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DEVELOPMENT OF METOPROLOL TARTRATE PULSATILE DRUG DELIVERY FORMULATION BY PRESS COATED TECHNOLOGY

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ABSTRACT

Pulsatile drug delivery is novel chronotherapeutic drug delivery system. In the present research work pulsatile drug delivery system of Metoprolol tartrate tablets were formulated and developed 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 pharmacopoeial limits. In vitro release of Metoprolol tartrate core tablet formulations F1-F3were conducted, F1 showed faster drug release after 20 min. faster drug release can be correlated with the high disintegration and friability observed in this study. The pulsatile formulations C1, C2, and C3 showed maximum drug release after 3 hour. 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%.

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INTRODUCTION

In recent years, a major goal for the drug delivery research is renewed towards the development of efficacious drug delivery systems with already existing active ingredients in case of new drug discovery1. Many of pharmaceutical therapeutic agents are mostly effective when made available at constant rates or near to absorption sites2. Much effort has been going on to develop sophisticated drug delivery systems such as osmotic devices for oral application. Oral drug delivery system is more favored on popular controlled drug delivery system in pharmaceutical research and development (R & D) business due to increase in awareness of medical and pharmaceutical community about the importance of safe and effective use of drug. This system aims to maintain plasma drug concentration within the therapeutic window for long period of time3.

Traditionally, it is becoming increasingly more evident with the specific time that patients have to take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hr period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms4. In the human body systems such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day5. They are naturally followed by the internal body clocks and are controlled by the sleep wake cycle. This system focused on controlled or sustained release of drug of which has such advantages of nearly constant level of drug at site of administration, minimizing peak - valley fluctuation of drug concentration in body and avoidance of adverse effect5.

MATERIALS AND METHODS:

Metoprolol Tartrate was a gift sample from Alkem Laboratories, Hyderabad, India. Mefenamic acid was obtained from Alexo pharma (India). HPMC K100M, Avicel PH-102, Starch pregelatinized, Aerosil 200 were purchased from Drugs India Pvt. ltd (India). Poly ethylene glycol 400 was obtained from Fischer scientific. All the remaining ingredients and chemicals utilized were of analytical grade.

ANALYTICAL METHOD DEVELOPMENT:

Preparation calibration curve:

10mg of Metoprolol tartrate pure drug was dissolved in 10ml of methanol (stock solution) 1ml (1000µg/ml) stock-I. From this 1ml was taken and make up with 10 ml of 0.1N HCL (100µg/ml) stock-II. 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. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The procedure was repeated with required buffers**.**

DRUG – EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) spectroscopy:

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.

Pre formulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical 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.

Angle of repose[7]:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. 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.

$$\textbf{Tan } \theta = h / r \quad \textbf{Tan } \theta = \textbf{Angle of repose}$$

h = Height of the cone, r = Radius of the cone base.

Table1: Angle of Repose values (as per USP).

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 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:

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

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:

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

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 propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle 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:

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

Where: b = Bulk Density

Tap = Tapped Density

Table2: Carr's index value (as per USP).

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

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 no.3. Powder mixtures of Metoprolol tartrate, microcrystalline cellulose, polyplasdoneXL, 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 stearte, 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 **4**00 mg of mixed blend as given in Table.No. 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

Table3: Formulation for preparation core tablets.

S.NO	MATERIALS	F1	F2	F3
1	Metoprolol tartrate	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

Table4: Composition of coat over Metoprolol tartrate core tablet.

S.NO	MATERIALS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Ethyl cellulose 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

EVALUATION TESTS

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 Sisco, 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 were weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W_{final}) and the percentage friability was calculated for each batch by using the following formula.

$$(\%)F = \frac{Winitial - Wfinal}{Winitial} \times 100$$

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 than 10%.

Drug content

The Metoprolol tartrate tablets were tested for their drug content. Ten tablets were finely powdered. The require quantities of the powder equivalent to 100 mg of Metoprolol tartrate 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. Dilute 1 mL of the resulting solution to 100 mL with distilled water and measure the absorbance of the resulting solution at the maximum at 222 nm using UV spectrophotometer (Labindia, Mumbai, India). The linearity equation obtained from calibration curve as described previously was use for estimation of Metoprolol tartrate in the tablets formulations.

Disintegration time of core tablets

Disintegration test was carried out using the tablet disintegration test apparatus (Serve well Instruments pvt. Ltd., Electrolab ED-2L, India) specified in Indian pharmacopoeia. Distilled water at 37 ± 0.5 ºC was used as the disintegration media and the time in second taken for complete disintegration of the tablet with no palpable mass remaining on the screen was measured in seconds.

