RESEARCH PAPER

Development and evaluation of chronomodulated drug delivery system of Captopril

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ABSTRACT
The primary goal of the investigation presented herewith is to is to develop and optimize chronomodulated Captopril (CPT) tablets for the treatment of hypertension by effectively employing Box-Behnken design (BBD). For development of rapidly disintegrating core tablet of CPT by direct compression, the amount of croscarmellose (X1), Avicel PH102 (X2), and magnesium stearate (X3) were the independent factors, and the dependent factors were disintegration time (Y1) and drug release (Y2). Based on the evaluation parameters, batch F8 that showed 91.88% drug release in 60 minutes, was selected for further development of press coated tablet using BBD. The press-coated tablets were prepared using hydrophilic polymers such as HPMC K4M, HPMC K100, and Sodium alginate to obtain the desired lag time of 7 hrs. The optimized press-coated tablets showed lag time followed by rapid drug release. The statistical analysis showed that the formulation factors significantly affected the disintegration time and drug release profile. Overall, the investigation concluded that the time-dependent release of the CPT can be achieved using the press-coating formulation of fast disintegrating core tablet by effectively applying BBD.
Keywords: Chronotherapeutics, Captopril, Press-coated tablet, Box-Behnken design, Chronomodulation

How to cite this article: Bhoyar MN, Sathe BS, Khathuriya R. Development and evaluation of chronomodulated drug delivery system of Captopril. Int J Drug Deliv Technol. 2026;16(54s): 48-60. DOI: 10.25258/ijddt.16.54s.7

INTRODUCTION

Hypertension, commonly known as high blood pressure, is a long-term cardiovascular condition marked by elevated blood pressure levels and is regarded as one of the primary contributors to cardiovascular issues like stroke and heart attacks. A notable aspect of hypertension is the presence of a daily rhythm in blood pressure, indicating that blood pressure varies throughout a 24-hour cycle.1 In most patients, there is a fall in blood pressure during sleep, or a nocturnal dip. There is a sudden rise in blood pressure in the early morning hours when a person wakes up. This is referred to as the "morning surge." This surge in blood pressure in the early hours of the morning is clinically important as there is an increased incidence of cardiovascular complications, such as stroke, sudden death, and myocardial infarction. The causes of the "morning surge" include increased activity of the sympathetic nervous system, increased cortisol levels, increased platelet aggregability, and changes in vascular tone[2].

Conventional immediate-release antihypertensive drug dosage forms may not align with circadian rhythms. When given at conventional times, the peak plasma concentration may occur too early or too late relative to the time when the risk is greatest. Therefore, there may be inadequate therapeutic coverage during the vulnerable early morning hours. In response to this limitation, chronotherapeutic or chronomodulated drug

delivery systems have been developed to coincide with the body's natural rhythm[3].

Chronotherapeutic systems are designed to administer drugs so that the drug's maximum concentration is reached at the precise time when it is most needed. Such chronotherapeutic systems are found to be effective for diseases such as hypertension, asthma, arthritis, and peptic ulcers, as symptoms often manifest at specific times of day[4]. For example, in the treatment of hypertension, the ideal chronotherapeutic system would involve minimal drug release during the night and would increase the concentration of the drug before or during the morning surge[5].

Angiotensin-converting enzyme inhibitors like CPT are used to treat hypertension6. However, CPT has a short half-life, requiring many doses of conventional CPT formulations[7]. This not only lowers patient compliance but also makes it difficult to manage early-morning blood pressure spikes. A customized drug delivery system that can provide CPT at a delayed rate in accordance with the natural rhythm of hypertension is required.

For chronotherapeutic drug delivery systems, chronomodulated press-coated tablets seem to be a promising option. This is made out of a core tablet that contains the preferred medication and dissolves rapidly. An exterior coating layer made of hydrophilic or hydrophobic polymers covers the tablet us core. For a set amount of time, the outer coating functions as a barrier to stop medication release. The core tablet is exposed to the dissolution medium for quick medication release when the outer coating erodes or ruptures as a result of the polymers' hydration and subsequent swelling[9].

The type, concentration, and viscosity of the polymers in the coating solution are among the variables that can be changed to regulate the lag time. For example, when hydrophilic polymers like sodium alginate and hydroxypropyl methylcellulose come into contact with GI fluids, they swell and produce a gel barrier that slows the release of medication. Therefore, if the formulation is administered at bedtime, it is conceivable to modify parameters to create a formulation that releases CPT six hours after dosage in order to maximize drug concentration in the early morning[10].

Statistical experimental design techniques are applied to systematically optimize such a complicated formulation. A well-liked response surface methodology that makes it easier to assess different formulation elements and their interactions is the Box Behnken Design (BBD). Because it needs fewer experimental runs than a full factorial design and offers a wealth of information about the system, BBD is an effective tool for assessing complex formulations[11].

In BBD, the dependent variables (responses) like disintegration time, drug release, and lag time are assessed in relation to the independent variables (factors) like polymer concentration, disintegrant content, and lubricant content, which are varied at three levels (low, medium, and high). A second-order polynomial equation linking the factors and the answers can be constructed thanks to the experimental design, which offers a variety of experimental runs[11].

The capacity of BBD to assess the individual and combined impacts of factors is one of its main advantages as a crucial statistical tool in drug design. For instance, it is possible to investigate the combined impact of viscosity and polymer concentration on lag time, which is crucial when creating press-coated tablets. Additionally, response surface and contour plots from BBD facilitate optimization by making it simple to see how variables affect responses12.

With little trial, researchers can quickly identify the best set of factors in a medication formulation that produces the intended drug release profile by using BBD. This saves time and improves the efficiency of drug formulation. BBD is crucial for obtaining the appropriate lag duration and quick drug release during the lag time in CPT press-coated tablets, which permits chronotherapeutic drug release[13].

In conclusion, a potential strategy for the treatment of hypertension is provided by the combination of modern formulation techniques like press coating and statistical optimization using Box Behnken design with chronotherapeutic ideas. It has the potential to significantly increase therapeutic efficacy by regulating the drug's release in accordance with the body's circadian rhythm[14].

