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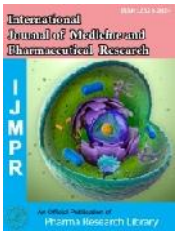

Research Article Open Access

Formulation and Characterisation of Pulsatile Drug Delivery System of Bisoprolol Fumarate Prepared by Press Coated Method

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A B S T R A C T

Pulsatile dosage form taken at bed time with a programmed start of drug release in the early morning hours, can prevent a sharp increase in the incidence of heart attacks during the early morning hours. In the present study, an attempt was made to design and characterize pulsatile drug delivery system in order to release the drug after 7-8hr in the intestine, and intentionally delaying the drug absorption from therapeutic point of view in the treatment of heart attacks, where peak symptoms are observed in the early morning. Thus this study attempts to design and evaluate a chronomodulated drug delivery system of Bisoprolol Fumarate selectively blocks catecholamine stimulation of β1-adrenergic receptors in the heart and vascular smooth muscle. Eight formulations (F1–F8) of core tablets were prepared by direct compression technique and evaluated for various physico chemical parameters. *In vitro* drug release study of Bisoprolol Fumarate core tablets revealed F6 as best formulation and press coated and enteric coated using different polymers like Ethyl cellulose and Eudragit L100 (C1 – C5) to find out the changes in the release rate of the Bisoprolol Fumarate from enteric coated tablets. This enteric coat has enabled us to achieve definite non release lag phase for 8 hours.

Keywords: Bisoprolol Fumarate, Pulsatile drug delivery, Ethyl cellulose, Eudragit L100.

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1. Introduction

Modified release dosage forms have acquired a great importance in the current pharmaceutical R&D business. Such systems offer control over the release pattern of drug and provide better control over drug regimen [1]. A release pattern of drug is not suitable in certain disease condition. At that time release profile of a delivery system

characterized by lag time. In other words, the drug should not release during its initial period of administration, followed by a rapid and complete release (pulse release) of drug that is called pulsatile drug delivery system (PDDS). This system aims to deliver a drug via the oral route at a rate different than constant i.e., zero order release [2]. PDDS increases its attention in treatment of peak symptoms in early morning and exhibit circardian rhythm [3]. Bisoprolol is a cardioselective β1-adrenergic blocking agent used for secondary prevention of myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension [4,5]. So in the present research an attempt was made to formulate Bisoprolol as PDDS using polymers like Ethyl cellulose and Eudragit L100 at different concentrations.

2. Materials and Methods

Drug–Excipient compatibility studies

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

Angle of repose:

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

Bulk density:

10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where,

M = weight of sample, V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the property of a powder to be compressed. It is determined from the bulk and tapped densities. For poorer flowing materials, there are frequently greater antiparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density, Tap = Tapped Density

Formulation development of Tablets:

Formulation of core tablets by direct compression:

The inner core tablets were prepared by using direct compression method as shown in the table no6.3. Powder mixtures of Bisoprolol Fumarate, microcrystalline cellulose, SSG, talc, ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 100mg of resultant powder blend was manually compressed using , Lab press Limited, India with a 8mm punch and die to obtain the core tablet. .

Formulation of mixed blend for barrier layer:

The various formulation compositions containing Ethyl cellulose , Eudragit L100,Eudragit S100, magnesium stearate, talc and microcrystalline cellulose. Different compositions were weighed dry blended at about 10 min. and used as press coating material to prepare press-coated pulsatile tablets respectively by direct compression method.

Preparation of press-coated tablets:

The core tablets were press-coated with250 mg of mixed blend as given in Table. No 4.125mg of barrier layer material was weighed and transferred into a 10mmdie then the core tablet was placed manually at the center. The remaining **125**mg of the barrier layer materiel was added into the die and compressed by using Lab press Limited, India

Evaluation [8, 9, 10]

Post compression parameters of core and press coated tablets: The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, hardness, friability, drug content and *in vitro* drug release studies.

Hardness

The prepared tablets were subjected to hardness test. It was carried out by using Monsanto, Mumbai, India and expressed in Kg/cm^2**.**

Thickness

The prepared tablets were subjected to thickness test. It was carried out by using the Vernier caliper Mitutoyo, Japan and expressed in millimeter.

Friability Test

The friability was determined using friability test apparatus Labindia, Mumbai, India and expressed in percentage (%). 10 tablets from each batch was weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for100 revolutions at 25rpm. The tablets were reweighed (W_{final}) and the percentage friability was calculated for each batch by using the following formula.

$$\text{Friability} = [(W1-W2) / W] \times 100$$

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Weight variation Test

Twenty tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than10%.

