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FORMULATION AND EVALUATION OF TIME DEPENDENT DRUG DELIVERY SYSTEM FOR ANTIHYPERTENSIVE DRUG

[1]Bajirao B. Tarase, [2]Dr. N.N. Bobade, [3]Dr. S.C Atram, [4]Dr. V.V. Wankhade,[5]Dr. S.D. Pande

[1]Student, [2,3,4]Assistant Proffesor, [3]Principal

[1]Department of Pharmaceutics,

[1]Vidyabharati College of Pharmcy Amravati

Abstract: Metoprolol tartrate, a beta-blocker used for the management of hypertension, was formulated into a time-dependent drug delivery system to align with the circadian rhythm of blood pressure. The aim was to develop a press-coated tablet with a lag time followed by a rapid drug release, targeting the morning surge in blood pressure. Core tablets were prepared by direct compression using various superdisintegrants. The core tablets were then coated with different ratios of HPMC K4M and Ethyl Cellulose using the compression coating technique. Systematic optimization using a 3^2 factorial design identified the optimal composition of 125 mg Ethyl Cellulose and 100 mg HPMC K4M, which provided a 6-hour lag time followed by rapid drug release. The formulation exhibited controlled drug release kinetics, following a Korsmeyer-Peppas model. Stability studies under accelerated conditions confirmed the robustness of the optimized press-coated pulsatile tablet. The developed system demonstrates the potential of time-dependent drug delivery to improve the chronotherapeutic management of hypertension

Index Terms - Metoprolol tartrate, Chronotherapy, Time-dependent drug delivery, Press-coated tablet, Pulsatile release

INTRODUCTION

Cardiovascular diseases, including hypertension, exhibit distinct circadian rhythms in their pathophysiology and clinical manifestations[1]. The morning surge in blood pressure, which typically occurs between 6 am and 12 pm, is associated with an increased risk of adverse cardiovascular events, such as myocardial infarction and stroke[2]. This circadian variation in blood pressure is regulated by complex neuroendocrine mechanisms and is influenced by factors like the sleep-wake cycle, physical activity, and sympathetic nervous system activity[3].

Conventional drug delivery systems for antihypertensive medications, which aim to maintain a constant drug concentration throughout the day, may not be optimally aligned with the body's natural circadian rhythms[4]. This mismatch between drug availability and the body's physiological needs can lead to suboptimal therapeutic efficacy and an increased risk of adverse events. To address this challenge, the concept of chronotherapy has emerged, which focuses on tailoring the drug delivery to coincide with the body's circadian fluctuations[5].

Time-dependent drug delivery systems, such as pulsatile or delayed-release formulations, offer a promising approach for the chronotherapeutic management of hypertension[6]. These systems are designed to release the drug after a predetermined lag time, coinciding with the morning rise in blood pressure, thereby providing the optimal therapeutic effect when it is most needed[7]. The development of such time-dependent drug delivery systems for antihypertensive medications can potentially improve clinical outcomes, reduce adverse effects, and enhance patient compliance[8].

Metoprolol tartrate, a cardioselective beta-blocker, is a widely prescribed medication for the management of hypertension, angina, and other cardiovascular conditions[9]. Due to its relatively short half-life, metoprolol tartrate often requires twice-daily dosing, which can impact patient adherence[10]. Formulating metoprolol tartrate into a time-dependent drug delivery system could address this limitation and provide a more convenient once-daily dosing regimen while optimizing the drug's chronotherapeutic potential.

The present study aims to develop a time-dependent drug delivery system for metoprolol tartrate using a press-coated tablet approach. The core tablet formulation will be optimized for rapid disintegration and drug release, while the press-coated layer will be designed to provide a predetermined lag time followed by a pulsatile drug release, targeting the early morning surge in blood pressure associated with hypertension.

MATERIAL AND METHOD

MATERIAL

Metoprolol tartrate was obtained from Aalidhra Pharmachem Pvt. Ltd. (India). Hydroxypropyl methylcellulose (HPMC K4M) and ethyl cellulose were procured from Signet Excipients Pvt. Ltd. (India). Microcrystalline cellulose (MCC), croscarmellose sodium, crospovidone, sodium starch glycolate, talc, and magnesium stearate were supplied by Glenmark Pharmaceutical Ltd. (India). All other chemicals and solvents used were of analytical grade.

METHOD

Preformulation Studies

Drug Characterization

The physical appearance, solubility, and melting point of the received metoprolol tartrate sample were determined. Solubility studies were performed by the saturation method in various solvents, including water, ethanol, and acetone. The melting point was measured using the capillary method.

Spectroscopic Analysis

The UV absorption spectrum of metoprolol tartrate was recorded using a UV-visible spectrophotometer (Shimadzu UV-1800, Japan) to determine the λmax. Fourier-transform infrared (FTIR) spectroscopy was performed to assess the compatibility between the drug and the selected polymers (HPMC K4M and ethyl cellulose).