MATERIALS AND METHOD

Materials

CPT is the active pharmaceutical ingredient that was received as a gift sample of Cipla Ltd., Mumbai, India. Colorcon Asia Pvt. Ltd., Goa, India, supplied Hydroxypropyl methylcellulose (HPMC K4M) which was used as a hydrophilic polymer to regulate drug release. Ethyl cellulose which was procured in Loba Chemie Pvt. Ltd., Mumbai, India was used as a release-retarding hydrophobic polymer. A diluent was microcrystalline cellulose (Avicel PH-102), which was purchased at HI Media Laboratories Pvt. Ltd., Mumbai, India. SD Fine Chemicals Ltd., Mumbai, India, supplied croscarmellose sodium and magnesium stearate was used as a superdisintegrant and lubricant.

Methods

Preformulation Studies:

To ascertain CPT's physicochemical properties and how it interacts with certain excipients, preformulation was carried out[15]. The infrared spectra of the pure medication, individual excipients, and their physical mixes were obtained using the Shimadzu FTIR spectrophotometer. Potassium bromide (KBr) was used in the pellet technique of sample preparation[16]. The pellets were scanned in the spectral range of 4000-500 cm-1. The obtained spectra were utilized to ascertain whether any alterations in distinctive peaks could result from chemical interactions with the drug and formulation excipients.

Several micromeritic characteristics were examined in order to assess the medication and powder mixture's flowability. The angle of repose was calculated using the fixed funnel approach in order to examine how the powder flowed. Bulk density and tapped density were computed using a tapped density instrument. These numbers were used to calculate the Hausner ratio and the Carr compressibility index in order to evaluate the powder blend's flowability and compressibility[17].

Formulation of CPT core tablets by direct compression

Blends of 13 distinct CPT formulations (100 mg per tablet) were made using the BBD design while taking independent variables into account. After passing through Sieve Number 120, all materials—aside from magnesium stearate—were weighed and thoroughly mixed. After adding more magnesium stearate, the powder was thoroughly mixed. Tablets were made using a 16-station single-roller tablet-punching machine (Cadmach) at a slow rate and with 2-3 tons of compression pressure in order to prevent capping (Table 1).

Table no 1. Presentation of factors and factor levels investigated using BBD for CPT core tablet

Code	Coded level			Polymer concentration (in mg)		
	X1	X2	X3	Croscarmellose	Avicel	Mag. Stearate
1	-1	-1	0	50	40	5.5
2	-1	1	0	50	80	5.5
3	1	-1	0	90	40	5.5
4	1	1	0	90	80	5.5
5	-1	0	-1	50	60	3
6	-1	0	1	50	60	8
7	1	0	-1	90	60	3
8	1	0	1	90	60	8
9	0	-1	-1	70	40	3
10	0	-1	1	70	40	8
11	0	1	-1	70	80	3
12	0	1	1	70	80	8
13	0	0	0	70	60	5.5

Evaluation of CPT core tablets

The core tablets were assessed for appearance, weight variation, thickness using a screw gauge, hardness using a Monsanto hardness tester, and friability using a Roche friabilator. Twenty pills were triturated in a glass mortar and pestle to ascertain the drug content. A 250 ml volumetric flask was filled with additional powder equal to 100 mg CPT, diluted to 100 ml with deionized water, and sonicated for 60 minutes. The aliquots were gathered, filtered, and measured at 271 nm using UV spectrophotometry. Tablet disintegration test equipment was used to calculate the disintegration time.

Wetting time and water absorption ratio were calculated using previously published techniques. In short, a folded sheet of absorbent paper was placed in a glass plate with ten milliliters of deionized water. The experimental tablet was retained after a few drops of eosin dye were added, and the wetting time the amount of time it took for the color to develop on the topmost layer of the tablet was noted. Similarly, weighing the wetted tablet gathered using the same procedure allowed us to calculate the water absorption ratio using the equation below. Table No. 2 presents the evaluation test results.

$$Water\ absorption\ ratio = \frac{Wa - Wb}{Wb} \times 100$$

Where, Wa is weight of tablet after absorption of water, and Wb is weight of tablet before absorption of water

Table no.2 Evaluation of physical properties of Core tablet of CPT

Batch	Weight Variation (%)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio	Content Uniformity (%)
F1	173.36±1.23	3.21±0.04	4.10±0.52	0.80±0.02	72.45±0.66	10.40±1.10	96.85±0.48	98.25±0.36
F2	213.97±1.06	3.18±0.06	3.95±0.44	0.78±0.01	69.30±0.58	10.22±1.05	97.40±0.41	98.80±0.42

F3	213.86±0.96	3.25±0.05	3.82±0.39	0.76±0.02	66.10±0.61	10.05±1.18	98.10±0.36	99.05±0.33
F4	253.87±1.20	3.19±0.03	3.70±0.41	0.74±0.01	61.42±0.55	9.88±1.12	98.62±0.44	99.30±0.29
F5	192.92±0.94	3.23±0.07	3.88±0.36	0.75±0.02	57.35±0.63	9.75±1.20	98.95±.39	99.42±0.35
F6	195.98±1.04	3.17±0.05	3.55±0.42	0.72±0.01	52.20±0.47	9.60±1.08	99.10±0.33	99.55±0.31
F7	232.68±1.59	3.26±0.04	3.90±0.38	0.73±0.02	64.15±0.54	10.10±1.09	97.85±0.52	98.95±0.44
F8	236.02±0.65	3.30±0.06	4.16±0.35	0.80±0.01	48.62±0.68	9.42±1.16	99.26±0.29	99.90±0.27
F9	193.07±1.11	3.22±0.05	3.40±0.31	0.69±0.02	45.90±0.71	9.30±1.13	99.40±0.25	99.82±0.25
F10	195.66±0.36	3.16±0.03	3.32±0.37	0.68±0.01	43.85±0.59	9.18±1.04	99.55±0.31	99.80±0.22
F11	232.98±1.05	3.28±0.04	3.92±0.40	0.72±0.02	59.40±0.46	9.95±1.15	98.30±0.47	99.15±0.38
F12	235.66±0.54	3.12±0.07	3.15±0.23	0.66±0.01	41.72±0.63	9.05±1.11	99.70±0.28	99.94±0.20
F13	212.69±1.22	3.20±0.05	3.62±0.45	0.71±0.02	55.10±0.52	10.02±1.17	98.75±0.36	99.36±0.34

In-vitro dissolution of CPT core tablets

The tablet disintegration profile was investigated using the USP dissolution test apparatus type II. The tablet was placed in a vessel with 900 milliliters of pH 6.8 buffer dissolution media, a paddle-style assembly spinning at 100 revolutions per minute, at a temperature of 37 ± 5ºC. Fixed aliquots were removed at regular intervals and replaced with an equivalent volume of buffer. Spectrophotometric analysis was performed on the gathered materials at the appropriate CPT wavelengths. For each tablet, the procedure was carried out three times.