Drug content

The Bisoprolol Fumarate tablets were tested for their drug content. Ten tablets were finely powdered. They require quantities of the powder equivalent to 100 mg of Bisoprolol Fumarate were accurately weighed and transferred to a 100-Ml of volumetric flask. The flask was filled with distilled water and mixed thoroughly. The solution was made up to Volume and filtered.Dilute1mL of the resulting solution to 100mL with distilled water and measure the absorbance of the resulting solution at the maximum at 222nm using UV spectrophotometer (Labindia, Mumbai, India). The linearity equation obtained from calibration curve as described previously was use for estimation of Bisoprolol Fumarate in the tablets formulations.

***In*-vitro drug release study of pulsatile Bisoprolol Fumarate tablets:**

***I) In-vitro* drug release of Bisoprolol Fumarate core tablets**: *In-vitro* dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. PH 6.8 phosphate buffer was used as dissolution medium. Release pattern was studied visually by taking sample of 5Ml at the specific time intervals. Also the sample was analyzed at 222nm for 0.1N HCL and 222nm for 6.8 phosphate buffers using a UV spectrophotometer.

***ii) In-vitro* drug release study of coated tablets**

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from upto 6 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 222nm using UV-spectrophotometer.

3. Results and Discussion

Fourier Transform Infrared Spectrophotometry:

Compatibility study of drug with the excipients was determined by FTIR spectroscopy. The spectra of the drug and other ingredients used in the formulation were compared with the spectra of binary mixture of drug and excipients mixed in the ratio of 1:1. The spectra for pure Bisoprolol Fumarate and for the physical mixture of Bisoprolol Fumarate and all the polymers were determined to check the intactness of the drug in the polymer mixture using FTIR–Spectrophotometer by Dataonly method. The comparative FTIR studies of Drug and excipients combination had shown negligible variation in the values as compared with that of only pure form of Drug. Therefore it implies good compatibility of drug and excipients. Results are given in fig 1-6**.** Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.48±0.01 to 0.53± 0.04 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.55±0.02 to 0.60±0.03 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 11 to 16 which were showed that the powder has good flow properties. All the formulations has shown the hausner ratio ranging from 0 to 1.2 indicating the powder has good flow properties. Results are given in table no 3,5. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits. Results are given in table no 4, 6.

***In-Vitro* Drug Release Studies of Bisoprolol Fumarate core tablet:** *In-vitro* dissolution studies of Bisoprolol Fumarate core tablets were performed using USP XXIII Type II rotating paddle dissolution apparatus by using phosphate buffer (pH 6.8) as a dissolution medium. From formulation F1toF8 Bisoprolol Fumarate core tablets, F6 showed faster drug release after 45 mins than the other formulations. Faster drug release can be correlated with the high disintegration and friability observed in this study. So, F6 Bisoprolol Fumarate core tablet formulation was selected as best formulation for further press coating and enteric coating formulations. *In vitro* drug release profiles of all Bisoprolol Fumarate core tablets were shown in table no 7 & fig no 7,8.

***In vitro* drug release study of Bisoprolol Fumarate pulsatile tablets**:

Based on the above characters formulation F6 was selected as best formulation and press coated and enteric coated to find out the changes in the release rate of the Bisoprolol Fumarate from enteric coated tablets. This enteric coat has enabled us to achieve definite non release lag phase for 8 hours. The formulations C1, C2, C3, C4 and C5 showed maximum drug release at immediately. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C3 with 99.38% drug release which meets demand of chronotherapeautic drug delivery. The formulations containing Eudragit L 100 was found to be optimum as enteric coating polymers. The data were shown in fig no 9 and table no 8.