***In* vitro drug release study of pulsatile Metoprolol tartrate tablets**

***In vitro* drug release of Metoprolol tartrate 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 analyzed 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[8]:

Various models were tested for explaining the kinetics of drug release. To analyze 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.

Zero order release rate kinetics:

To study the zero–order release kinetics the release rate data are e fitted to the following equation.

$$F = K_O t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics:

The release rate data are fitted to the following equation

$$Log (100-F) = kit$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model:

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K\ t^n$$

Where, M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100-Q_t)^{1/3} = 100^{1/3} - K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSIONS:

Pre-formulation Studies

Determination of λ max of Metoprolol tartrate

The λ max of Metoprolol tartrate was estimated by carrying out UV scan between the wavelength 200 to 400 nm which gave a highest peak at 221 nm and the same was selected for Metoprolol tartrate.

Standardization method for estimation of Metoprolol tartrate

Standard curves of Metoprolol tartrate were prepared in 0.1N HCl, phosphate buffer (pH 6.8).

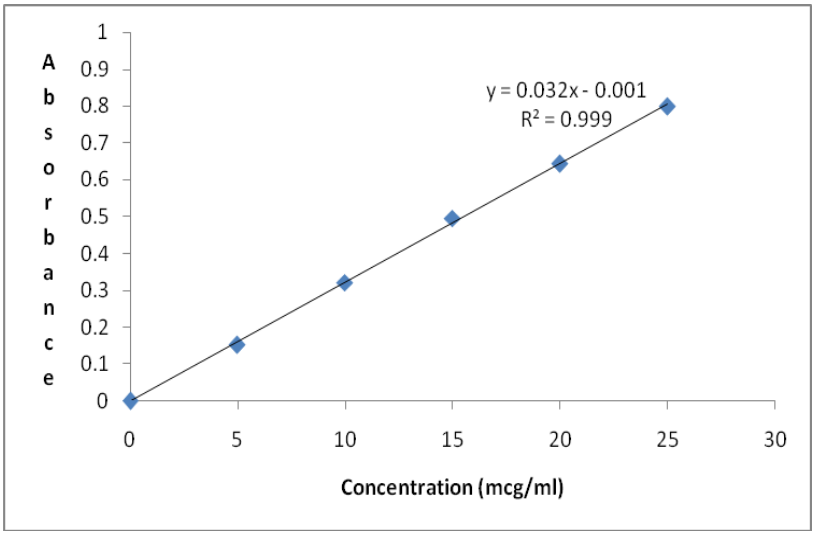

Fig: 1: Standard Graph of Metoprolol tartrate in 0.1N Hcl.

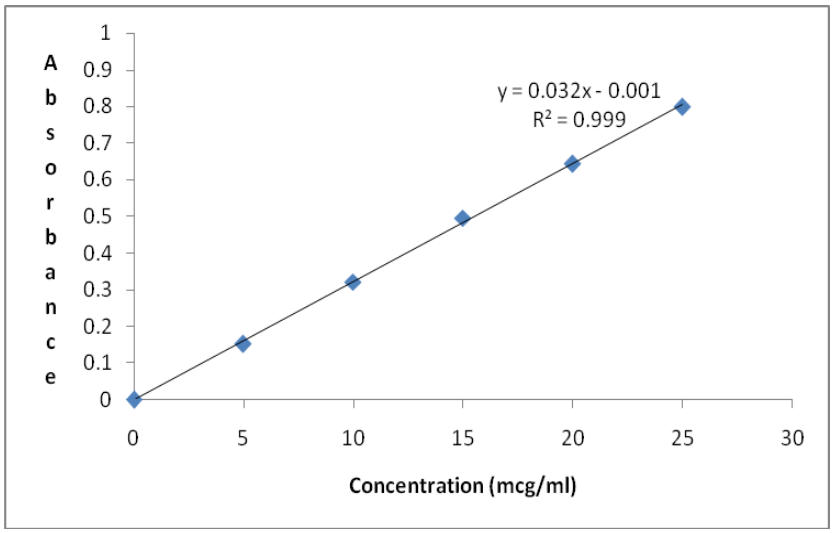

Fig: 2: Standard Graph of Metoprolol tartrate in pH 6.8 phosphate buffer.

