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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF METOPROLOL TARTRATE

K. SURENDRA KUMAR*, M. RAMA KOTAIAH[1], M.PRASADA RAO[1]
Department of pharmaceutics, Maderametla Anjamma & Masthanrao College of Pharmacy, Kesanupalli, Narasarao Pet, Guntur (DT), Andhrapradesh-India.

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Abstract: The objective of present investigation was to prepare and evaluate a pulsatile drugdelivery system of metoprolol tartrate. The prepared pulsatile delivery system consists of two different parts: a core tablet, containing the active ingredient, an erodible . The rapid release core tablet (RRCT) was prepared by using superdisintegrants along with active ingredient metoprolol tartrate. press coating of optimized RRCT was done by using different ratios of hydroxy propyl methyl cellulose (HPMC K100) and ethyl cellulose 5Cps. Developed formulations were evaluated for their physical characteristics, in vitro disintegration time and in vitro drug release profile (lag time).On the basis of these evaluation parameters it was found that optimized pulsatile release formulation (P3F3) showed time of 2hrs and in-vitro drug relrease time of 8hrs with97.8%released drug. The P3F3 formulation showed compliance with chronotherapeutic objective of hypertension.

Keywords: Pulsatile drug delivery, Metoprolol tartrate, rapid release core tablet, press coating, lag time

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Corresponding Author: MR. K. SURENDRA KUMAR

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INTRODUCTION

Conventional controlled release drug delivery systems are based on single or multiple – unit reservoir or matrix system, which are designed to provide constant drug levels over an extended period of time. However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for drugs with special the pharmacokinetic features designed according to the circadian rhythm of human. A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release. Pulsatile drug delivery systems are generally classified into time - controlled and site - specific delivery system [1-4].

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hours. [5]The release from the time controlled delivery is primarily controlled by the system, while the release from the sitespecific group is primary controlled by the biological environment in the gastro-intestinal tract such as pH of the site of action or enzymes.Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier can dissolve, erode or rupture during/after a certain lag time, after which the drug is released rapidly from the inner reservoir. The rupturing of the barriers is induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipient or swelling agents.[6,7]

Metoprolol tartrate is a cardioselective beta-adrenergic blocking agent used in hypertension, cardiac arrhythmias, angina pectoris, heart failure, hyperthyroidism and prophylactic, in the treatment of migraine. Metoprolol, with its incomplete bioavailability (due to first-pass metabolism), short halflife (4-6 h), multiple daily dosing, and high aqueous solubility is an ideal candidate for the pulsatile release system for improving patient compliance.[8,9]

The present study focuses on the development of pulsatile release tablets of Metaprolol Tartrate at a peroral, time - controlled single-unit dosage form. The proposed system consists of a core tablet coated with two layers, an inner swelling layer and an outer rupturable coating.

The swelling layer is composed of croscarmellose sodium, a super disintegrant and Micro crystalline celllose (MCC) as a diluent, while the rupturable coating is an ethyl cellulose.[10,11]

MATERIALS AND METHODS:

MATERIALS:

Metaprolol Tartrate (Chandra labs), MCC (Degussa India Pvt. Ltd., Mumbai L.R) , Cross povidone, Sodium starch glycolate (S.D. Fine Chem. Ltd., Mumbai L.R), HPMC K100, Ethyl cellulose 5Cps(L.R. Sisco Research Lab.Pvt. Mumbai). All materials used were of analytical grade.

METHOD:

Formulation of core tablets by direct compression:

The inner core tablets were prepared by using direct compression method as shown in Table.No.1. powder mixtures of metaprolol tartrate , microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol) ,SSG, crospovidone, lactulose monohydrate ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 150mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with a 9mm punch and die to obtain the core tablet.

