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RESEARCH ARTICLE

FORMULATION&EVALUATION OF OPTIMISED CHRONO RELEASE OF ANTIHYPERTENSIVE DRUG

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ABSTRACT

The aim of current research was to formulate the pulse-release tablets of Atenolol and investigate its in-vitro performance so the study was designed to firstly increase the solubility and bioavailability of drug by formulating the fast dissolving core tablet of cyclodextrin drug- complex, using spray dried lactose, spray dried mucilage -lactose & superdisintegrants by direct compression method. Then Pulsatile tablets were prepared by compression coating using 2^3 factorial design using different polymers as independent variables in whichlubritab, xanthan gum,Polyox WSR301 and dicalciumphosphate were used for maintaining lag time in different concentrations and controlling the drug release by direct compression and dependent variable as lag time. The formulations were investigated for lag time by in-vitro dissolution study. Formulation was optimized on basis of acceptable tablet properties and in *vitro* drug release. Formulation F7 was selected on basis of factorial design dependent variable i.e., the lag time.
Keywords: Atenolol**,** time controlled pulsatile release, Compression coating

INTRODUCTION

In recent years, biological control of drug delivery has been of interest to achieve improved drug therapies[1].Pulsatile drug delivery system has the advantageof avoiding drug tolerance[2-4]. The oral pulsatile release system was mainly for the treatment of disease symptoms such as hypertension, asthma, ischemic heart disease and rheumatoid arthritis, that exhibit circadian rhythms. The required amount of drug should be released from the drug delivery system at the required time of night or early morning. The object of the recent study was to develop newPulsatile release tablets of time-controlled or 'site specific' drug delivery[5-8].

Atenolol, a β-blocker, is prescribed widely in diverse cardiovascular diseases, eg. Hypertension, angina pectoris and arrhythmias. The drug is also indicated in prophylactic treatment of migraine. Administration of conventional tablet has been reported to exhibit fluctuation in the plasma drug level, resulting either in manifestation of side effect or reduction in drug concentration at the receptor site. Atenolol has half life of 6 to 7 hrs. & oral bioavailability is 50%. It get metabolised through hepatic metabolism & does not pass through first pass metabolism.Taking in consideration these parameters Atenolol is good candidate to administer through pulsatile system. Chronobiologically, hypertension peak isin the morningabout 5 to7 AM. Sopatients have to take conventional tablet at 2 or 3 PM which is non compliance to patients. In pulsatile drug delivery, tablets are prepared in such manner that they release drug immediately after a predetermined lag time. So it is the most popular system which deliver drug in time dependent manner and most importantlysuitable drug regimen for patientssuffering from cardiac disorders.Pulsatile tablet of antihypertensive drug should be taken after dinner so that it get released after a 5 to 6 hrs of lag time so it is available during morning session when there are chances of hypertension peak[9-12].

In the present study Lubritab, Dicalcium Phosphate andPolyox WSR301, in the form of compression coat applied over optimizedcore tablets of drug-cyclodextrin complex, andwere evaluated as a carrier for time dependent drug delivery. This presscoating prevent disintegration of core tablet containing Atenolol in gastric fluid. On reaching insmall intestine, the tablet will release drug after predetermined time, but the water solublehydrogel polymer i.e. Polyox WSR301 swell to create a lag phase that equal the small intestinal transittime. The proposed device can be manufactured using currently available pharmaceuticaltechnology and materials recognized as safe.

MATERIAL AND METHOD:

Material:

Atenolol was obtained as a gift sample from IPCA. Spray dried lactose, Lubritab& all otherchemicals and reagents used were either of analytical orpharmaceutical gradespurchased from local market.

Tablet Manufacturing Method:

Drug Excipients Compatibility Study

Sample of pure drug, coating, physical mixture of coating material and drug in (1 : 1) ratio was placed at accelerated stability condition 40±2 °C and 75±5% relative humidity for a period of 3 month. At the end of 3 month samples were evaluated for drug–excipients compatibility using Differential scanning colorimeter (DSC) (Mettler Toledo DSC 822e, Japan) and Fourier transformed infrared spectroscopy (FT-IR) (Shimadzu Corporation, Japan, 8400s).