Formulation of press coated tablets of CPT using BBD:

The lag time (Y1, minutes) and the amount of medication released in 450 minutes (Y2, percent) were selected as dependent factors, whereas the amounts of HPMC K4 M in coating (X1, mg), HPMC K100 (X2, mg), and sodium alginate (X3, mg) were selected as independent variables (Table no.3).

Table No. 3: Three-factor, two-level full factorial experimental design of CPT for press coated tablet

Factors	Responses
X1- Amount of HPMC K4M	Y1- Lag Time in Hours
X2- Amount of HPMC K100	
X3 – Sodium Alginate	Y2- Drug released in 450 Minutes

Table no. 4. Presentation of 13 experiments (N1–N13) with coded values and actual values of CPT for factor levels for the Box–Behnken design

Code	Coded level			Polymer concentration (in mg)		
	X1	X2	X3	HPMC K4	HPMC K100	Sodium Alginate
C1	-1	-1	0	140	90	250
C2	-1	1	0	120	90	250
C3	1	-1	0	130	90	400
C4	1	1	0	120	105	100
C5	-1	0	-1	140	120	250
C6	-1	0	1	140	105	400
C7	1	0	-1	130	120	100
C8	1	0	1	130	90	100
C9	0	-1	-1	140	105	100
C10	0	-1	1	120	105	400
C11	0	1	-1	120	120	250
C12	0	1	1	130	120	400
C13	0	1	-1	130	120	100

Evaluation of press coating powder blend:

The powder mix was assessed in a manner similar to that of the core tablet powder blend evaluation in the preceding section. Hausner's ratio, Carr's index, bulk and taped density, and angle of repose were the parameters assessed.

Press-coating of optimized CPT core tablets:

The press-coated tablet was made using the powder mixture that BBD advised. Compression coating was

applied using CPT's optimized core tablet (Batch F8). A mixture of coating polymers was added to a 10 mm die cavity in the tableting machine to carefully coat the corresponding core tablet from top to bottom. A hydraulic device was used to punch the tablets at pressures between three and four tons.

As mentioned in the previous sections on core tablets, the manufactured tablets were examined for appearance, thickness, weight variation, hardness, friability, drug content, wetting time, water absorption ratio, and disintegration time.

In vitro dissolution study of press coated tablet of CPT:

To see how varying viscosity grades of HPMC and sodium alginate affected release behavior, each batch of tablets underwent in vitro dissolution testing in an acidic solution (pH 1.2) for the first two hours and then in phosphate buffer (pH 6.8). The dissolution test was carried out at pH 1.2 and 6.8 utilizing a paddle-type dissolving equipment at 100 rpm paddle speed and 37 ± 5ºC. Throughout the experiment, the sink condition was maintained.

Lag time:

The dissolving profile displays formulation dissolution lag time. In 900 ml of buffer 6.8 pH, CPT press-coated tablets were added, and the mixture was stirred at 75 rpm at 37 ± 0.5ºC. The point where the dissolution curve's extended straight line meets and touches the time axis is known as the lag time. The delay time was determined by measuring how long it took for the exterior coat to burst. The press-coated formulations' lag time is displayed in Table No 9.

RESULTS AND DISCUSSION

Numerous bodily functions, such as metabolic rate, pathology, sleep, and hormone production, are regulated by circadian rhythms. The body's reliance on circadian rhythms is mostly controlled by heredity and is widely known in certain illness situations. Numerous hormones are released by the brain in the morning and throughout sleep. Early in the morning, heart rate and blood pressure rise rapidly, and in the late evening, they gradually decrease. These difficulties can help organisms anticipate and get ready for changes in their surroundings. Numerous environmental factors, such as sun exposure and the usage of certain drugs (including coffee), can have an impact on the body's immune system.

Symptoms of circadian rhythm variation appear between 2:00 and 8:00 am, with attacks peaking at 4:00 am. A pulsatile drug delivery system must distribute the medication in chronological sequence throughout the night in order to get around this problem.18. The goal of the current study is to successfully apply BBD in order to create, develop, and assess a press-coated tablet that contains a fast-disintegrating CPT tablet employing hydrophilic polymers.

Preformulation studies:

CPT and all the excipients were subjected to preliminary investigations to confirm their identity. The drug exhibited expected physical and spectral properties, confirming their purity and identity. This ensures that the drugs used in the study meet the required quality standards and are suitable for further formulation processing. FT-IR spectroscopy confirmed the identity of CPT and the other excipients.[19] Physical mixture of drug with excipients confirmed no interactions among the functional group of the drug (Figure 1).