Formulation of mixed blend for barrier layer:

The various formulation compositions containing Ethylcellulose and HPMC. 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 250 mg of mixed blend as given in Table.No.2 125mg of barrier layer material was weighed and transferred into a 13mm die then the core tablet was placed manually at the center. The remaining 125mg of the barrier layer materiel was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.[12]

Table.No.1. Formulation of Metoprolol Tartrate core tablets

Formulation Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol	25	25	25	25	25	25	25	25	25
Micro Crystalline Cellulose	118	126.5	125	118	126.5	125	118	126.5	125
Crospovidone	3	4.5	6	-	-	-	-	-	-
Cross Carmellose Sodium	-	-	-	3	4.5	6	-	-	-
Sodium Starch Glycollate	-	-	-	-	-	-	3	4.5	6
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150	150	150	150

Table.No.2: Formulation of Press Coat tablets using different percent ratios of HPMC K100& EC 5 Cps mixed blends

Press coat	P1	P2	P3	P4	P5
HPMC K 100(%)	1	0	1	3	1
E.C 5 Cps (%)	0	1	1	1	3
Total wt of tablet(mg)	400	400	400	400	400

EVALUATION OF PRESS COATED TABLETS

Evaluation of rapid release core (RRCT) and press-coated tablets of metaprolol tartrate sodium.

Weight variation[13] :

Twenty tablets were randomly selected from each batch weighed individually. The average weight and standard deviation was calculated**.**

Thickness:

Three tablets from each batch of formulation were collected and the thicknesses of the tablets were measured with the help of Vernier caliper. The average thickness was calculated.

Hardness :

Hardness was measured using Monsanto tablet hardness tester. The hardness of five tablets in each batch was measured and the average hardness was calculated in terms of kg/cm2 .

Friability (F)[14]:

Friability of the tablet determined using Roche friabilator. Pre-weighted sample of tablets were placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.

Wetting time :

Wetting time of dosage form is related to the contact angle. A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. Tablet was kept on the paper and the time for complete wetting was measured.

Disintegration time for RRCTs :

LABINDIA DT 1000 USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing phosphate buffer pH 6.8 at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the

liquid. The time taken for the complete disintegration of the tablets was noted.

In-vitro release studies for RRCTs

Tablet was introduced into the basket of the LABINDIA TS 8000 USP dissolution test apparatus and the apparatus was set in motion at 50 rpm for time period of 1 hr, 5 ml of sample was withdrawn for every 15min intervals and replaced by pH 7.2 phosphate buffer solutions. Samples withdrawn were analyzed by UV spectrophotometer for presence of drug using buffer solution as blank at 342 nm.

***In-vitro* Dissolution methods for press-coated tablets :**

In –vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method at 37 ± 0.5 °C using 0.5% w/v aqueous solution sodium lauryl sulfate in USP-II dissolution apparatus at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh 0.5% sodium lauryl sulfate solution maintained at the same temperature. The samples were analysed at 342nm using a UV spectrophotometer. The lag time and percentage release was determined of the each formulation.

Release Kinetics[15,16] :

As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, Higuchi and Peppa's- Korsemeyer equations. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's- Korsemeyer equation. The results are given in Table

$Q = k_o t$ (zero order release kinetics)

$\ln (1-Q) = - K_1 t$ (First order release kinetics)

$Q = K_2 t^{½}$ (Higuchi equation)

$M_t/M_\alpha = K.t^n$ Peppa's and Korsemeyer equation (Power Law)

Where Q is the amount of drug released at time t, $K_{0=}$ zero order rate constant, $K_{1=}$ first order rate constant, $K_{2=}$ Higuchi rate constant, M_t is the amount of drug released at time t and M_α is the amount released at time α, thus the M_t/M_α is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent.

Stability Studies[17] :

Stability studies of the optimised formulation of press coated tablets of Metaprolol tartrate were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation according to ICH guide lines. The studies were carried out at 25oC/60%RH, 30 ºC/65% RH and 40 ºC/75% RH for 90 days by storing the samples in stability chamber (Lab-care, Mumbai).

RESULTS &DISCUSSION

Pulsatile press coated tablets of Metoprolol tartrate were developed to prolong the gastric residence time and to increase the drug bioavailability. Metoprolol tartrate was chosen as a model drug because it is better absorbed in the stomach than the lower gastro intestinal tract.