Solubility enhancement:

Atenolol is slightly soluble in water &have low bioavailability so increasing solubility & bioavailability is important for faster dissolution core tablets. For that drug & β cyclodextrine complex were prepared in different

molar concentrations & selected by theirhighest absorption through UV method. Then selected molar concentration used to prepare drug-cyclodextrine complex by Freeze drying technique.

Formulation of Immediate release core tablets:

The inner core tablets were prepared by using direct compression method. As shown in Table 1 powder mixtures of drug , diluents and super disintergrants were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 100 mg of resultant powder blend was compressed using rotary tabletting machine with a 6mm punch and die to obtain the core tablet.

Coating of core tablets

Powder blend for press-coated tablet was prepared by dry blending together differentcompositions of the Lubritab, Polyox WSR301, Xanthum gum and Dicalcium Phosphate. These excipients were dry blended in different weight compositions using 2^3 factorial designin order to get suitable polymer composition. This composition is dry blended until uniformly blended mixture is obtained. This mixture is then used for the preparation of press – coated tablet using direct compression method (10mm punch).

2^3 Full Factorial Design

A $\mathbf{2^3}$ randomized full factorial design was used in this study. In this design 3 factors were evaluated, each at 2 levels, and experimental trials were performed at all 8 possible combinations. The ratio of Polyox WSR301: Lubritab (X1) and Amount ofXanthan Gum (X2) & presence of Dicalcium Phosphate (X_3)in Coating layer were selected as independent variables. The times required for maintaining lag time (Y) was selected as dependent variable. The experimental design with corresponding formulation outline in Table no. 2.

Table 1: Composition of core tablet

	F1	F2	F3	F4	F5	F6	F7	F8
DC(mg)	50	50	50	50	50	50	50	50
SDL(mg)	44	44	44	-	-	-	50	-
SDML(mg)	-	-	-	44	44	44	-	50
CCS(mg)	6	-	-	6	-	-	-	-
CP(mg)	-	6	-	-	6	-	-	-
SSG(mg)	-	-	6	-	-	6	-	-[1]

Table 2: Design and composition of compression coating Layer

Batch code	$\mathbf{X_1}$	$\mathbf{X_2}$	$\mathbf{X_3}$
F1	-1	1	1
F2	-1	-1	1
F3	-1	-1	-1
F4	1	-1	-1
F5	1	-1	1
F6	1	1	-1
F7	1	1	1
F8	-1	1	-1

Independent variables			
Levels	$\mathbf{X_1}$ (Ratio of Polyox WSR301:Lubritab) mg	$\mathbf{X_2}$ (Amount of Xanthan Gum) mg	$\mathbf{X_3}$ (Presence of Dicalcium Phosphate) mg
-1	50:100	50	Without
1	125:75	100	With (50)

Evaluation of core and press – coated tablet

Thickness:

Thickness of tablets was determined using Vernier caliper. Five tablets from batch wereused, and average values were calculated[13-14].

Average Weight:

To determine average weight, each tablet from formulation was weighed using an *electronicbalance (AUX-220, Shimadzu)*[13-14].

Hardness:

The hardness was tested using Monsanto tester. The force is measured in kilograms[13-14].

[1] *SSG-sodium starch glycolate,CP- crospovidone, CCS- cross carmellose sodium,SDL- spray dried lactose and SDML- spray dried ocimumbasilicum mucilage on lactose as carrier.*

Friability:

For each formulation, the friability of 6 tablets was determined using the *Roche friabilator(Lab Hosp.)*[13-14].