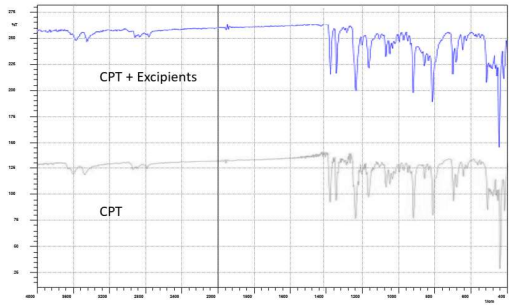

Figure 1: FT-IR spectra of CPT alone and with excipients

Investigations of the powder blend of CPT core tablets:

For tablet formulation, direct compression is thought to be the most dependable and popular technique. Standard sources state that it enhances content uniformity, compressibility, and powder flow. In line with these results, the current study determined that direct compression was the best technique for creating CPT core tablets. The process produced tablets with desired physical qualities by improving blending, flow characteristics, and compressibility. The micromeritic characteristics of all tablet mixtures were satisfactory[20]. The results are shown in Table No. 5

Table no. 5. Evaluation of CPT core tablet powder blend

Batch	Angle of Repose (θ)	Flowability	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner Ratio
F1	18.17 ± 0.41	Excellent	0.48 ± 0.02	0.49 ± 0.01	8.69 ± 0.65	1.09 ± 0.02
F2	16.47 ± 0.28	Excellent	0.46 ± 0.02	0.54 ± 0.03	7.05 ± 0.81	1.01 ± 0.02
F3	16.13 ± 0.40	Good	0.45 ± 0.03	0.53 ± 0.02	9.22 ± 0.52	1.03 ± 0.01
F4	18.63 ± 0.35	Excellent	0.46 ± 0.01	0.51 ± 0.02	8.74 ± 0.54	1.05 ± 0.03
F5	16.34 ± 0.56	Good	0.46 ± 0.02	0.48 ± 0.01	7.93 ± 0.66	1.01 ± 0.01
F6	16.04 ± 0.41	Excellent	0.42 ± 0.02	0.55 ± 0.02	6.0 ± 0.77	1.01 ± 0.02
F7	16.5 ± 0.26	Excellent	0.43 ± 0.03	0.53 ± 0.01	5.33 ± 0.53	1.11 ± 0.02
F8	17.51 ± 0.59	Good	0.46 ± 0.03	0.51 ± 0.01	7.07 ± 0.82	1.04 ± 0.03
F9	18.43 ± 0.5	Excellent	0.43 ± 0.03	0.51 ± 0.03	7.05 ± 0.88	1.07 ± 0.01
F10	16.53 ± 0.56	Excellent	0.46 ± 0.02	0.51 ± 0.02	5.77 ± 0.79	1.11 ± 0.03
F11	17.47 ± 0.35	Good	0.47 ± 0.02	0.48 ± 0.02	6.72 ± 0.89	1.07 ± 0.02
F12	18.79 ± 0.48	Excellent	0.47 ± 0.01	0.51 ± 0.02	7.29 ± 0.53	1.02 ± 0.02
F13	16.8 ± 0.57	Good	0.43 ± 0.03	0.51 ± 0.02	5.46 ± 0.72	1.08 ± 0.03

Formulation of core tablets of CPT by direct compression:

To guarantee quick disintegration and efficient drug release, the formulation of dispersible tablets necessitates careful selection of excipients and processing conditions.

The direct compression method was used in the current study to generate thirteen distinct CPT tablet formulations. The process was carried out in compliance with established techniques documented in the literature, which included properly blending the medicine and excipients after all ingredients were sieved through sieve number 120 to guarantee uniform particle size distribution. To avoid interfering with the powder blend, magnesium stearate was not included during the initial mixing.

Prior to compression, the dried powder combination was further sized and lubricated. To prevent flaws like capping and lamination, tablet compression was done under controlled conditions utilizing a multi-tooling lab-scale punching machine. Uniform tablet formation was guaranteed by the slow compression speed and compression pressure optimization. The process's outcomes showed that the direct compression approach yielded tablets that were suitable.

Evaluation of core tablets of CPT:

Good formulation and compression properties are indicated by a uniform appearance free of flaws like chipping, cracking, or mottling. All of the CPT and CPT tablet formulations in this investigation had a consistent look and no obvious flaws, indicating that the contents were properly mixed and compressed [21,22].

According to Table No. 6, the thickness of CPT tablets in the current study ranged from 3.12 ± 0.07 to 3.30 ± 0.06 mm. For every batch, consistent compression and appropriate die filling are indicated by the low fluctuation in thickness values. Pharmacopoeial requirements are met by these findings.

In the present study, the weight of CPT tablets ranged from 68.12 ± 1.59 to 103.04 ± 0.94 mg as shown in Table no. 6. All formulations complied with pharmacopoeial limits, indicating uniform distribution of drug and excipients. This confirms that the blending and compression processes were properly controlled [23,24].

The hardness of CPT tablets ranged from 4.16 ± 0.35 to 3.15 ± 0.23 kg/cm², as shown in Table no. 6. These values indicate adequate mechanical strength without significant variation among batches. The results suggest that tablets are strong enough to withstand mechanical stress during handling and transportation. [25]

Friability values for CPT tablets ranged from 0.66 ± 0.01 to 0.80 ± 0.02%, as shown in Table no. 6. All formulations showed friability values below 1%, indicating excellent mechanical resistance.[26]

In the present study, CPT tablets showed drug content uniformity values between 98.25 ± 0.36 to 99.94 ± 0.20%, as presented in Table no. 6. These results confirm uniform distribution of drug within the tablets and indicate accuracy of the formulation process.

In the present study, wetting time CPT tablets ranged from 9.05 ± 1.11 to 10.40 ± 1.10 seconds, as shown in Table no. 6. These results indicate rapid water uptake and good wettability of tablets. Faster wetting time is attributed to the presence of superdisintegrant (crosscarmellose sodium), which enhances water penetration.[27]

In the present study, CPT tablets showed water absorption ratios between 96.85 ± 0.48 and 99.70 ± 0.28%, with formulation F12 showing the highest

value, exhibiting the highest water absorption, as shown in Table no. 6. The high-water absorption is due to higher concentration of hydrophilic excipients, which enhances swelling and facilitates rapid disintegration.[28]

In the present study, CPT tablets showed disintegration time values between 41.72 ± 0.63 to 72.45 ± 0.66 seconds, as presented in Table no.6. Among all formulations, F12 exhibited the fastest disintegration, which can be attributed to higher concentration of superdisintegrant and improved water absorption. These results indicate that the prepared tablets meet the criteria for dispersible tablets and are capable of rapid drug release.