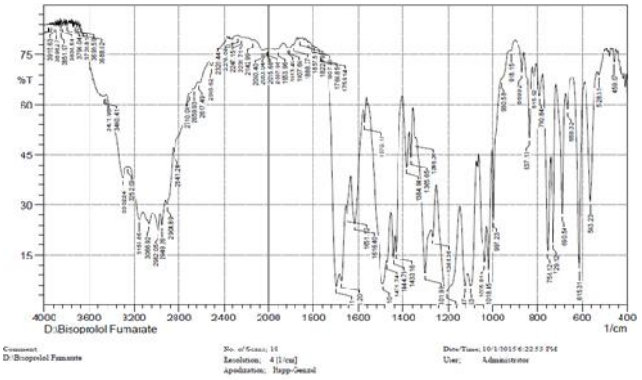

Figure 1: FTIR spectra of Bisoprolol Fumarate pure drug

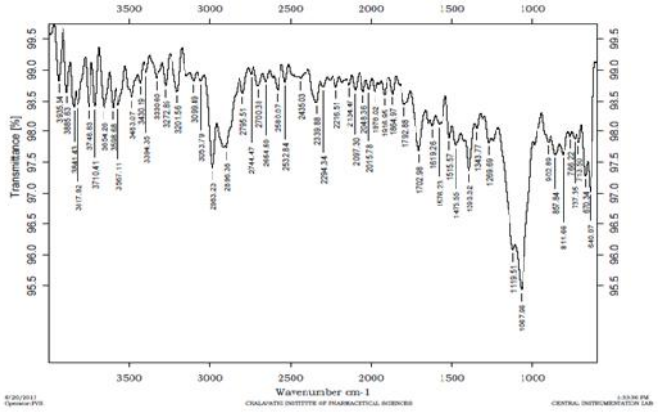

Figure 2: FTIR spectra for Eudragit L 100

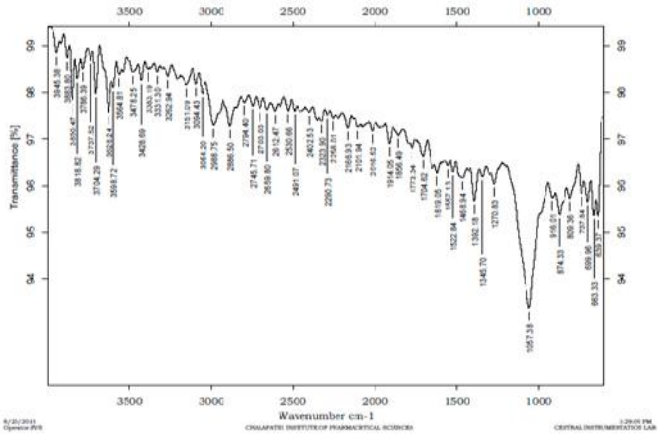

Figure 3: FTIR spectra for Ethyl cellulose

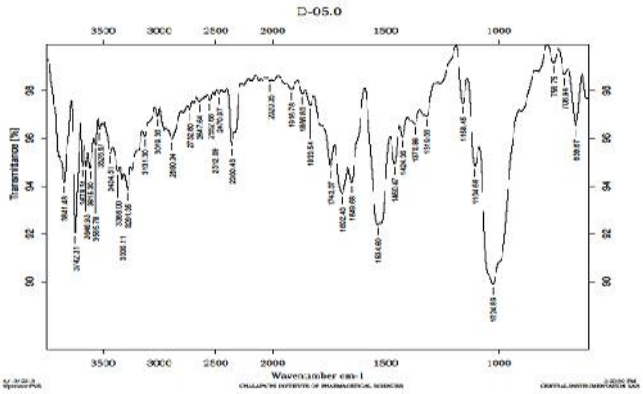

Figure 4: FTIR Spectra of MCC

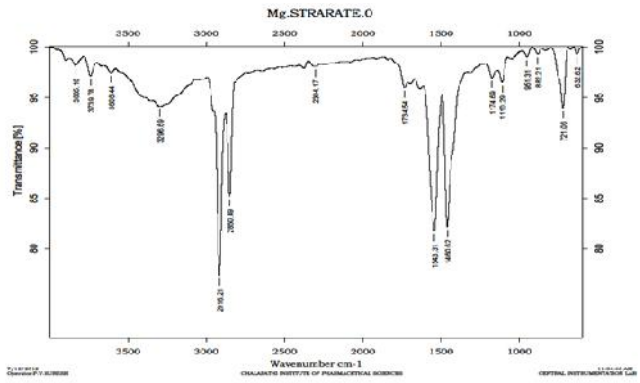

Figure 5: FTIR Spectra data of Magnesium Stearate

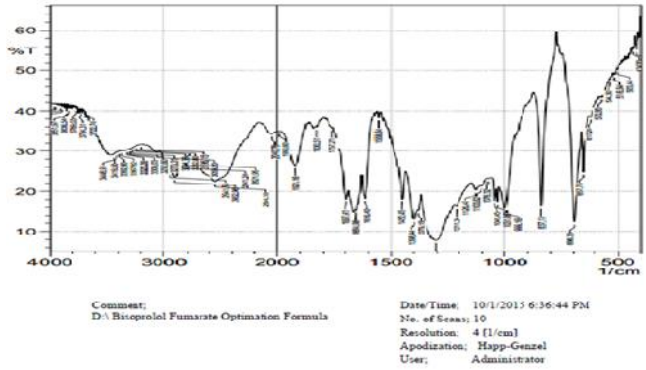

Figure 6: FTIR spectra of Bisoprolol Fumarate optimized formula

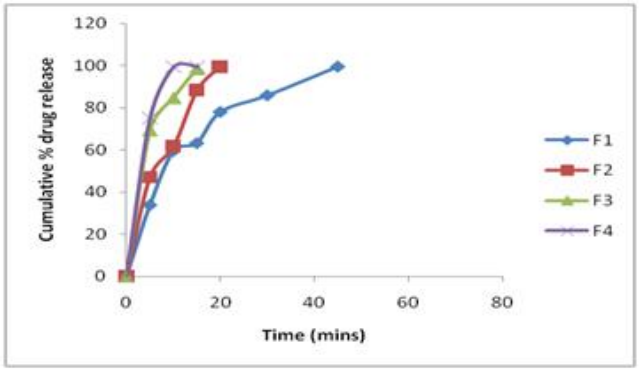

Figure 7: Cumulative % *drug* released of Bisoprolol Fumarate core tablets using SSG

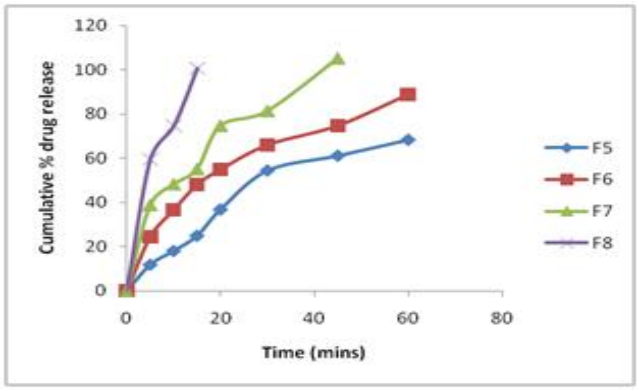

Figure 8: Cumulative % drug released of Bisoprolol Fumarate core tablets using CP