In vitro drug release study of press – coated tablets

In-vitro dissolution studies were performed on the press-coated tablets prepared by directcompression method using 0.1N HCL for 2 hrs& 6.8 ph phosphate buffer in USP apparatus II with the paddle speed of 50 rpm. Then 1 ml of filteredaliquot was withdrawn at pre-samples wereanalysed at 225 nm using a UV spectrophotometer. The lag time and percentage releasewas determined for the each formulation[13-14].

RESULT & DISCUSSION :

Solubility enhancement :

Atenolol belongs to a group of beta blocker (selective β1 antagonist) used as antihypertensive, antianginal and antiarrythmic. Due to its slightly solubility in water, low bioavailability (50%) makes it suitable candidate for increase its solubility.

Solubility of Atenolol was enhanced by complexation with βcyclodextrine. It was done by different molar ratioswhich were stirred saturated solutions for 5-6 hrs, then filtered & UV reading taken. By this 1:1 ratio was selected which gives highest absorption 0.130 and solubility0.03505 mg/ml at 225 nm.

By this complexation solubility of drug increased in HCL & 6.8 phosphate buffer. But it was more soluble in phosphate buffer shown in table 3.

Table 3: Solubility study

Materials/Solubility in	HCL(mg/ml)	6.8 Phosphate Buffer(mg/ml)
Drug	0.01964736	0.026
Drug:Cyclodextrine	0.03652	0.04836

Compatability study

Drug-Excipient Interactions:

The IR spectra of Formulation were compared with the standard spectrum of Atenolol (Fig 1.). IR spectrum of Atenolol was characterized by the absorption of-C=O group at1651 cm−1&-CONH- group at 1736.73.In spectra of Formulation; band was same absorption pattern as that of pure drug. Mentioned evidences thus lead to the conclusion that changes were not seen as there was no physical interaction between the drug and polymers.

In DSC study also drug was characterized by its melting point & formulation was also showing same results as drug, by these mentioned evidences lead to the conclusion that changes were not seen s there was no physical interaction between the drug & polymers (Fig 2).

