variables of factorial design

Batch code	Coded value		Response		
	X_1	X_2	Y_1	Y_2	Y_3
F1	-1	+1	6.73	11.42	10.39
F2	-1	0	6.01	38.21	8.80
F3	-1	-1	2.86	99.45	5.781
F4	0	+1	7.93	4.79	11.95
F5	0	0	7.01	9.53	9.894
F6	0	-1	6.01	62.54	8.264
F7	+1	+1	9.01	3.57	12.996
F8	+1	0	7.62	4.71	11.856
F9	+1	-1	6.94	10.43	10.205

A three factor and two level (32) full factorial design was applied in this study to optimize the formulations. Total amount of coating and % of HPMC K4M were chosen as the independent variables while lag time (t_{10}), drug release at 7^{th} hour and time require for release 90 % of drug were taken as dependent variable.

The polynomial equation for 32 full factorial design is described as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, Y is the dependent variables, β_0 is the arithmetic mean response of the nine runs, and β_1 is the estimated coefficient for the factor X_1. 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 terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_{11} and X_{22}) are included to investigate non-linearity.

The polynomial equations (equations 1-3) relating the response lag time (Y_1), drug release at 7th hour (Y_2) and time require for release 90 % of drug (Y_3) with the independent variables are given below.

$$Y1 = 7.17+1.33X_1+1.30X_2-0.46X_1X_2-0.44X_1X_1-0.29X_2X_2 \ (r2 = 0.946) \_ \_ \_ \_ \ (1)$$

$$Y2= 15.92-21.72X_1-25.44X_2+20.29X_1X_2+2.34X_1X_1+14.55X_2X_2 \ (r2 = 0.977) \_ \_ \_ \_ \ (2)$$

$$Y3= 10.20+1.68X_1+1.84X_2-0.45X_1X_2-0.03X_1X_1-0.25X_2X_2 \ (r2 = 0.992) \_ \_ \_ \_ \ (3)$$

When amount of total polymer was increased(X1), lag time (Y_1) and time require for 90% drug release (Y_3) was increased and when % of HPMC K4M was increased(X_2), lag time (Y_1) and time require for 90% drug release (Y_3) was increased, while when amount of total polymer was increased(X_1) drug release at 7th hour was decreased (Y_2) and when % of HPMC K4M was increased(X_2) drug release at 7th hour was decreased (Y_2).

The relationship between the dependent and independent variables was further elucidated using surface plot and contour plot as shown in Figure 4.

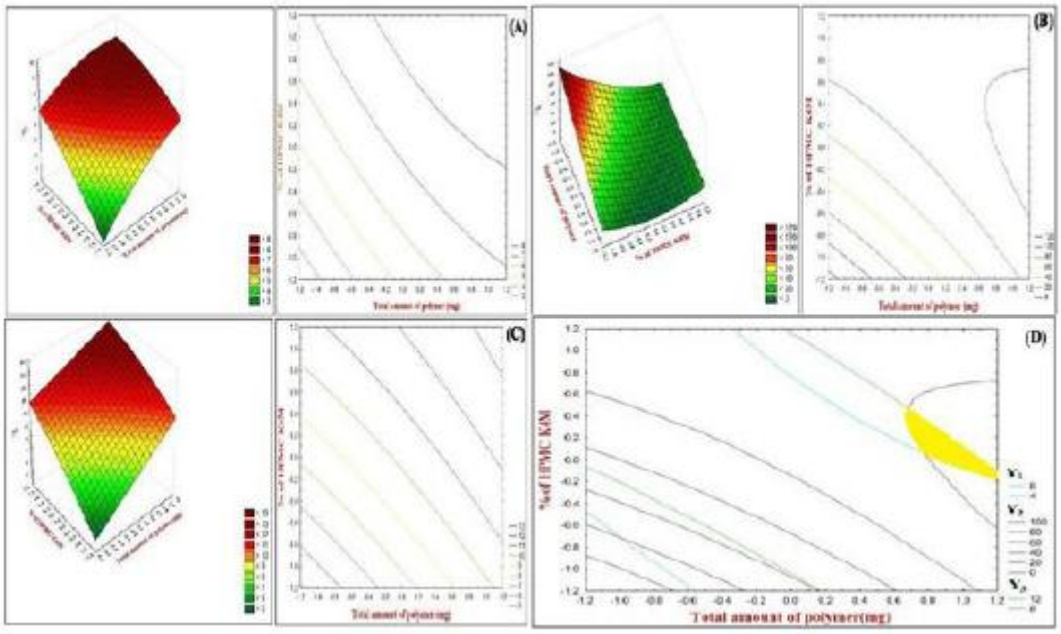

Figure 4: Surface and Contour plot of (A) lag time, (B) drug release at 7th hour, (C) time require for 90 % of drug release and (D) overlay contour plot of response Y_1, Y_2 and Y_3

For validation of the statistical model check point batch was prepared by taking the level of X_1=0.45 and X_2= 0.5 .The values of X_1 and X_2 were substituted in the equations to obtain the theoretical (predicted) values of responses. The % relative error for check point batch of all dependent variables was less than 8 %.

Table 9 Responses of checkpoint batch

Parameters	Observed value	Predicted value	% Relative error
Lag time(t_{10})	7.34	7.736	5.1
Drug release at 7th hour.	4.37	4.092	6.79
Time require for release 90 % of drug	10.874	10.254	6.046

So it was concluded that the theoretical (predicted) values and obtained values for responses were in reasonably good agreement.

CONCLUSION

A press coated pulsatile drug delivery system for Doxophylline to mimic the circadian rhythm of the disease by releasing the drug at appropriate time (At the time of symptoms exacerbates). The formulation consisted of a core tablet containing a drug Doxofylline and outer layer of combination of swellable hydrophilic polymer of HPMC K4M and HPMC E50 LV. From all the batches, it was concluded that Formulation F6 was the ideal formulation with lag time of 6 hrs followed by burst release of drug and also meeting all specifications of pre-compression and post compression parameters and stability studies. Thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours i.e. at the time of symptoms.

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