FORMULATION DEVELOPMENT

Preparation of Core Tablets

The core tablets of metoprolol tartrate were prepared by the direct compression method. Different superdisintegrants, namely croscarmellose sodium, crospovidone, and sodium starch glycolate, were evaluated at concentrations ranging from 10 to 30 mg to optimize the disintegration time. The core tablet formulations were further evaluated for pre-compression and post-compression parameters to select the optimized composition.

TABLE NO. 1: - FORMULATION TABLE OF CORE TABLE

Name of Ingredients	Formulation Code with their Quantity								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metoprolol tartrate(mg)	50	50	50	50	50	50	50	50	50
Croscarmellose Sodium (CCS)(mg)	10	20	30	-	-	-	-	-	-
Crospovidone (mg)	-	-	-	10	20	30	-	-	-
Sodium Starch Glycolate (SSG) (mg)	-	-	-	-	-	-	10	20	30
Microcrystalline Cellulose (MCC) (mg)	170	160	150	170	160	160	160	160	150
Talc (mg)	10	10	10	10	10	10	10	10	10
Magnesium Stearate (mg)	10	10	10	10	10	10	10	10	10
Total (mg)	250	250	250	250	250	250	250	250	250

Preparation of Press-Coated Tablets

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 presscoating material to prepare press-coated pulsatile tablets respectively by direct compression method.

The optimized core tablets were press-coated with varying ratios of HPMC K4M and ethyl cellulose using the compression coating technique. The core tablet was placed in the center of the die cavity, and the coating mixture was carefully added in equal proportions above and below the core. The samples were then compressed using a hydraulic press.

Table No.2:- Formulation table of Press Coated Tablets

Ingredient	CF1	CF2	CF3	CF4	CF5	CF6	CF7
HPMC K4M (mg)	0	250	125	166	187.5	84	62.5
Ethyl Cellulose (mg)	250	0	125	84	62.5	166	187.5
MCC (mg)	38	38	38	38	38	38	38
Talc (mg)	6	6	6	6	6	6	6
Mg.Sterate (mg)	6	6	6	6	6	6	6
Core tablets(mg)	250	250	250	250	250	250	250
Total WT(mg)	550	550	550	550	550	550	550

Factorial Design

A 3^2 factorial design was employed to systematically optimize the press-coated tablet formulation. The independent variables were the concentrations of ethyl cellulose (X1) and HPMC K4M (X2), while the dependent variables were the lag time and the drug release profile. The optimal formulation was identified based on the desired in-vitro performance characteristics. By testing all possible combinations of the two factors at the specified levels, you can determine lag time, drug release other relevant quality attributes. This factorial design provides a systematic approach to investigate the formulation variables and optimize the press-coated metoprolol tablet. In this factorial batch we use HPMCK4M and ethyl cellulose as a polymer and other eccipients with different concentration. the formulation table of factorial batch given below **Table No 3.**

Table No 3. Factorial Batches formulation of Press Coated Tablet

Sr.No.	Batch Code	X1 (mg)	X2 (mg)	MCC (mg)	Talc (mg)	Mg. sterate (mg)	Total (mg)
1	FF1	75	75	138	6	6	300
2	FF2	75	100	113	6	6	300
3	FF3	75	125	88	6	6	300
4	FF4	100	75	113	6	6	300
5	FF5	100	100	88	6	6	300
6	FF6	100	125	63	6	6	300

7	FF7	125	75	88	6	6	300
8	FF8	125	100	63	6	6	300
9	FF9	125	125	38	6	6	300

EVALUATION OF CORE TABLET

Precompression Parameter of Core Tablets

Angle of repose: to assess the flow properties of the powder blend

Bulk density and tapped density: to determine the packability of the powder

Hausner ratio and Carr's index: to evaluate the compressibility and flowability of the powder.

Post-Compression Parameter of Core Tablet

The formulated core tablets of Metoprolol tartrate were evaluated for the following evaluation parameters;

Weight variation[11]: 20 tablets were selected for each drug and were weighed. Percentage weight variation was calculated comparing with average weight.

Thickness: The thickness of the formulatated core tablets were measured by using digital vernier calipers. Randomly 10 tablets were taken and thickness was measured.

Hardness test: Hardness of the tablets was determined using the digital hardness tester. The plunger was then compressed till the tablet was broken. Randomly withdrawn 10 tablets were taken for hardness test.

Friability test[12]: Required number of previously weighed tablets were placed in the friability apparatus. Then it was moved at 100 revolutions per minute. Tablets were collected and reweighed. The percentage friability was calculated by using the following formula;

Percentage friability = [(Initial weight-Average weight) / (Initial weight)] X 100

Disintegration test: Tablet disintegration study was performed in disintegration apparatus. Six tablets were placed in six tubes.Temperature was maintained at 37◦C±2◦C. The machine was operated until the tablets were completely disintegrated.

Drug content: Drug content of the core tablets was determined as per procedure mentioned in IP, 2010. For measuring the drug content of Metoprolol tartrate tablets twenty tablets were randomly selected and powered. 20 mg equivalent weight of drug was taken and diluted unto 20ml with water .50 ml of methanol was added and shaken well; further volume was made up to 100 ml with methanol. It was then filtered. 10 ml of filtrate was taken and diluted to 50 ml with methanol. Absorbance of the resulting solution was measured at 222 nm using a UV spectrophotometer.