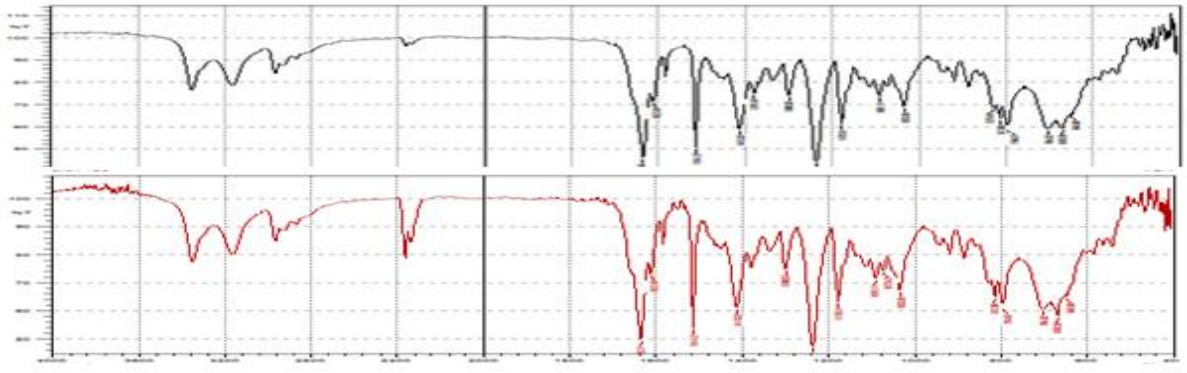

Figure 1a: IR Spectrogram of Atenolol Drug & formulation

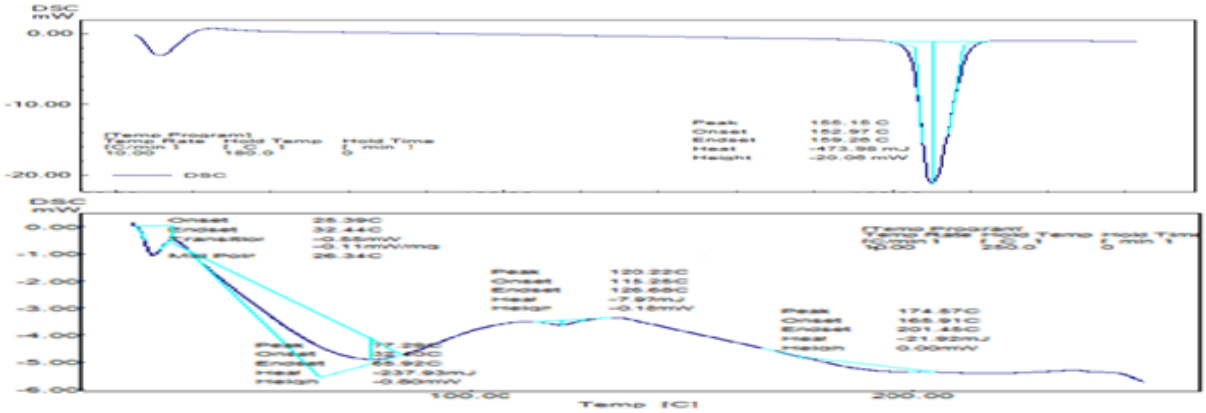

Figure 1b: DSC of Atenolol Drug & formulation

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Preparation of core tablets

Drug-Cyclodextrine complex was prepared to increase the solubility & bioavailability. To improve the dissolution process of immediate release core, different diluents used were spray dried lactose, spray dried mucilage lactose,alone and along with superdisinterants(cross caramellose sodium, crospovidone, sodium starch glycolate). Spray dried lactose was used as filler; binder but spray dried mucilage lactose had a property of binding as well as disintegrating. But by result that we obtained it shows that spray dried lactose with superdisintegrant shows good disintegration & dissolution properties. Spray dried lactose is highly water soluble & along with superdisintegrant the release was very fast. Whereas in spray dried mucilage-lactose, might have increased the viscosity & might have acted as barrier for diffusion & faster dissolution.

Precompression Parameters of Core Tablet Powder Blend

The results of bulk density, tapped density and compressibility index are shown in Table 4. The powder blends indicated good flowability with the angle of repose values ranging from 29 to 35° according to fixed funnel method.. The result of compressibility index was between 12 to 17, which indicates good to fair flow properties& for Hausners ratio was near/less about 1.2, which indicates free flowing powder.

Characterization of Core Tablets

The tablet hardness, friability, weight variation of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 4. The hardness of all the tablets was between 3to5kg/cm^2. In the present study, the loss in total weight in friability test was in the range of 0.77 to 0.91% that indicates,the percentage friability for allthe formulations was found below 1% indicating that friability (%) is within the acceptablelimits. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets weighing more than 80 mg is ±7.5%. The average percentage deviation of all tabletformulations was found to be within limit, and hence all formulations passed the test foruniformity of weight as per official requirement. F2 formulation shows good characteristic properties compared to other formulations. F2 formulation gives90% drug release in 30 min. F2 formulation was selected by possessing good characteristics.