Drug-excipient compatibility:

IR spectra for drug and optimised formulation(Figure.No.1&2) revealed that there was no incompatibility between drug and excipients because of no change in the wave numbers of functional groups of metoprolol tartrate

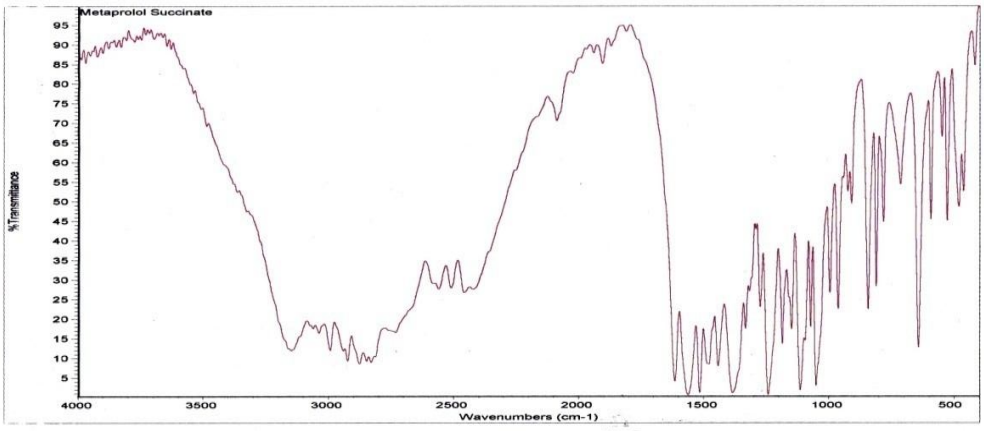

Figure.No.1: FTIR Studies of the pure drug

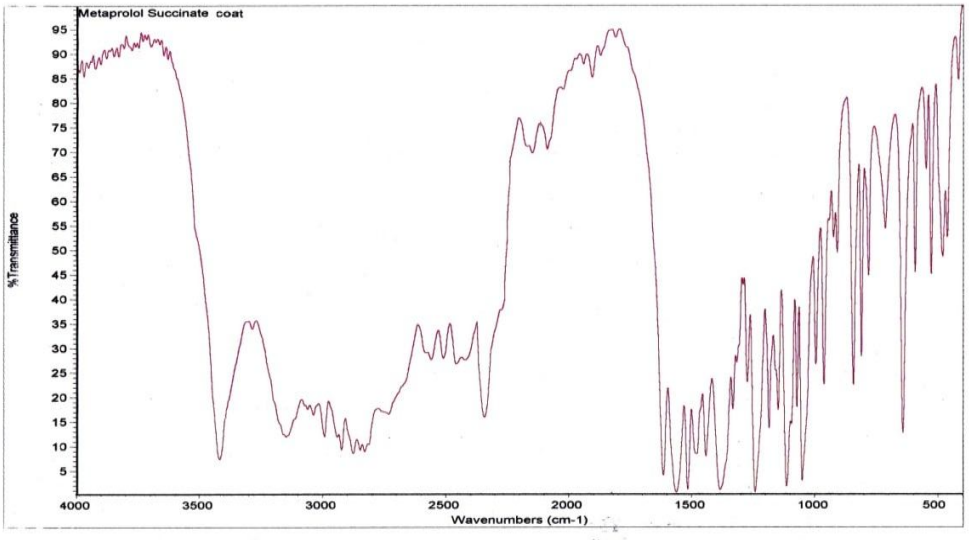

Figure.No.2: FTIR Studies of the optimized formulation

Post compressional parameters of core tablets:

Weight variation, Thickness, Hardness, Friability, Disintegration time and wetting time:

The values of weight variation, thickness, hardness, friability and assay of the twenty tablets

(Table.No.3) were found to be within the limits of conventional oral tablets stated in the Indian Pharmacopoeia (IP, 1996). The average mass ranged from 1.18 to 1.62 %, thickness of the tablets varied from 2 mm to 2.5 mm, hardness of the tablets was in the range 4 to 4.5 kg/cm^2, the friability ranged from 0.52 to 0.7%. disintegration time 1.5min to 4minand wetting time 46 to 59 sec. The mass, thickness, hardness, friability, and disintegration time of all compressed tablets were within the limits as per USP.