***In vitro* drug dissolution study**: The USP type 2 (Paddle) apparatus was used to determine the amount of Metoprolol tartrate release from core tablets. The paddle rotation speed and temperature was set to 100 rpm and37±0.5o C respectively. The dissolution medium was 900 ml of the 6.8 phosphate buffer at particular time interval 5 ml sample was withdrawn and analyzed in UV spectrophotometer at 222 nm.

Evaluation of Press Coated Tablets

The formulated press coated tablets of Metoprolol Tartrate were evaluated for the following evaluation parameters;

Weight variation: 20 tablets were selected for each drug and were weighed. Percentage weight variation was calculated comparing with average weight.

Thickness: The thickness of the formulated press coated tablet were measured by using digital vernier calipers. Randomly 10 tablets were taken and thickness was measured.

Hardness test: Hardness of the tablets was determined using the digital hardness tester. The plunger was then compressed till the tablet was broken. Randomly withdrawn 10 tablets were taken for hardness test.

Friability test: Required number of previously weighed tablets were placed in the friability apparatus. Then it was moved at 100 revolutions per minute. Tablets were collected and reweighed. The percentage friability was calculated by using the following formula;

Percentage friability = [(Initial weight-Average weight) / (Initial weight)] X 100

***In-vitro* drug dissolution study:** The USP type 2 (Paddle Type) apparatus was used to determine the amount of Metoprolol succinate released from the compression coated tablets. The paddle rotation speed and temperature was set to 100 rpm and 37±0.5oC, respectively. The dissolution medium was 900 ml of the 0.1N HCl for initial 2 hr subsequent in pH 6.8 phosphate buffer for the remaining period. At particular time interval samples were withdrawn and analyzed in UV spectrophotometer at 222nm.

KINETICS OF DRUG RELEASE[13,14]

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

Zero-order Kinetics $Q_t = Q_0 + K_0 t$

Where, Q_t- amount of drug dissolved in tim(t) ,Q_0- initial amount of drug in the solution, K_0 - Zero order release constant.

First order kinetics $\log Q_t = \log Q_0 + K_1 t/2.333$

where, Q_t- the amount of drug released in time, Q_0-initial amount of drug in the solution, K_1-first order release rate constant

Higuchi mode $Q_t = K_H t^{1/2}$

Where Qt - amount of drug released in time t K_H - Higuchi dissolution constant.

Korsmeyer - Peppas model $M_t / M_\infty = K. t^n$

Where, M_t/M_∞- a fraction of drug released at time t, K- Release constant, n- release exponent

Hixson-Crowell model $W_0^{1/3} - W_t^{1/3} = K_s t$

Where, W_0 -is the initial amount of drug in the pharmaceutical dosageform, W_t - remaining amount of drug in the pharmaceutical dosage form at time t, Ks -constant incorporating the surface-volume relation.

STABILITY STUDIES[15]

The optimized press-coated tablet formulation was subjected to stability studies under accelerated conditions (40°C ± 2°C/75% RH ± 5% RH) for 6 months, as per ICH guidelines. The samples were evaluated for drug lag time, in-vitro drug release, and physical appearance at regular intervals.

RESULT AND DISCUSSION

Selection of Active Pharaceuitical Ingredients

Metoprolol Tartrate: Metoprolol tartrate, a selective beta-1 adrenergic receptor antagonist, effectivFor these study Metoprolol Tartrate was selected. The reason behind choosing this drug have a relatively short half-life, typically ranging from 3 to 7 hours, which necessitates a twice-daily dosing regimen for the management of hypertension.

The press-coated tablet design can help to prolong the drug's residence time in the body and extend the duration of action, potentially allowing for a once-daily dosing regimen and improved patient compliance.

Result: For development of Time Dependent Drug Delivery For antihypertensive Drug the metoprolol tartrate was selected as active drug

IDENTIFICATION AND CHARACTERIZATION OF DRUG:

Description

- **Colour:** white to off-white crystalline powder.
- **Odor:** Odorless.
- **Texture:** Crystalline, powdery texture.

Determination of Solubility

Table No.4 Solubility of Metoprolol tartrate

Solvent	Solubility of Metoprolol Tartrate
Water	Freely soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Acetone	Freely soluble
Ether	Practically insoluble

Melting Point Determination

The melting point of metoprolol tartrate using this method is typically in the range of 120 to 124°C.