Table 4: Pre and post -compression parameter of core tablet

Pre-compression parameter for powder blend of core tablet								
Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Bulk Density(g/cm3)	0.526	0.55	0.55	0.55	0.55	0.526	0.55	0.526
Tapped Density(g/cm3)	0.625	0.625	0.666	0.666	0.625	0.625	0.666	0.625
Angle of Repose(θ)	34.13	29.24	33.87	32.11	34.45	33.58	31.19	33.74
Carrs index (%)	15.84	12	17.41	17.41	12	15.84	17.41	15.84
Hausners ratio (HR)	1.18	1.13	1.21	1.21	1.13	1.18	1.21	1.18
Post-compression parameters for core tablets								
HARDNESS (Kg/cm2) (n=3)	3.5±0.50	3±0.50	4± 0.50	5±0.50	3.5± 0.00	3±0.50	5± 0.00	5± 0.00
THICKNESS(mm) (n=3)	2.67±0.005	2.52±0.014	2.58±0.016	2.55±0.007	2.64±0.018	2.54±0.016	2.67±0.018	2.64±0.014
DIAMETER(mm)	6.01±0.007	6.00±0.015	6.00±0.008	6.02±0.016	6.01±0.011	6.01±0.003	6.01±0.011	6.01±0.008
Weight Variation (%) (n=20)	101±0.79	100±0.57	101±0.83	99±1.36	99±0.87	101±0.68	101±0.72	100±0.48
DISINTEGRATION TIME (MIN.)	8.25	7.15	8.55	16	8.10	15	16	24
% RELEASE IN 30 MIN.	53.59	95.8	51.37	59.16	61.61	52.00	36.72	38.31
FRIABILITY(%)(n=10)	0.78	0.87	0.81	0.91	0.77	0.82	0.67	0.84

Preparation of press-coated tablets

Press coated tablets were prepared by using 3 independent variables as different concentrations of polymers by using 2^3 factorial design. In press coating polymers used were Polyox WSR301, Lubritab, Xanthan gum &Dicalcium phosphate. Extremely fast hydration and gel forming property of polymer Polyox WSR301 results into decrease in drug release with increase in polymer concentration. Lubritab was a hydrogenated vegetable oil, which was hydrophobic in nature with good binding property played a role in controlled release of the formulation. Xanthan gum, a polysaccharide-based natural gum, has been widely employed as a hydrophilic polymer to prepare controlled release matrices because of its cost effectiveness and regulatory acceptance. It has been used as a release retardant polymer.The use of higher proportions of xanthan gum resulted in the formation of a thick polymeric gel layer, which acted as a barrier to drug diffusion. Dicalcium phosphate may be a simpler, cheaper, and a viable way to formulating directly compressible sustained release formulations due to its water insoluble nature.

Data fitting to the model

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A three-factor, two-level optimal design as the response surface methodology (RSM) provides 8 runs. All the responses observed for 8 formulations were fitted to main effect model when using Design Expert (State ease – Ver. 8.0.7.1) and the values of R^2 and standard deviation are given in Table 7 along with the regression equation generated for each response. Only statistically significant ($p < 0.05$) coefficients are included in the equations.