Table.No.3. Post compressional Parameters of Core tablets:-

Formulation Code	Weight Variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time	Wetting Time
F1	1.65	4.5	2.5	0.7	4min	59Sec
F2	1.57	4.2	2.3	0.55	3.5min	56Sec
F3	1.42	4	2.4	0.62	1.5min	46 Sec
F4	1.54	4.1	2.2	0.52	2min	49 Sec
F5	1.18	4.3	2.4	0.62	2.12min	50 Sec
F6	1.35	4.4	2	0.57	2.2min	51Sec
F7	1.44	4.2	2.3	0.55	2.45min	55 Sec
F8	1.23	4.3	2.4	0.62	2.2min	51 Sec
F9	1.48	4.4	2	0.52	2.3min	54 Sec

In-Vitro release studies of RRCT:

In-Vitro release studies of rapid release core tablets (Figure.No.3) revealed that the formulation F3 showed faster dissolution rate with 97.8% drug release at the end of 60 th min. This can be explained by

comparing with wetting time of F3. Here the super disintegrant Cross Povidone possess more capillary action for water absorption when compared to Cross carmellose sodium and sodium starch glycolate.

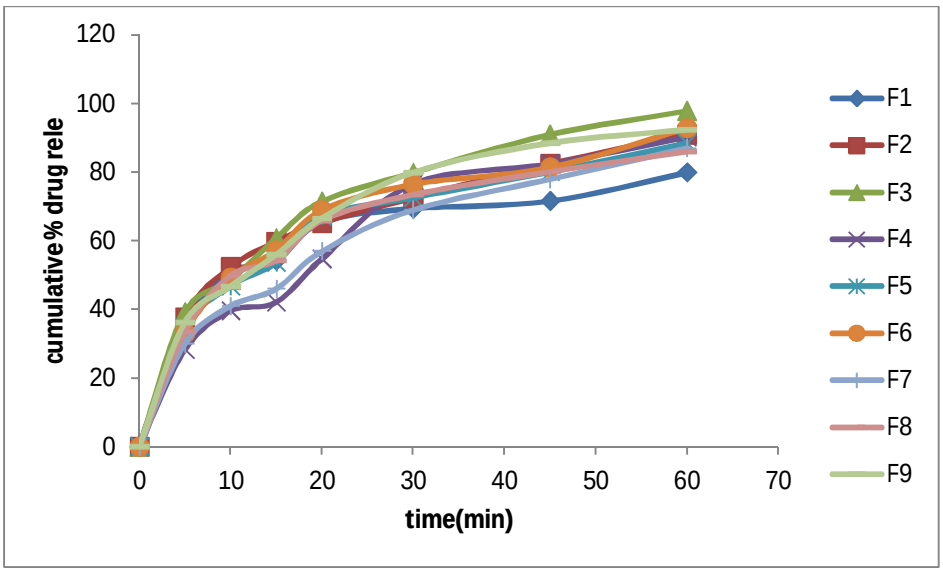

Fig.No.3: Comparative dissolution profile of Metaprolol Tratrate tablets containing different concentrations of super disintegrants(F1-F9)

Post compressional parameters of Metoprolol Tartrate press coated tablets

The post compressional parameters(Tale.No.4) of Metaprolol tartrate press-coated pulsatile tablets(PF1 to PF5) prepared by using different polymer ratios(HPMC K100:EC) also satisfied the compendial requirements.