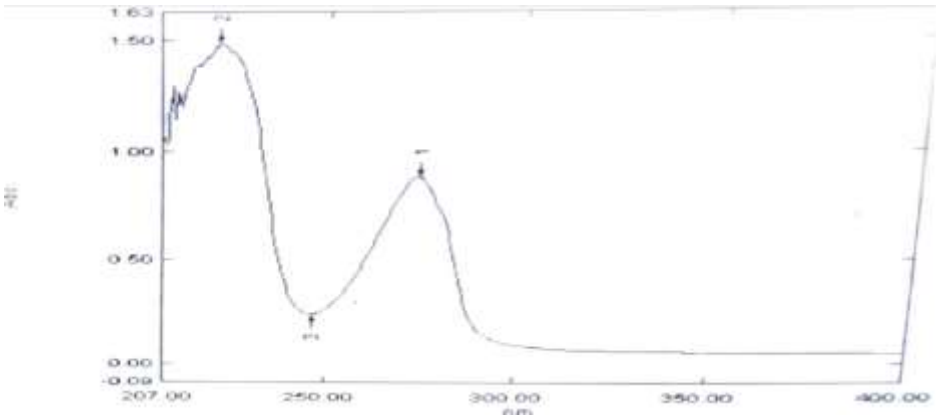
Micromeritic Characterization of Metoprolol tartrate: - In the micrometric properties, the Angle of repose, tapped density, bulk density, Carr's index andHausner’s ratio of the pure drug were determined. All the parameters were done as per the research paper.

Result: All parameters are within ranges.

SPECTROPHOTOMETRIC METHOD FOR THE ESTIMATION OF METOPROLOL TARTRATE

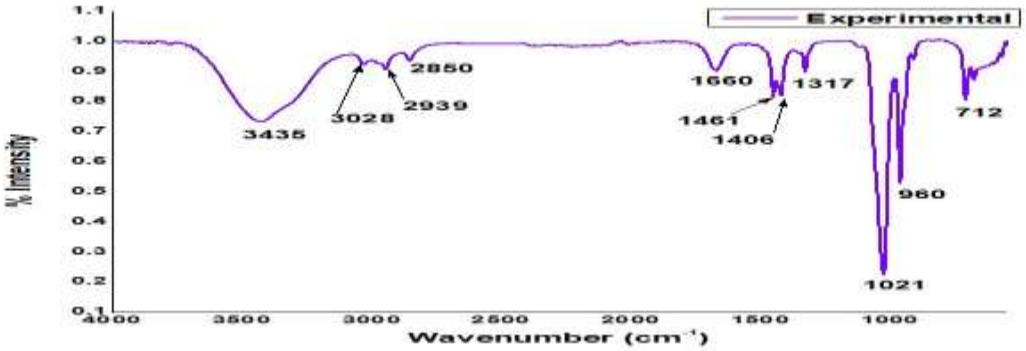
Determination of a λ max

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 222 nm and the same was selected for Metoprolol Tartrate.



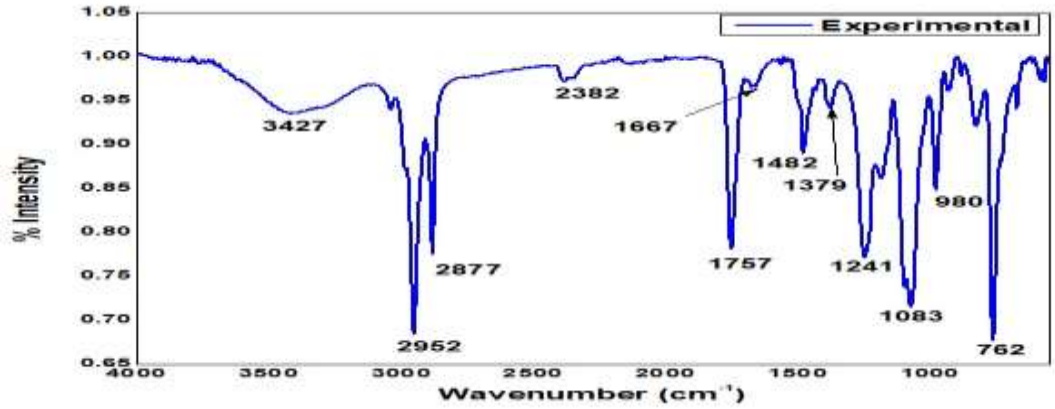
Graph No.1: UV Spectra of Pure Drug

DRUG AND EXCIPIENT COMPATIBILITY STUDY: IR spectra for drug and optimized formulation (Graph.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