Table no. 6. Evaluation of core tablets of CPT

Batch	Weight Variation (mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio	Content Uniformity (%)
F1	173.36±1.23	3.21±0.04	4.10±0.52	0.80±0.02	72.45±0.66	10.40±1.10	96.85±0.48	98.25±0.36
F2	213.97±1.06	3.18±0.06	3.95±0.44	0.78±0.01	69.30±0.58	10.22±1.05	97.40±0.41	98.80±0.42
F3	213.86±0.96	3.25±0.05	3.82±0.39	0.76±0.02	66.10±0.61	10.05±1.18	98.10±0.36	99.05±0.33
F4	253.87±1.20	3.19±0.03	3.70±0.41	0.74±0.01	61.42±0.55	9.88±1.12	98.62±0.44	99.30±0.29
F5	192.92±0.94	3.23±0.07	3.88±0.36	0.75±0.02	57.35±0.63	9.75±1.20	98.95±.39	99.42±0.35
F6	195.98±1.04	3.17±0.05	3.55±0.42	0.72±0.01	52.20±0.47	9.60±1.08	99.10±0.33	99.55±0.31
F7	232.68±1.59	3.26±0.04	3.90±0.38	0.73±0.02	64.15±0.54	10.10±1.09	97.85±0.52	98.95±0.44
F8	236.02±0.65	3.30±0.06	4.16±0.35	0.80±0.01	48.62±0.68	9.42±1.16	99.26±0.29	99.90±0.27
F9	193.07±1.11	3.22±0.05	3.40±0.31	0.69±0.02	45.90±0.71	9.30±1.13	99.40±0.25	99.82±0.25
F10	195.66±0.36	3.16±0.03	3.32±0.37	0.68±0.01	43.85±0.59	9.18±1.04	99.55±0.31	99.80±0.22
F11	232.98±1.05	3.28±0.04	3.92±0.40	0.72±0.02	59.40±0.46	9.95±1.15	98.30±0.47	99.15±0.38
F12	235.66±0.54	3.12±0.07	3.15±0.23	0.66±0.01	41.72±0.63	9.05±1.11	99.70±0.28	99.94±0.20
F13	212.69±1.22	3.20±0.05	3.62±0.45	0.71±0.02	55.10±0.52	10.02±1.17	98.75±0.36	99.36±0.34

In vitro dissolution profile of CPT core tablets:

In vitro drug release study is a critical parameter for evaluating the performance of dispersible tablets, as it indicates the rate and extent of drug availability for absorption. According to standard dissolution principles, fast dispersible tablets should exhibit rapid drug release due to quick disintegration and enhanced surface area.

In the present study, all batches of CPT tablets were subjected to dissolution studies under simulated physiological conditions. The results demonstrated that all formulations showed rapid drug release, which is characteristic of dispersible tablet formulations. However, slight variations in release profiles were observed among different batches due to variation in excipient concentrations, particularly crosscarmellose sodium and Avicel.

CPT formulations, batches F1, F2, and F3 exhibited comparatively slower drug release, likely due to lower superdisintegrant concentration and reduced wettability. As the formulation variables were optimized in batches F4 to F7, drug release improved gradually. Batches F8, F9, F10, F11, F12, and F13 demonstrated rapid drug release profiles, with F8 showing the maximum release among all formulations. This can be attributed to optimal balance of excipients, leading to rapid wetting, high water absorption, and faster disintegration. The findings of the in vitro drug dissolution profile are provided in Figure no. 1.

The variation in drug release profiles among different batches can be explained based on the concentration of formulation components. Crosscarmellose sodium, being a superdisintegrant, plays a major role in enhancing drug release by promoting rapid swelling and tablet breakup. Higher concentrations of this excipient resulted in faster disintegration and increased drug release. Microcrystalline cellulose (MCC) contributed to tablet hardness and structure, which indirectly influenced drug release by affecting porosity and water penetration. Magnesium stearate, being a lubricant, slightly reduced drug release when used in higher concentration due to formation of a hydrophobic layer around particles.

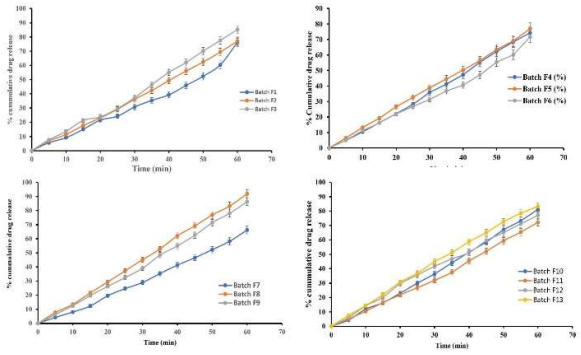

Figure no. 1. In vitro dissolution profile of CPT core tablets

Effect of composition ingredients on disintegration time and amount of drug released of CPT core tablet:

One important factor that eventually affects medication dissolving is the amount of time needed for formulation disintegration. The concentration and interactions between the formulation variables used to prepare a tablet have a major impact on how long it takes for it to dissolve. One important factor that ultimately affects the medicine's availability in the bloodstream is the amount of drug solubilized. The concentrations and interactions between the formulation factors employed in the manufacture of the drug have a major impact on how much of it dissolves.

The polynomial equation generated for the response Disintegration Time (Y_1) in terms of coded factors is as follows:

Y_1 (Disintegration Time) $=55.10 - 3.21X_1 - 5.98X_2 - 0.4475X_3 + 4.42X_1X_2 - 2.96X_1X_3 + 4.67X_2X_3 - 4.51X_1^2 - 1.01X_2^2 + 8.17X_3^2$

where, X_1 = Croscarmellose, X_2 = Avicel, X_3 = Mag. Stearate

The polynomial equation generated for the response drug release (Y2) in terms of coded factors for is as follows:

Y_2 (% drug release) $=87.91 - 5.48X_1 + 0.9600X_2 + 3.30X_3 - 3.26X_1X_2 + 1.80X_1X_3 + 2.39X_2X_3 - 2.79X_1^2 - 1.38X_2^2 - 4.78X_3^2$

where, X_1 = Croscarmellose, X_2 = Avicel, and X_3 = Mag. Stearate

Optimization using BBD for CPT core tablets:

BBD approach was applied to CPT core formulations to evaluate the influence of formulation variables on disintegration time and drug release.

