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Preparation and Evaluation of Pulsatile Drug Delivery System of Bisoprolol Fumarate

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Abstract: In the present research work pulsatile drug delivery system of Bisoprolol fumarate tablets were formulated by employing compression coating technology. Initially the core tablets were prepared by using various concentrations of super disintegrates, the formulated core tablets were coated with the polymers by using compression coating technology. All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests for core and press coated tablets. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopeia limits. In vitro release of Bisoprolol fumarate of core tablet formulations F1-F3, F1 showed faster drug release after 20 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. The enteric coated formulations C1, C2, and C3 showed maximum drug release after 3 hours. C5 and C9 showed maximum drug release after 8th hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C9 with 98.37% and 99.9%.

Keywords: Bisoprolol fumarate, Super disintegrates, Ethyl cellulose, Pulsatile tablets.

INTRODUCTION

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. This system aims to deliver a drug via the oral route at a rate different than constant i.e., zero order release. The lag time is the time interval between the dosage forms is placed into the aqueous environment and drug get to release from its dosage form after rupturing or eroding outer layer. The lag time between 0.5 hr to 4 hr is desire for upper region of gastrointestinal tract and more than 4 hr for lower portion of small intestine. Pulsatile Drug Delivery System (PDDS) is to deliver a drug in a rapid, burst-like manner at a predetermined time and/or specific site of action after a programmable, release-free lag phase. This system shifts away from traditional continuous-release profiles to align medication delivery with the body's natural circadian rhythms (biological clocks). It provides optimal therapeutic treatment for diseases whose symptoms peak at specific hours, such as nocturnal asthma, angina, rheumatoid arthritis, and hypertension. In present study a reliable dosage form that guarantees a strictly controlled delay before releasing the active

ingredient was built and evaluation was done to ensure the synthesized formulation meets required physical limits, possesses chemical stability, and strictly maintains its precise timing mechanisms.

METHODOLOGY

Analytical method development:

a) Preparation calibration curve:

10 mg of bisoprolol fumarate tartrate pure drug was dissolved in 10ml of methanol (stock solution). The above stock-II solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5,10,15,20 and 25µg/ml of solution. The absorbance of the above dilutions was measured at 221 nm for 0.1N HCL by using UV-Spectrophotometer taking 0.1N HCL as blank.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

The sample was made 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.

Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physic chemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

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 tartrate, microcrystalline cellulose, polyplasdone XL, 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, Cemach Limited, India with a 4mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer: The various formulation compositions containing Ethyl cellulose N 50, methocel k100, magnesium stearate, talc, pvpk-30 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 with 400 mg of mixed blend as given in Table.No6.4. 200mg of barrier layer material was weighed and transferred into a 10mm die then the core tablet was placed manually at the center. The remaining 200 mg of the barrier layer materiel was added into the die and compressed by using Lab press Limited, India

Table 6.3: Formulation for preparation core tablets

S. NO	MATERIALS	F1	F2	F3
1	Bisoprolol fumarate	50	50	50
2	Polyplasdone XL	25	-	-
3	Explotab	-	25	-
4	Tulsion 339	-	-	25
5	Magnesium state	2	2	2
6	Talc	2	2	2
7	Microcrystalline cellulose	QS	QS	QS
8	TOTAL WT	100	100	100

Table 6.4: Composition of coat over Bisoprolol fumarate core tablet

S. NO	MATERIALS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Ethylcellulose N 50	40	80	120	160	200	-	-	-	-	-
2	Methocel k100m	-	-	-	-	-	40	80	120	160	200
3	Pvp k-30	40	40	40	40	40	40	40	40	40	40
4	Talc	4	4	4	4	4	4	4	4	4	4
5	Mg.sterate	4	4	4	4	4	4	4	4	4	4
6	Mcc	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
7	TOTAL WT	400	400	400	400	400	400	400	400	400	400

EVALUTIONS

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, disintegration time were studied.

In vitro drug release of bisoprolol fumarate core tablets

In vitro dissolution studies were carried out using USP XXIII Type II (paddle method) apparatus. Distilled water was used as dissolution medium. Release pattern was studied visually by taking sample of 5 mL at the specific time intervals. Also, the sample was analysed at 221 nm for 0.1N HCL and 222nm for 6.8 phosphate buffer using a UV spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

7. RESULTS AND DISCUSSION

Present study was done on pulsatile tablets with different formulations C1 to C10. Formulations had weight ratio of polymers like Ethyl cellulose, Tulsion 334, polyplasdone, Explotab along with various excipients. Ethyl cellulose is an insoluble. Aim of the formulation was to get effect of drug in early morning Hypertension like disease. This section gives detailed description of the results and discussion on pulsatile Bisoprolol fumarate tablets.