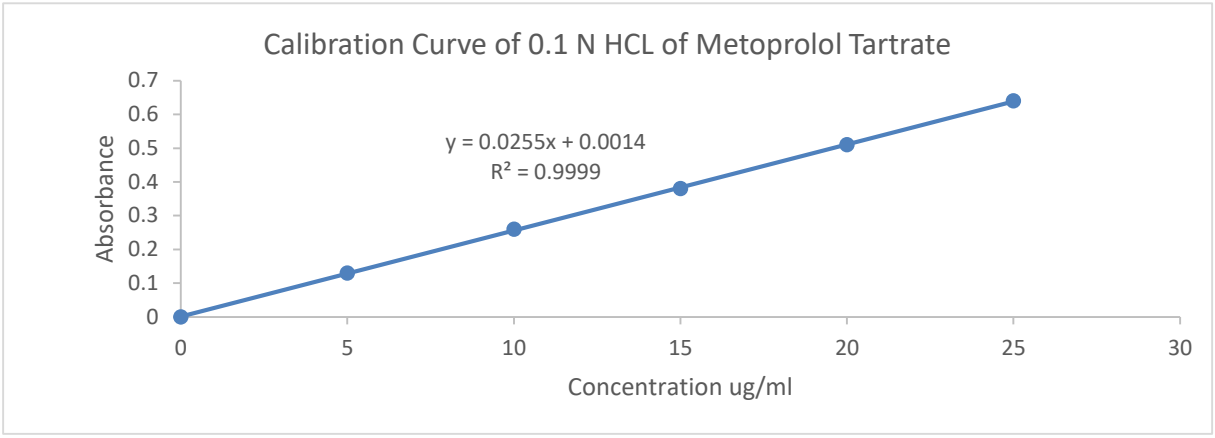
Graph No.2 IR spectrum of Pure Drug



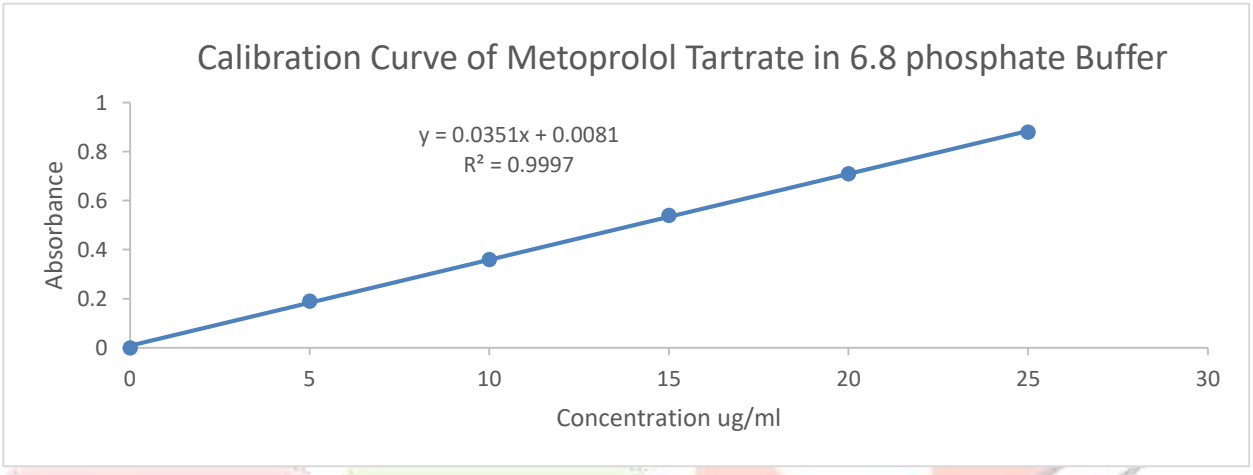
Graph No.3 IR Spectrum of Drug and Polymer

STANDARD CALIBRATION CURVE

Standard Calibration Curve Metoprolol Tartrate In 0.1N HCl



Graph No.4 STD Calibration Curve of Metoprolol Tartrate IN 0.1N HCL



Graph No. 5 STD Calibration Curve of Drug in 6.8 phosphate Buffer

Results:- The standard calibration curve of Metoprolol Tartrate was plotted using a UV visible Spectrophotometerat λ max 222 nm by using 0.1 N HCl. From the standard curve, it was observed that the drug obeys Beers law in the concentration range of 5-25 µg/ml in 0.1N HCL and 6.8 Phosphate Buffer.

FORMULATION OF CORE TABLETS

Pre-compression Parameter of Core powder

Table No.4 Pre-compression Parameter of Core powder

Sr No.	Formulation Code	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Angle of Repose	Carrs index	Hausners ratio
1	F1	0.52±0.02	0.58±0.03	28.40±0.03	10.34±0.49	1.11±0.03
2	F2	0.51±0.04	0.58±0.04	28.00±1.28	12.06±0.50	1.13±0.03
3	F3	0.53±0.05	0.61±0.15	27.02±1.83	13.11±1.83	1.15±0.02
4	F4	0.52±0.62	0.59±0.79	26.01±0.55	11.86±1.64	1.13±0.03
5	F5	0.55±0.42	0.63±0.08	26.40±0.34	12.69±1.77	1.14±0.04
6	F6	0.51±0.80	0.57±0.08	25.83±0.63	10.52±1.98	1.11±0.01
7	F7	0.53±0.23	0.59±0.03	26.59±0.96	10.16±1.01	1.11±0.01

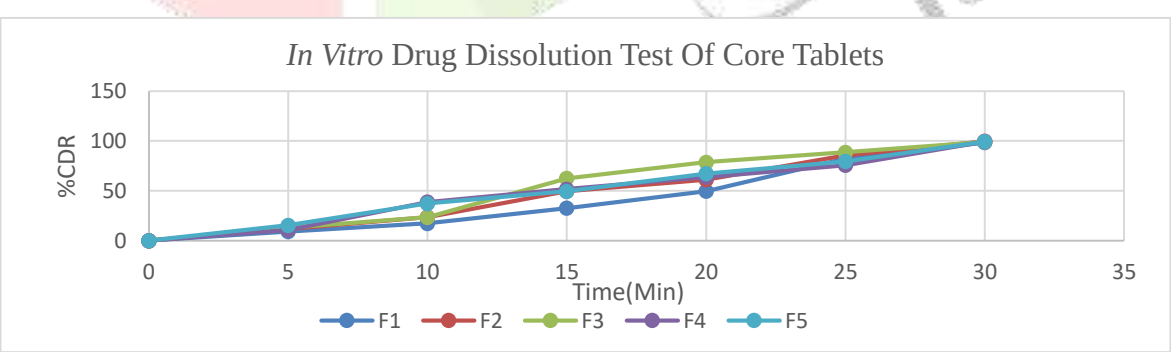
8	F8	0.53±0.82	0.60±0.01	27.35±0.35	11.66±0.84	1.13±0.02
9	F9	0.51±0.97	0.58±0.08	27.76±0.62	10.64±0.49	1.13±0.02