The polynomial equation for disintegration time (Y_1) indicates that all three variables positively contribute to disintegration time, suggesting that increasing their concentration tends to increase the disintegration time. The interaction terms, particularly X_1X_2 and X_1X_3, show negative coefficients, indicating that combined optimization of these variables can reduce disintegration time.

The response surface and 3D plots shown in Figure no. 2, demonstrate that disintegration time is significantly affected by the interaction between crosscarmellose sodium and MCC. The plots suggest that moderate concentrations of these variables result in optimum disintegration performance.

For drug release (Y_2), the polynomial equation indicates that MCC and magnesium stearate positively influence drug release, while crosscarmellose sodium shows a minimal negative effect. The interaction terms reveal that the combined effect of variables plays a significant role in controlling drug release. The response surface and 3D plots clearly show that optimized concentrations of excipients lead to enhanced drug release (Figure no. 3).

The normal probability plot confirms the adequacy of the model, indicating that the experimental data fits well with the predicted model. Overall, the factorial design study for CPT demonstrates that formulation variables significantly influence both disintegration time and drug release, and optimization is essential to achieve desired tablet performance.

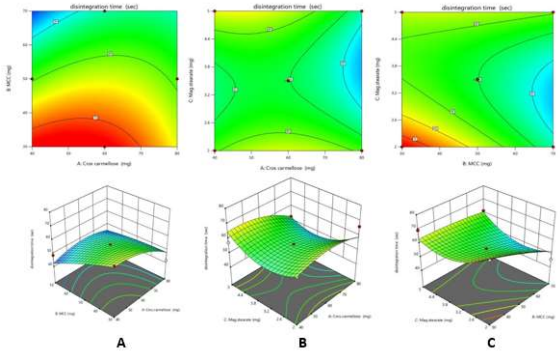

Figure no. 2: Response surface and 3D contour plots generated by BBD for CPT core tablets. A. Effect of Croscarmellose and MCC on Disintegration Time, B. Effect of Croscarmellose and Mag. Stearate on Disintegration Time, C. Effect of MCC and Mag. Stearate on Disintegration Time

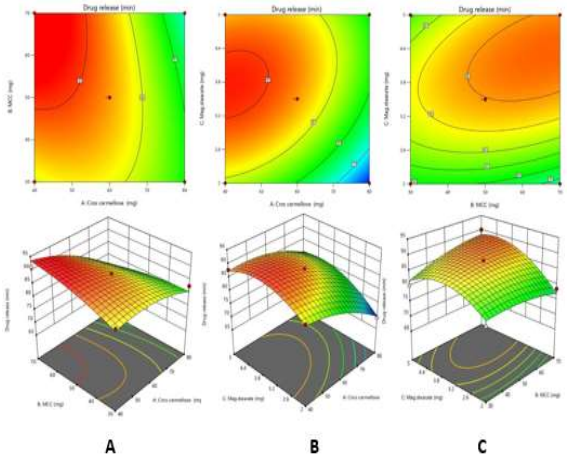

Figure no. 3: Response surface and 3D contour plots generated by BBD for CPT core tablets. A. Effect of Croscarmellose and MCC on drug release, B. Effect of Croscarmellose and Mag. Stearate on drug release, C. Effect of MCC and Mag. Stearate on drug release

Preparation of powder blends for press coated tablets using BBD:

Powder blends for CPT press coated tablets were prepared as given in table no. 4. These blends were further analysed for various powder associated properties as given in previous section. The findings are given in table no. 7. All the powder blends reflected satisfactory compressibility and flow properties.

Bulk density and tapped density are useful in determining the packing ability and compressibility of powders. Bulk density represents the initial packing, whereas tapped density indicates the maximum packing under mechanical tapping. In the present study, bulk density values ranged approximately from 0.428±0.008 to 0.478±0.010 g/cc and tapped density ranged from 0.572±0.019 to g/cc (Table No. 7). The increase in tapped density compared to bulk density indicated good compressibility of the powder blends.

Compressibility index and Hausner ratio are indicators of flowability and interparticle interactions. Compressibility index below 20% and Hausner ratio below 1.25 indicate good flow properties. In the present study, compressibility index values ranged from approximately 15.40± 1.900 to 16.80± 2.900 and Hausner ratio ranged from 1.18 ± 0.025 to 1.20 ± 0.080 (Table No. 7), indicating fair to good flow properties and suitability for direct compression.

Table no. 7. Preformulation characteristics of press coating polymer blends of CPT

Batch code	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Hausner's ratio	Compressibility index	Angle of repose
C1	0.428 ±0.008	0.508 ± 0.005	1.19 ± 0.021	15.95±1.480	29.40±1.02
C2	0.437 ± 0.015	0.514 ± 0.008	1.18 ±0.025	15.40± 1.900	29.60±0.71
C3	0.442 ± 0.018	0.526 ± 0.006	1.20 ±0.045	16.10±3.300	29.95±0.85
C4	0.478 ± 0.010	0.572 ± 0.019	1.20 ± 0.040	16.80±2.900	29.00±1.10
C5	0.455 ± 0.017	0.542 ± 0.030	1.20 ±0.080	16.10±5.800	29.80±0.65
C6	0.430 ± 0.006	0.509 ± 0.008	1.19 ±0.005	15.70±0.360	29.70±1.50
C7	0.452 ± 0.022	0.538 ± 0.021	1.20 ±0.038	16.40±2.800	29.45±1.05
C8	0.443 ± 0.011	0.528 ± 0.018	1.20 ±0.027	16.30±2.000	29.20±1.08
C9	0.454 ± 0.021	0.538 ± 0.029	1.19 ±0.007	15.90±0.450	29.10±0.82
C10	0.439 ± 0.013	0.520 ± 0.007	1.19 ±0.050	215.70±3.600	30.00±1.65
C11	0.460 ± 0.014	0.545 ± 0.010	1.18 ± 0.009	15.85±1.200	28.95±0.90
C12	0.470±0.016	0.560±0.015	1.19 ± .030	16.20± 2.100	29.30±1.00
C13	0.445±0.012	0.530±0.012	1.19 ±0.015	16.00± 1.500	29.55± 0.95

Formulation of press coated tablet of CPT:

Various powder blends prepared according to BBD were compressed by direct compression, and the prepared tablets were further evaluated for various properties as those determined for CPT core tablets. The evaluation parameters of press coated tablets are given in table no. 8.