PREFORMULATION STUDIES

Table 7.3: Pre compression parameters of Bisoprolol fumarate core tablets

Formulation code	Angle of repose (°) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio	Weight variation (mg)	Hardness (kg/cm ²)	Friability (%loss)	Thickness (mm)	Drug content (%)
C1	26.8	0.49	0.56	12.56	1.14	97.2	2.5	0.45	2.8	98.5
C2	25.6	0.52	0.59	11.86	1.13	102.6	2.4	0.51	3.2	99.5
C3	29.8	0.48	0.55	12.7	1.15	98.96	2.4	0.43	3.1	102.2

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 0.49 to 0.52 (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 to 0.59 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 11.86 to 12.56 which show that the powder has good flow properties. All the formulations have shown the Hausner ratio ranging between 1.13 to 1.15 indicating the powder has good flow properties.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits

Table 7.5: Pre compression Parameters of Bisoprolol fumarate coated Tablets

Formulation code	Angle of repose (°) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio	Weight variation (mg)	Hardness (kg/cm ²)	Thickness	Friability (%loss)	Drug content
C1	27.01	0.51	0.56	16.21	1.09	505.5	4.1	0.53	4.7	99.76
C2	25.8	0.55	0.63	16.87	1.14	506.4	4.2	0.55	4.8	99.45
C3	26.74	0.56	0.68	17.1	1.21	501.6	4.0	0.59	4.9	99.34
C4	25.33	0.55	0.65	17.67	1.18	498.6	4.3	0.56	4.6	99.87
C5	24.24	0.56	0.68	16.92	1.21	497.4	4.5	0.57	4.8	99.14
C6	23.12	0.54	0.61	17.65	1.12	496.7	4.4	0.49	4.4	98.56
C7	22.08	0.49	0.58	16.43	1.18	503.3	4.3	0.57	4.7	98.42
C8	24.12	0.51	0.56	17.97	1.09	506.2	4.4	0.51	4.8	99.65
C9	26.45	0.53	0.63	17.54	1.18	499.3	4.2	0.51	4.6	99.12
C10	28.69	0.55	0.62	18.25	1.12	501.5	4.2	0.53	4.7	99.76

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 0.49 to 0.56 (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 0.56 to 0.68 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations have shown the Hausner ratio ranging between 1.09 to 1.21 indicating the powder has good flow properties.

7.7. Invitro quality control parameters for tablets

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In-Vitro* Drug Release Studies of Bisoprolol fumarate tartrate 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 F1-F3 Bisoprolol fumarate core tablets, F1 showed faster drug release after 20 mins than the other formulations. Faster drug release can be correlated with the high disintegration and friability observed in this study. So, F1 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 7.5** and **Figure.7.6**

Table 7.7: Cumulative % drug release of bisoprolol fumarate core tablets

Time (min)	F1	F2	F3
5	54.6	29.50	37.5
10	71.6	41.5	48.5
15	88.5	54.6	56.7
20	98.5	69.2	57.81

30		72.4	70.6
45		89.6	88.2
60		91.5	98.5

Based on the above characters formulation F1 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, and C3 showed maximum drug release after 3th hour. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C9 with 98.37% and 99.9% drug release which meets demand of Chrono therapeutic drug delivery. The formulations containing Ethyl cellulose N 50, Methocel k 100 in 200 mg and 160 mg respectively were found to be optimum as enteric coating polymers. The data were shown below.

Sl. No	Time (min)	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
1	0.5	0.12	0.14	0.28	0.10	0.28	0.13	0.10	0.13	0.10	0.56
2	1.0	28.54	0.20	12.56	0.95	2.43	2.17	0.14	0.28	0.12	2.26
3	2.0	50.34	5.43	28.18	18.50	6.56	32.95	5.27	0.35	6.21	4.96
4	3.0	96.37	35.68	54.56	30.34	12.54	69.12	15.25	0.30	15.14	9.96
5	4.0	-	56.32	60.30	52.12	15.68	95.23	56.9	2.38	58.28	12.5
6	5.0	-	93.62	85.17	75.34	40.34	-	96.5	9.39	62.30	26.5
7	6.0	-	-	90.52	88.66	56.56	-	-	25.59	73.31	35.6
8	7.0	-	-	-	90.5	62.12	-	-	53.30	80.34	49.5
9	8.0	-	-	-	91.5	98.37	-	-	62.12	99.9	69.5

CONCLUSION

The pulsatile tablet of Bisoprolol fumarate tablets is composed of three components, a drug containing core tablet (rapid release function), the press coated with swellable hydrophobic polymer (explotab) and hydrophobic polymer (ethyl cellulose) alone and / or in different weight ratio. An enteric coating layer

The formulation mixtures of powders for core tablets (F1-F3) prior to the compression step have been evaluated for pre-compression parameters. All the formulation mixtures showed good to excellent compressibility.

All the core and press coated tablet formulations were subjected to various physical and chemical evaluation tests for core and press coated tablets. The thickness, hardness and weight variation shown by all the tablet formulations were found within the official pharmacopeia limits. All the formulations showed favourable drug loading with uniformity of drug content in the tablets and disintegration time. Based on the friability and disintegration time, formulation A1 was selected as best formulation and press coated and enteric coated for further evaluations studies.

In vitro release of Bisoprolol fumarate of core tablet formulations F1 showed faster drug release after 20 mins. Faster drug release can be correlated with the high disintegration and friability observed in this study. The enteric coated formulations C1, C2, and C3 showed maximum drug release after 3 hours. C5 and C9 showed maximum drug release after 8th hr.

Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C9 with 98.37% and 99.9%, drug release which meet demand of Chrono therapeutic drug delivery. Formulation of time release pulsatile bisoprolol fumarate tablets which breaks after 5-6 hr. was studied. The pulsatile bisoprolol fumarate tablets did not release the drug in acidic environment (0.1N HCl) due to protective polymer coating and released the drug after pre-determined time period of 6-7 hours in phosphate buffer (pH 6.8).

A once-daily time-controlled release pulsatile tablet of Bisoprolol fumarate Tartrate having short half-life was found to exert a satisfactory time-controlled release profiles which may provide an increased therapeutic efficacy.

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