Table.No.4: Evaluation parameters for press coated tablets

Formulation Code	Weight Variation (%)	Hardness (kg/cm^2)	Thickness (mm)	Friability %
P1F3	1.65	6.5	6.5	0.7
P2F3	1.57	6.7	6.45	0.55
P3F3	1.42	6.6	6.4	0.62
P4F3	1.3	7.2	6	0.54
P5F3	1.18	7.1	6.1	0.62

In-vitro release studies of press coated tablets:

In-vitro release profiles of press coated pulsatile tablets (Figure.No.4) of Metaprolol Tartrate revealed that P3F3 formulation showed (96.3%) best release at the end of 8th hr. Here the composiion of coat consists of HPMC K100,(responsible for swellability) and ethyl Cellulose(responsible for erodabilility). The lag time of the system could be modified by several factors such as core composition& composition of swelling layer and rupturable layer.

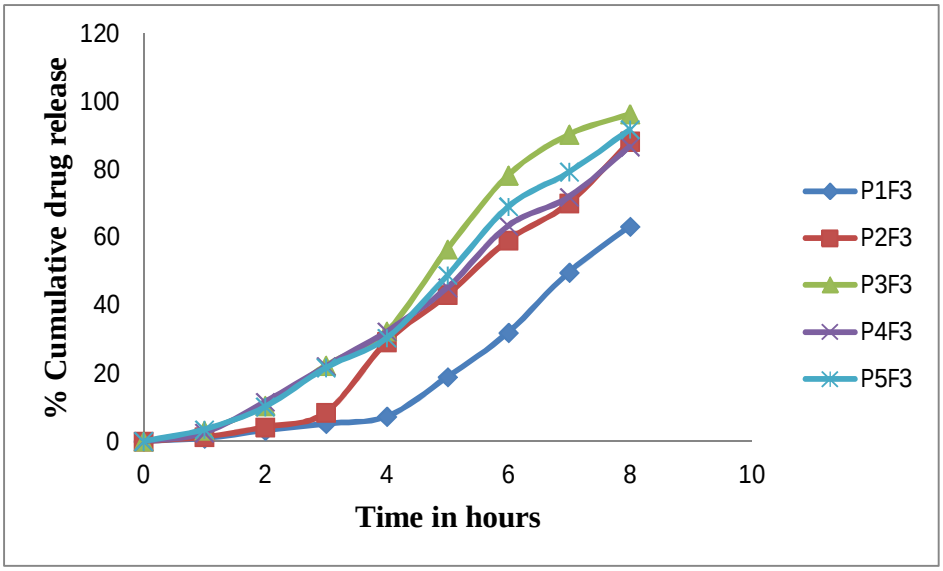

Fig.No.4: Comparative dissolution profile of Metaprolol Tratrate press coated tablets containing different concentrations of ethyl cellulose and HPMC(P1F3 – P5F3).

Release kinetics:

Release kinetics of Metoprolol (Table.No.5) from the optimized formulation P3F3 was found to follow First order kinetics (correlation coefficient, r^2 value 0.981).Higuchi plot showed an r^2 valve of 0.986 for formulationP3 F3 suggesting that the diffusion plays an important role in the controlled release.

Table.No.5: Release kinetics: Coefficient of correlation (r) values of different batches of Metoprolol tartrate press coated tablets

Formulation	Zero order	First order	Higuchi's	Peppa's
P1F3	0.976	0.870	0.929	0.934
P2F3	0.975	0.915	0.954	0.971
P3F3	**0.979**	**0.981**	**0.986**	**0.994**
P4F3	0.971	0.990	0.994	0.995
P5F3	0.983	0.923	0.957	0.966

Stability studies:

Stability studies(Table.No.6) of the optimised formulation P3F3 showed that there was no significant change in the physical property and percent of drug release.

Table.No.6: Stability studies of optimized formulation

Sampling interval	% of drug release during 8 hours		
	25 0C/60%RH	30 0C/65% RH	40 0 C/75% RH
0th Days	92	92	92
15thDays	91.5	91.45	91.40
45thDays	90.96	90.85	90.82
90thDays	90.45	90.42	90.38

CONCLUSION

A once-daily time-controlled release pulsatile tablet of Metoprolol Ttartrate having short halflife was found to exert a satisfactory time-controlled release profiles which may provide an increased therapeutic efficacy.

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