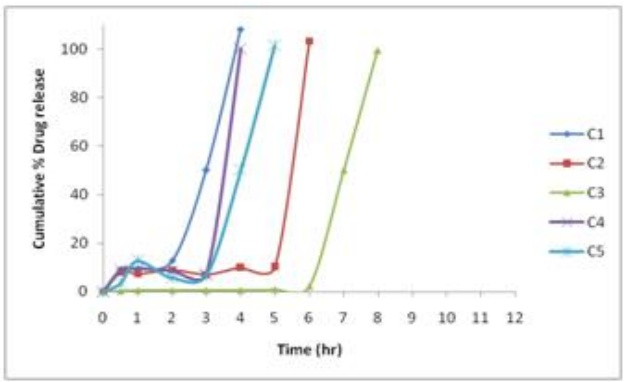

Figure 9: Cumulative % drug Release of Coated Bisoprolol Fumarate Tablets

Table 1: Formulation for preparation core tablets

S.No	Materials	F1	F2	F3	F4	F5	F6	F7	F8
1	Bisoprolol Fumarate	20	20	20	20	20	20	20	20
2	SSG	2	4	6	8	-	-	-	-
3	Cross Povidone (CP)	-	-	-	-	2	4	6	8
4	Magnesium stearate	2	2	2		2	2	2	2
5	Talc	2	2	2	2	2	2	2	2
6	Microcrystalline cellulose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
7	Total Wt	100	100	100	100	100	100	100	100

Table 2: Formulation for preparation of coating tablets

S.No	Materials	C1	C2	C3	C4	C5
1	Ethyl cellulose	5O	5O	25	50	75
2	Eudragit L100	50	50	75	25	25
3	Talc	5	5	5	5	5
4	Mg.sterate	5	5	5	5	5
5	Mcc	Q.S	Q.S	Q.S	Q.S	Q.S
6	TOTAL WT	250	250	250	250	250