Drugs Polymer Interaction Study by FTIR spectrophotometer

In order to investigate the possible interaction between drug and selected polymers, FTIR studies were carried out. IR spectrum for pure drug and physical mixture of drug- polymers were obtained and analyzed for principle peaks The studies suggest that there is no incompatibility between drug and polymer.

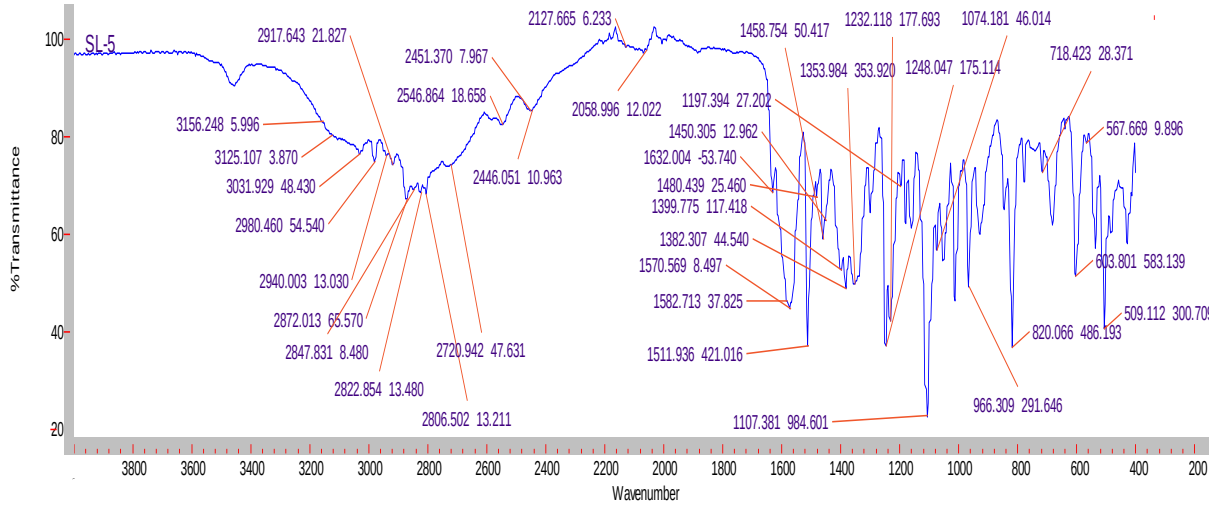

Fig 3: FTIR Spectrum of Metoprolol tartrate pure drug.

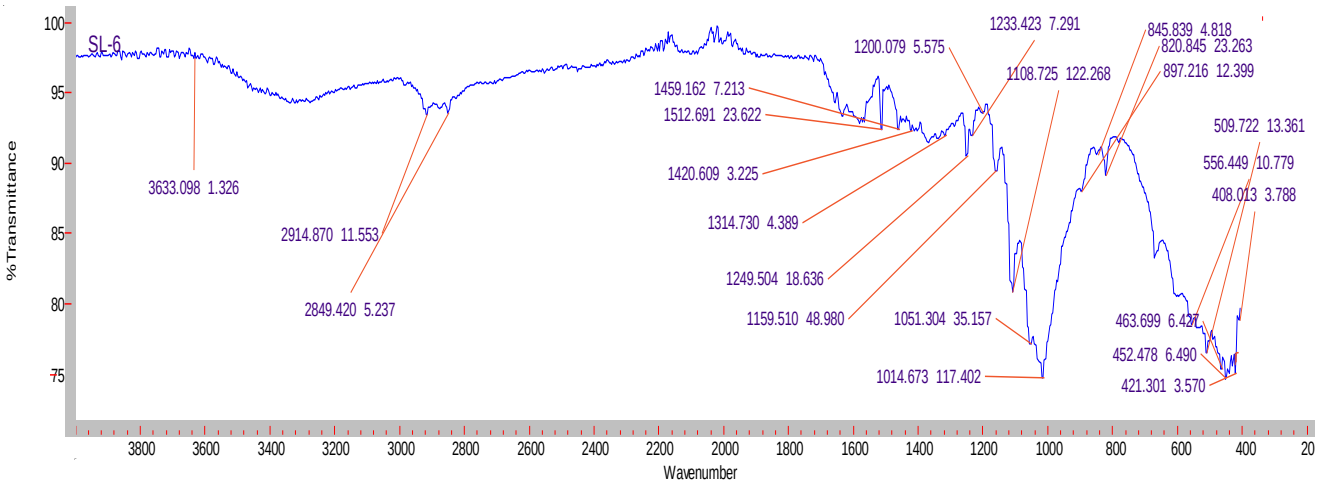

Fig 4: FTIR spectrum of Optimized formulation.