Postcompression parameter of Core Tablets

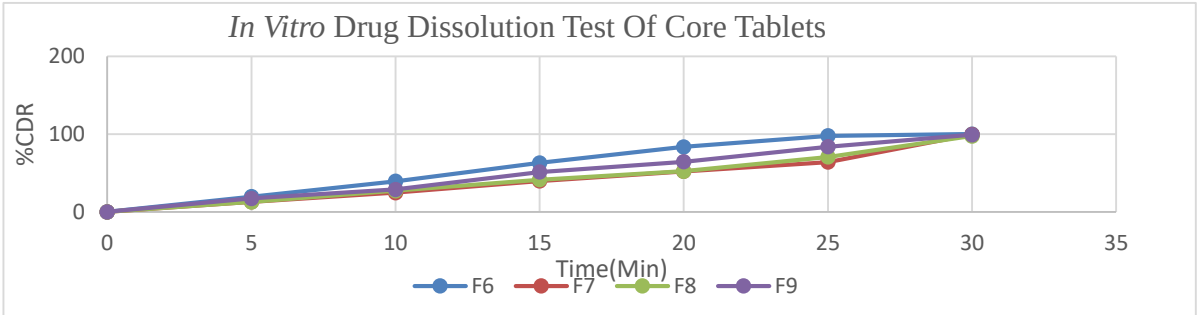
Table No.5 Postcompression parameter of Core Tablet

Parameters	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight Variation(mg)	251.9 ± 1.68	251.0 ± 0.40	251.4 ± 0.55	250.8 ± 0.77	250.2 ± 0.051	250.1 ± 1.01	249.9 ± 1.68	248.2 ± 1.18	249.6 ± 0.83
Thickness (mm)	4.051 ± 0.572	4.111 ± 0.542	4.39± 0.617	4.43± 0.625	4.57± 0.12	4.18± 0.439	4.5± 0.480	4.38± 0.597	4.86± 0.177
Hardness (kg/cm2)	4.2± 0.20	3.8± 0.30	4.0± 0.20	3.8± 0.25	3.7± 0.30	3.9± 0.31	3.7± 0.37	3.6± 0.37	3.7± 0.45
Friability (%)	0.22± 0.19	0.32± 0.08	0.27± 0.23	0.33 ±0.21	0.37± 0.15	0.29± 0.19	0.36± 0.04	0.40± 0.85	0.37± 0.60
D.T (min)	6.40± 0.34	5.00± 0.67	3.30± 0.31	6.00± 0.56	4.30± 0.45	3.00± 0.10	6.50± 0.64	4.20± 0.56	3.40± 0.45
Drug Content (%)	99.43± 0.02	99.66± 0.05	99.31 ±0.03	99.35 ±0.06	99.21 ±0.07	99.92 ±0.03	99.32 ±0.02	99.12 ±0.04	99.77 ±0.02

Result for In-Vitro drug release of the Core Tablets:



Graph No.6 *In-Vitro* drug release of the Core Tablets (F1to F5)



Graph No.7 *In-Vitro* drug release of the Core Tablets (F6 to F9)

Key reason for selecting F6 batch of core for coating in press coated tablets are given below:

Optimized disintegrant concentration: F6 contains the highest level of the disintegrant Crospovidone at 30 mg, which facilitated the rapid disintegration and dissolution of the tablet. formulation F6 had one of the fastest disintegration times at 3.0 ± 0.10 minutes. Fastest and most complete drug release: Formulation F6 exhibited the fastest and most complete drug release profile, reaching nearly 100% drug release within 30 minutes. This is the highest performance among the 9 formulations tested.