The thickness ranged of CPT press coated tablets ranged from 2.99 ± 0.06 to 4.25 ± 0.07 mm, showing minimal variation and confirming uniform compression. Weight variation of all the press coated tablets were between 556.12±0.84 to 881.03±0.75 mg. Friability ranged of CPT from 0.62 ± 0.01 to 0.88 ± 0.02%, confirming good mechanical resistance and durability of tablets (Table No. 8).

Drug content of CPT press coated tablets ranged from 96.36 ± 0.53 to 99.92 ± 0.35%, indicating uniform distribution of drug throughout the formulation. Wetting time of CPT press coated tablets ranged from 9.28 ± 1.04 to 10.55 ± 1.25 sec, indicating rapid wetting, which facilitates faster hydration and disintegration. Water absorption ratio indicates the swelling capacity of polymers. Higher values indicate better swelling. In the present study, water absorption ratio ranged from CPT tablets ranged from 90.30 ± 0.36 to 99.55 ± 0.39%, with higher values indicating greater swelling ability due to polymer content (Table No. 8).

Table no. 8. Evaluation of press-coated tablets of CPT

Batch	Weight Variation (in mg)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio (%)	Content Uniformity (%)
C1	716.02±0.89	3.32±0.04	4.13 ±0.52	0.79±0.02	60.45±0.66	10.30±1.10	90.85±0.48	97.25±0.36
C2	695.95±0.39	2.99±0.06	3.99 ±0.44	0.78±0.01	66.30±0.58	10.42±1.05	96.40±0.41	98.80±0.42

C3	854.99±0.83	3.55±0.05	4.22 ±0.39	0.71±0.02	65.10±0.61	10.35±1.18	90.30±0.36	96.05±0.33
C4	562.06±0.36	3.66±0.03	3.77 ±0.41	0.75±0.01	60.42±0.55	9.68±1.12	91.62±0.44	99.30±0.29
C5	746.15±0.12	4.15±0.07	4.61 ±0.36	0.88±0.02	57.35±0.63	10.55±1.20	99.55±0.39	99.92±0.35
C6	880.58±0.98	4.10±0.05	4.55 ±0.42	0.70±0.01	51.20±0.47	10.15±1.08	92.10±0.33	99.55±0.31
C7	586.09±0.66	3.45±0.04	3.55 ±0.38	0.77±0.02	63.15±0.54	10.10±1.09	94.85±0.52	98.95±0.44
C8	555.22±0.78	3.55±0.06	4.36 ±0.35	0.81±0.01	50.62±0.68	9.42±1.16	97.26±0.29	99.90±0.27
C9	580.69±0.64	3.70±0.05	3.52 ±0.31	0.66±0.02	45.90±0.71	9.40±1.13	96.40±0.25	99.82±0.25
C10	859.98±0.55	3.23±0.03	4.32 ±0.37	0.62±0.01	54.85±0.59	9.28±1.04	97.55±0.31	99.80±0.22
C11	726.32±0.43	3.91±0.04	3.98 ±0.40	0.77±0.02	60.40±0.46	9.95±1.15	90.30±0.47	99.15±0.38
C12	887.01±0.61	4.12±0.07	3.56 ±0.33	0.67±0.01	57.72±0.63	10.05±1.11	91.70±0.28	99.64±0.20
C13	585.88±0.29	3.20±0.05	3.86 ±0.45	0.77±0.02	65.10±0.52	10.22±1.17	98.75±0.36	99.36±0.34

In vitro drug release study of press coated CPT tablets:

Press-coated tablets show a lag phase followed by rapid drug release. In the present study, all formulations showed negligible drug release up to initial hours, followed by rapid release after coat rupture. All formulations of CPT press coated exhibited a lag phase followed by rapid drug release. Among all batches, CPT batch C5 showed optimized performance with 95.91% drug release at 12 hours, indicating effective controlled release behavior (Figure no. 3). In the present study, CPT press coated tablet Batch C5 release reached approximately 95% after 12 hours in both media, indicating pH-independent release behavior, while slightly lower in acidic medium, indicating better release in intestinal pH conditions.

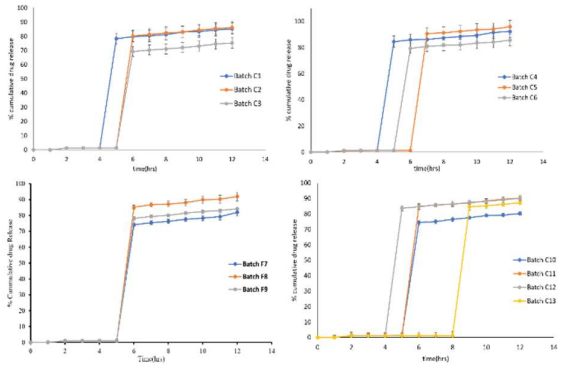

Figure no. 3. In vitro release profile of various press coated tablets of CPT

Lag time of press coated CPT tablets:

A crucial factor in pulsatile medication distribution is lag time. The lag time in this investigation was between four and seven hours. Formulation C5 had the longest lag time, suggesting that polymer concentration had a significant impact.Higher polymer concentrations resulted in longer lag times because they delayed coating erosion (Table No. 9). The findings showed that a higher polymer content resulted in a longer lag time because the coated layer eroded more slowly. Lag time was also greatly impacted by the interaction between variables. Due to a higher diffusion barrier and decreased coating permeability, an increase in polymer concentration decreased the rate of drug release.

Table 9: Lag time of press-coated formulations of CPT

Formulations	Lag Time (Hours)
C1	5
C2	6
C3	6
C4	5
C5	7
C6	6
C7	6
C8	5
C9	5
C10	6
C11	6
C12	5
C13	9

Optimization of press coated tablets of CPT using BBD:

Quadratic expressions and optimal design were selected for the experimental design in order to validate polynomial analysis. The concentration levels for HPMC K4M, HPMC, and sodium alginate were predicted using a mathematical model designed for optimal preparation. Experiments were conducted to determine the mathematical link between the system's interacting parts and its reaction, and the percentage bias was calculated after comparing the experimental results to the projected values. Design Expert was used to statistically evaluate the results in order to determine the ideal concentrations of HPMC K4M, HPMC, and sodium alginate to be released from press-coated tablets.