Table 5: Pre compression parameters of Metoprolol tartrate core tablets.

Formulation code	Angle of repose (^{0}) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	26.8	0.49	0.56	12.56	1.14
C2	25.6	0.52	0.59	11.86	1.13
C3	29.8	0.48	0.55	12.7	1.15

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 0.49to 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, shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 1.13 to 1.15 indicating the powder has good flow properties

Table 6: Post compression Parameters of Metoprolol tartrate Core Tablets.

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (% loss)	Thickness (mm)	Drug content (%)
C1	97.2	2.5	0.45	2.8	98.5
C2	102.6	2.4	0.51	3.2	99.5
C3	98.96	2.4	0.43	3.1	102.2

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

Table 7: Pre compression Parameters of Metoprolol tartrate coated Tablets.

Sl.No	Time (min)	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
1	0	0	0	0	0	0	0	0	0	0	0
2	0.5	0.12	0.14	0.28	0.10	0.28	0.13	0.10	0.13	0.10	0.56
3	1.0	28.54	0.20	12.56	0.95	2.43	2.17	0.14	0.28	0.12	2.26
4	2.0	50.34	5.43	28.18	18.50	6.56	32.95	5.27	0.35	6.21	4.96
5	3.0	96.37	35.68	54.56	30.34	12.54	69.12	15.25	0.30	15.14	9.96
6	4.0	-	56.32	60.30	52.12	15.68	95.23	56.9	2.38	58.28	12.5
7	5.0	-	93.62	85.17	75.34	40.34	-	96.5	9.39	62.30	26.5
8	6.0	-	-	90.52	88.66	56.56	-	-	25.59	73.31	35.6
9	7.0	-	-	-	90.5	62.12	-	-	53.30	80.34	49.5
10	8.0	-	-	-	91.5	98.37	-	-	62.12	99.9	69.5

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.

Table 8: Invitro quality control parameters for tablets.

Formulation code	Angle of repose (^{0}) *	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
C1	27.01	0.51	0.56	16.21	1.09
C2	25.8	0.55	0.63	16.87	1.14
C3	26.74	0.56	0.68	17.1	1.21
C4	25.33	0.55	0.65	17.67	1.18
C5	24.24	0.56	0.68	16.92	1.21
C6	23.12	0.54	0.61	17.65	1.12
C7	22.08	0.49	0.58	16.43	1.18
C8	24.12	0.51	0.56	17.97	1.09
C9	26.45	0.53	0.63	17.54	1.18
C10	28.69	0.55	0.62	18.25	1.12

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

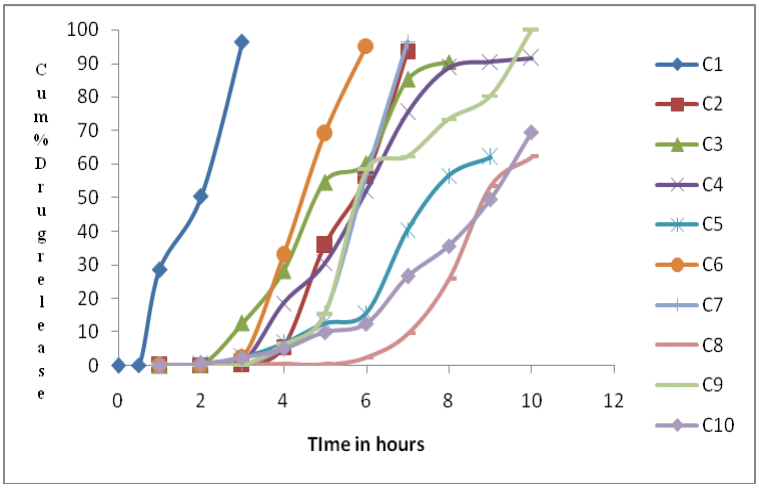

Fig: 6: Cumulative % release study of Metoprolol tartrate pulsatile tablets.

CONCLUSION

From the results it was concluded that, A once-daily time-controlled release pulsatile tablet of Metoprolol Tartrate prepared with Methocel K 100 m, PVP K30 (50mg: 160mg: 40mg) having short half-life was found to exert a satisfactory time-controlled release profiles which may provide an increased therapeutic efficacy. Hence Metoprolol Tartrate pulsatile tablets may be prepared by using Methocel K100m.

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