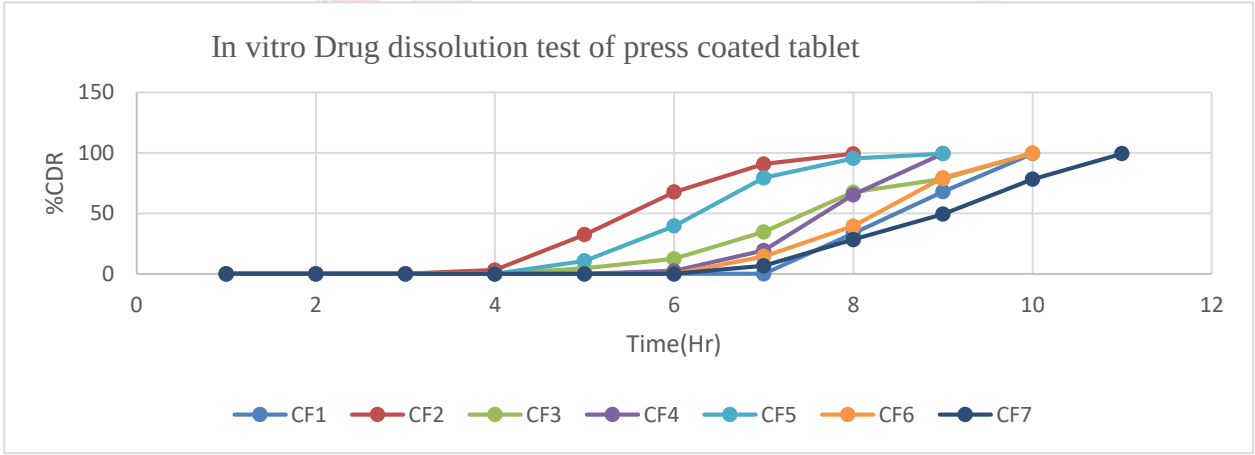
The rapid disintegration and dissolution of the F6 core can be effectively modulated by the press-coating layer to achieve the desired extended or delayed release characteristics. In summary, the selection of F6 as the core tablet is well-justified based on its superior overall performance across the various quality attributes evaluate

FORMULATION OF PRESS COATED TABLET

Table No.6 Evaluation of Post-compression Parameter of press Coated Tablets

Parameters	Formulation Code						
	CF1	CF2	CF3	CF4	CF5	CF6	CF7
Weight Variation test	550.4± 1.05	548.8± 1.41	551.7±1.23	551.1 ±0.70	549.7±1.23	552.1±1.65	549.2.9 ±0.90
Thickness(mm)	6.44 ± 0.30	6.45 ±0.56	6.45 ± 0.05	6.43 ± 0.05	6.44 ± 0.50	6.40 ± 0.32	6.41 ± 0.03
Hardness (kg/cm^2)	7.1 ± 0.35	6.9 ± 0.17	7.3 ± 0.36	7.2 ± 0.32	6.9 ± 0.43	7.0 ± 0.32	7.1 ±0.25
Friability(%)	0.37 ± 0.68	0.49 ± 0.96	0.21 ± 0.60	0.29 ± 0.98	0.50 ± 0.85	0.48 ± 0.69	0.41 ±0.93

In Vitro Drug Dissolution test of Press Coated Tablets



Graph no.8 *In Vitro* Drug Release of Press Coated Tablets

The reasons for conducting the factorial batches are:

CF3, CF4, CF5, CF6, and CF7: These batches have varying ratios of HPMC K4M and Ethyl Cellulose. They exhibit either incomplete drug release or an initial burst release, indicating the need for further optimization. Identify the optimal composition: The factorial design provides a systematic approach to determine the optimal combination of HPMC K4M and Ethyl Cellulose that will result in the desired drug release kinetics from the press-coated tablets.

Improve drug release control: The initial coated tablet formulations (CF1 to CF7) did not seem to provide adequate control over the drug release, as evident from the rapid and/or incomplete drug release profiles. The factorial batches aim to fine-tune the polymer composition to achieve better control over the drug release from the press-coated tablets.

FACTORIAL DESIGN

Table No.7 Postcompression Parameter of Press compression parameter for Factorial Batches

Parameters	Formulation Code								
	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
Weight Variation (mg)	550.9 ± 0.68	552.7 ± 0.45	549.6 ± 0.08	548.6 ± 0.70	549.7 ± 0.05	549.9 ± 1.01	549.2 ± 1.60	550.1 ± 1.10	550.5 ± 0.80
Thickness (mm)	6.47 ± 0.45	6.50 ± 0.54	6.45± 0.42	6.40± 0.60	6.45± 0.12	6.44± 0.42	6.42± 0.48	6.47± 0.50	6.46± 0.10
Hardness (kg/cm^2)	7.1 ± 0.20	7.4± 0.30	7.2± 0.20	6.9± 0.25	7.0± 0.30	7.3± 0.31	7.2± 0.37	6.8± 0.37	7.2± 0.45
Friability (%)	0.41± 0.10	0.30 ± 0.02	0.39 ±0.23	0.47 ±0.34	0.43 ±0.05	0.34 ±0.12	0.36 ±0.43	0.51 ±0.78	0.38 ±0.50