Table 3: Pre compression parameters of Bisoprolol Fumarate core tablets

Formulation Code	Angle of repose (^{0}) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25^o 7'±0.263	0.357±0.0	0.429±0.02	16.6±4.12	1.202±0.06
F2	26^{o}6 '±0.51	0.407±0.04	0.484±0.26	15.3±13.32	1.200±0.17
F3	24^o 6 '±0.58	0.545±0.0	0.518±0.32	12.12±5.24	1.14±0.07
F4	29^o 7 '±0.36	0.518±0.13	0.578±0.58	10.37±8.30	1.12±0.13
F5	27^o 8 '±0.46	0.488±0.05	0.560±0.06	12.8±4.77	12.14±0.06
F6	22^o 4' ±0.98	0.341±0.03	0.446±0.04	22.86±0.64	1.30±0.008
F7	28^o 2' ±0.48	0.350±0.02	0.431±0.04	18.46±7.17	1.23±0.11
F8	27^o 3 '±0	0.349±0.0	0.407±0.04	13.65±11.27	1.17±0.16

Table 4: Post compression parameters of Core tablet

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness	Friability (%loss)	Drug content (%)
F1	99.5±0.1	2.3±0.1	2.9±0.001	0.58±0.11	98.76±0.005
F2	99.8±0.1	2.5±0.1	2.9±0.15	0.61±0.057	99.56±0.01
F3	99.9±0.057	2.5±0.1	2.86±0.01	0.59±0.057	97.34±0.005
F4	100.0±0.01	2.5±0.1	2.9±0.01	0.52±0.1	99.45±0.011
F5	99.8±0.58	2.7±0.1	2.9±0.01	0.66±0.057	99.14±0.01
F6	99.6±0.1	2.9±0.15	2.86±0.015	0.64±0.1	98.87±0.01
F7	99.3±1.10	2.8±0.57	2.7±0.005	0.64±0.1	99.42±0.005
F8	99.2±0.1	2.9±0.11	2.51±0.01	0.57±0.057	98.65±0.057

Table 5: Pre compression Parameters of Bisoprolol Fumarate coated Tablets

Formulation Code	Angle of repose (^{o}) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
	27^o 6'± 0.67	0.333±0.0	0.384±0.0	13.3±0.0	1.15±0.0
C2	28^o 8'± 0.73	0.375±0.015	0.441±0.02	15.02±0.63	1.18±0.008
C3	23^o 3'± 1.06	0.545±0.016	0.602±0.039	8.96±8.11	1.10±0.09
C4	28^o 6'± 0	0.484±0.013	0.569±0.05	14.60±5.24	1.17±0.07
C5	25^o 3' ±0.653	0.375±0.008	0.545±0.0	17.4±1.80	1.21±0.02

Table 6: Post compression parameters of Coated tablet:

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
C1	349.5±0.57	4.0±0.14	0.4±0.24	4.5±0.1	±0.47
C2	348.0±0.51	4.7±0.12	0.42±0.24	5.4±0.15	±0.53
C3	350.0±0.24	5.0±0.15	0.5±0.24	5.0±0.29	±0.61
C4	350.0±0.24	5.0±0.24	0.55±0.24	5.0±0.24	
C5	349.2±0.24	6.0±0.24	0.4±0.24	5.0±0.24	

Table 7: *In-Vitro* Drug Release Studies of Bisoprolol Fumarate core tablet

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	33.86	47.16	69.44	74.96	11.83	24.41	38.9	59.4
10	59.48	61.64	84.8	99.33	18.065	36.63	48.3	74.56
15	63.23	88.38	98.55	99.45	24.93	48.05	55.2	100.6
20	78.03	99.52	---	---	36.8	54.95	74.8	---
30	85.91	---	---	---	54.44	66.07	81.5	---
45	99.53	---	---	---	61.13	74.8	105.3	---
60	---	---	---	---	68.3	88.9	---	---

Table 8: Cumulative % drug Release of Coated Bisoprolol FumarateTablets

Time	C1	C2	C3	C4	C5
0	**0**	**0**	**0**	**0**	**0**
0.5	9.37	7.87	0.345	8.6	3.3
1	9.7	7.47	0.502	9.4	12.7
2	12.7	8.91	0.503	8.67	5.7
3	50.06	7.05	0.504	7.37	6.7
4	108.06	9.78	0.668	100.2	50.06
5	---	10.12	0.836	---	101.2
6	---	103.38	2.17	---	---
7	---	---	50.06	---	---
8	---	---	99.38	---	---

4. Conclusion

All the formulations of press coated tablets showed almost uniform size, shape and appearance. The physico-chemical properties of all the formulations (F1-F8) like thickness, friability, hardness and drug content ranged lies within pharmacopoeial limits. *In-vitro* release of Bisoprolol Fumarate of core tablet formulations F1-F8, F6 showed faster drug release after 60mins. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C3 with 99.38% drug release which meets demand of chronotherapeutic drug delivery.

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