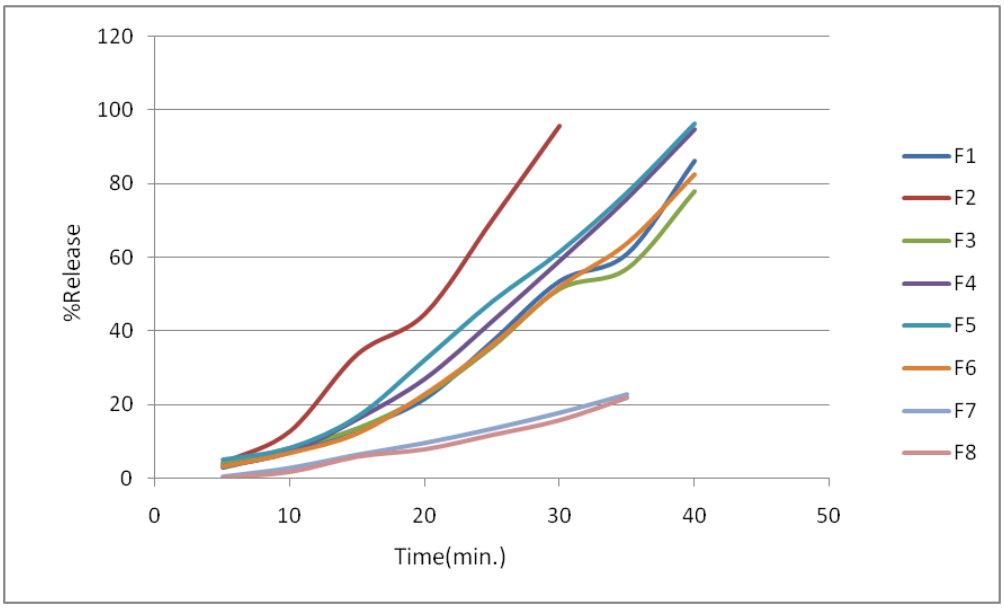

Figure 2: % Drug Release of core tablets

Table 5: Summary of Results of Regression Analysis for Response Y1

Response	Models	F value	Prob > F	R^2	Adjusted R^2	Predicted R^2	S.D.	Remarks
Y_1(Lag time)	Main effect	261.53	0.0001	0.9949	0.9911	0.9797	3.95	Suggested
Equation: $Y1=175.63+5.62X_1+36.88X_2-11.88X_3$								

In the following graphs (Fig 4&5), as the amount of Xanthan gum, Ratio of polox:lubritab & Dicalcium phosphate increases lag time also increases.

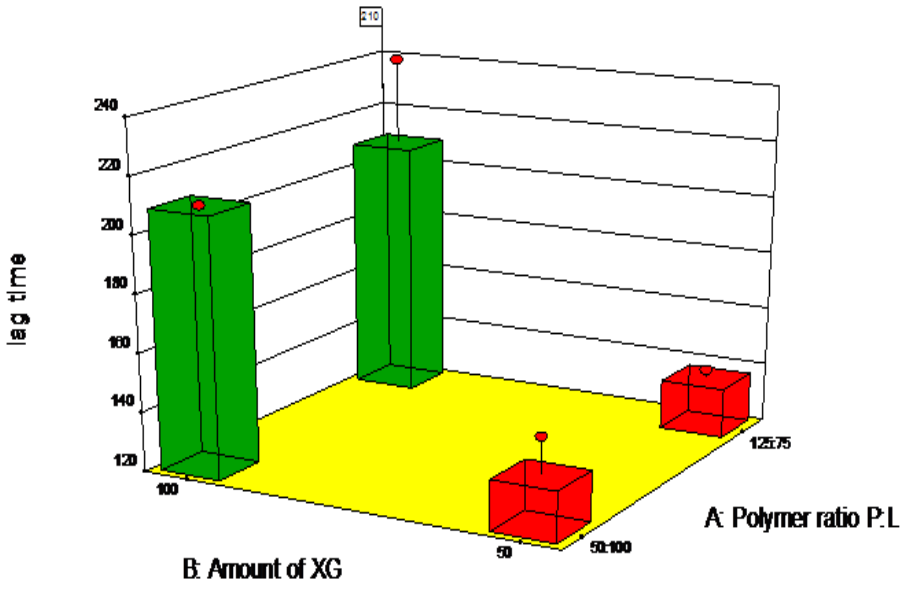

Figure 3: Effect of Xanthan gum & ratio of Polyox WSR301: Lubritab on lag time

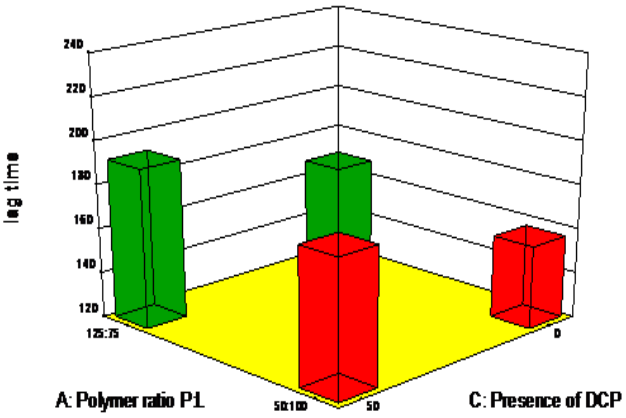

Figure 4 Effect of Dicalciumphosphate(DCP) & ratio of Polyox WSR301:Lubritab on lag time

Lag time is the important criteria to deliver drug. In following formulations different polymers in different concentration were used. In this F7 formulation which contains Xanthan gum 100mg, Ratio of polox:lubritab 125:75mg & Dicalcium phosphate 50mg shows good lag time of about 4 hrs.