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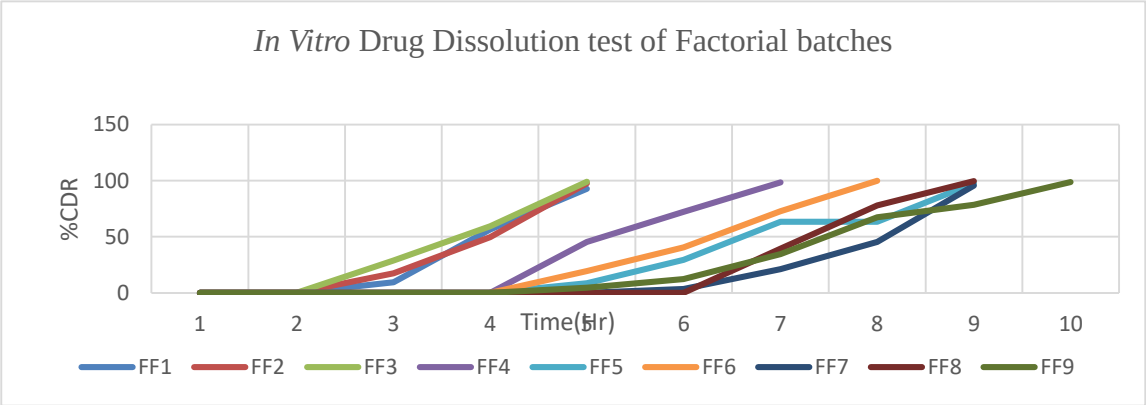
In Vitro Drug Release of Factorial Batch



Graph No.9 *In Vitro* drug release of Factorial Batch

Discussion: he seven batches (FF1 to FF9) exhibited varying drug release profiles, with different degrees of suitability for a pulsatile drug delivery system targeting hypertension. Batches FF1, FF2, and FF3 had short lag times (3 hours) followed by rapid drug release, reaching over 90% within 5 hours. These profiles were less suitable for a pulsatile system. Batches FF4 to FF6 demonstrated incomplete drug release, not reaching 100% even after 8 hours, and their release patterns were not well-suited for a pulsatile system. Batch FF7 showed a very slow and delayed drug release, with only 45.56% release at 8 hours, making it unsuitable for the target application. Batch FF8, with a combination of 125 mg Ethyl Cellulose and 100 mg HPMC K4M, was identified as the optimized formulation. It exhibited the most desirable characteristics, including a prolonged lag time of up to 6 hours, a rapid pulse release reaching 99.70% at 9 hours, and a well-controlled drug release profile, making it the most suitable for a pulsatile drug delivery system targeting hypertension.

KINETICS OF DRUG RELEASE

Factorial Batch	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
	R	R	R	R	R	R	R	R	R
Zero Order	0.7284	0.8726	0.9282	0.8165	0.8334	0.8195	0.6176	0.6842	0.8267
1st Order	0.6930	0.8022	0.8535	0.6205	0.5808	0.5521	0.4368	0.4681	0.5740
Higuchi Matrix	0.6429	0.7622	0.8197	0.7151	0.7268	0.7088	0.5021	0.5021	0.7128
Hix. Crowell	0.7043	0.8156	0.8674	0.7243	0.6988	0.7161	0.7088	0.5818	0.7048
Korsmeyer-Peppas	0.8981	0.8865	0.8633	0.7885	0.8884	0.8583	0.7161	0.6993	0.9197
Best Fit Model	Peppas	Peppas	Zero order	Zero order	Peppas	Peppas	Peppas	Peppas	Pepas

Table No.8 Model Fitting of Drug release for Factorial batch

Discussion: Optimized batch FF8 follows a Korsmeyer-Peppas drug release mechanism, which is likely an anomalous (non-Fickian) transport, indicating a combination of diffusion and polymer erosion processes controlling the drug release.

STABILITY STUDY

Table No. 24 Stability Study of FF8 Batch at 40ºC±2ºC/ 75±5%RH

Stability Study	% drug release	Lag time (Hr)	Apperance
0 Days	**99.70±1.70**	**6.0±0.21**	**No change**
1 week	**99.01±0.12**	**6.0±0.45**	**No change**
2 week	**97.90±0.45**	**6.0±0.81**	**No change**
3 week	**96.92±0.17**	**6.0±0.98**	**No change**
4 week	**95.80±0.34**	**6.0±1.08**	**No change**

The stability study data for the press-coated tablet formulation is highly promising, demonstrating the robustness and consistent performance of the product. The drug release remained consistently high, with only a slight decrease from 99.70% to 95.80% over 4 weeks under accelerated conditions. Importantly, the critical lag time of 4.0 ± 0.5 hours was maintained throughout the study, indicating the stability of the press-coating. Additionally, the physical appearance of the tablets did not change, confirming the integrity of the formulation. These results provide a strong foundation for the continued development and potential commercialization of the press-coated tablet, as the product has shown the ability to meet the necessary quality standards even under stress.

CONCLUSION

The press-coated tablet formulation (FF8) developed in this study exhibited the most desirable characteristics for a pulsatile drug delivery system targeting hypertension management. The formulation demonstrated a prolonged lag time of up to 6 hours, a rapid drug release reaching 99.70% at 9 hours, and well-controlled drug release, making it the optimal choice for the target application. The combination of 125 mg Ethyl Cellulose and 100 mg HPMC K4M provided the ideal balance for achieving the desired pulsatile release profile. The robust performance and consistent quality of the FF8 formulation, even under stress conditions, establish a strong foundation for its continued development and potential commercialization as a viable pulsatile drug delivery system for the treatment of hypertension.

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