Characterization of press-coated Tablets

The tablet hardness, friability, weight variation of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 6. The hardness of all the tablets was between7 and 8kg/cm^2. In the present study, the loss in total weight in friability test was in the range of 0.68 to 0.92% that indicates,the percentage friability for allthe formulations was found below 1% indicating that friability (%) is within the acceptablelimits. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets weighing more than250mg is ±5%. The average percentage deviation of all tabletformulations was found to be within limit, and hence all formulations passed the test foruniformity of weight as per official requirement. In case of press coated tablets formulations were characterised & optimised by 2^3 factorial design & formulation F7 shows good lag time of 3.5 hrs.

Table 6: Post-compression parameters for press-coated tablets

	F1	F2	F3	F4	F5	F6	F7	F8
HARDNESS (Kg/cm2)(n=3)	7±0.40	7.5±0.27	7±0.63	7±0.28	8±0.29	7.5±0.13	8±0.45	7±0.50
THICKNESS (mm)(n=3)	6.02±0.15	6.13±0.17	5.95±0.26	5.97±0.15	6.09±0.27	5.93±0.26	5.89±0.15	6.17±0.027
DIAMETER (mm)(n=3)	10±0.01	10±0.002	10±0.02	10±0.01	10±0.02	10±0.02	10±0.02	10±0.01
WEIGHT VARIATION (%)(n=20)	400±1.29	351±1.13	300±1.24	350±0.87	402±0.73	400±1.17	451±0.63	350±0.82
FRIABILITY (%)(n=10)	0.88	0.93	0.68	0.73	0.77	0.73	0.86	0.92

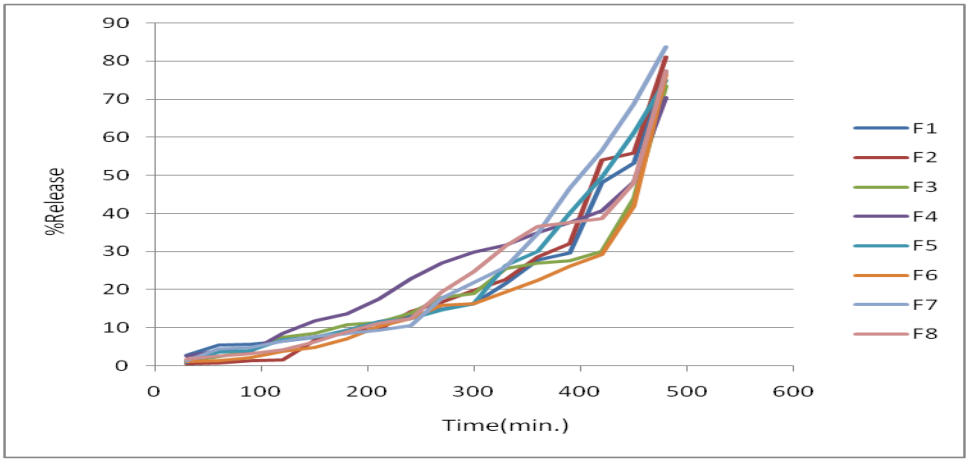

Figure 5: % Drug Release of coated formulations

CONCLUSION

Optimization of press-coated pulsatile tablet for atenolol was carried out usinga three-factor, two-level, full factorial design. This allowedrapid evaluation and identification of the parameters importantin determining the desired responses, ie, the lag timefor atenolol release.The present study demonstrates that theAtenolol compression coated tablet could be successfullydeliverdrug in right time, right place. It was better formulation compared to conventional tablet. So it is also a patient compliant. It was concluded that Formulation F2 was good formulation as it was meeting all specifications for post compression characteristic & by the factorial model.

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