The polynomial equation generated for the response Lag Time (Y_1) is as follows:

$$Y_1 \text{ (Lag Time)} = 9.00 + 0.0000X_1 + 0.25X_2 + 0.25X_3 + 0.50X_1X_2 + 0.0000X_1X_3 - 0.50X_2X_3 - 1.50X_1^2 - 1.50X_2^2 - 2.00X_3^2$$

where, X_1 = Amount of HPMC K4M, X_2 = K100, and X_3 = Amount of Sodium Alginate

The polynomial equation generated for drug release at 450 min (Y_2) in terms of coded factors is given below:

$$Y_2 \text{ (\% drug released at 450 min)} = 94.54 + 0.3875X_1 + 4.78X_2 - 4.19X_3 + 3.87X_1X_2 + 4.58X_1X_3 + 7.20X_2X_3 - 6.53X_1^2 - 2.53X_2^2 - 7.51X_3^2$$

where, X_1 = Amount of HPMC K4M, X_2 = K100, and X_3 = Amount of Sodium Alginate

Effect of various formulation variables according to BBD:

The impact of formulation factors on drug release and lag time was assessed using BBD. Lag time and drug release were regarded as dependent responses in this investigation, while HPMC K4M, HPMC K100M, and sodium alginate were chosen as independent factors. The obtained polynomial equation for lag time (Y_1) showed that lag time was significantly impacted by coated polymer concentration. Due to the creation of a thicker gel barrier that postponed the dissolving medium's penetration, it was found that increasing polymer concentration lengthened the lag time. Lag time variation was also greatly influenced by the interaction between the variables.

Similarly, polymer concentration has a considerable impact on drug release behavior, as demonstrated by the polynomial equation for drug release (Y_2). Drug release was slowed by an increase in polymer content because the coating layer's permeability reduced and the diffusion channel lengthened. The release profile was further impacted by the formulation factors' interaction effects. These findings were corroborated by residual, response surface, and three-dimensional plots (Figure No. 4), which amply illustrated how formulation variables affected drug release and lag time.

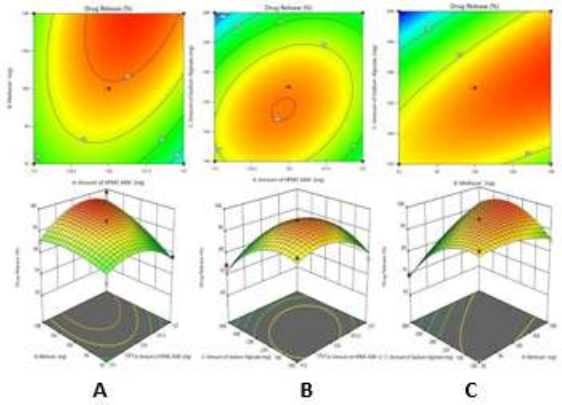

Figure no. 4: Response surface and 3D contour plots generated by BBD for CPT press coated tablets A. Effect of HPMC K4M and HPMC K100M on Lag Time for CPT press coated tablet, B. Effect of HPMC K4M and Sodium Alginate on Lag Time for CPT press coated tablet, C. Effect of HPMC K100M and Sodium Alginate on Lag Time for CPT press coated tablet

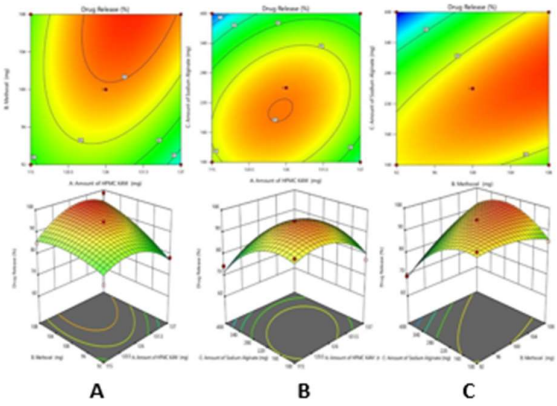

Figure no. 4: Response surface and 3D contour plots generated by BBD for CPT press coated tablets. A. Effect of HPMC K4M and HPMC K100M on % drug release for CPT press coated tablet. B. effect of HPMC K4Mand Sodium Alginate on % drug release for CPT press coated tablet, C. Effect of HPMC K100M and Sodium Alginate on % drug release for CPT press coated tablet

CONCLUSION

The goal of the research is to create a chronomodulated press-coated CPT tablet for efficient and prompt hypertension treatment. By attaching an exterior polymeric coat that regulates the lag time before medication release, press-coated tablets are specifically made to achieve time-dependent drug release. In this study, the formulation of CPT dispersible core tablets was optimized using BBD. Magnesium stearate, Avicel, and crosscarmellose sodium were chosen as independent variables since they are known to have a major impact on tablet characteristics such flowability, hardness, and disintegration. Different density and flow-related parameters of tablet mixtures were assessed. The outcomes of these formulations showed that while MCC reduced tablet hardness and compressibility, variations in crosscarmellose sodium concentration had a substantial impact on disintegration time.

A number of evaluation criteria, including appearance, weight variation, drug content uniformity, friability, hardness, water absorption ratio, wetting time, disintegration time, and in vitro dissolution profile, were applied to the compressed tablets. Higher doses of this excipient appear to have accelerated disintegration and enhanced drug release, according to the experimental designs. By influencing porosity and water penetration, microcrystalline cellulose (MCC) indirectly affected drug release by contributing to tablet

hardness and structure. Due to the creation of a hydrophobic barrier around particles, magnesium stearate, a lubricant, somewhat decreased medication release at greater concentrations.

Additionally, factorial design was used to create press-coated tablets of an optimized CPT batch in order to assess the impact of formulation factors on drug release and lag time. Lag time and drug release were regarded as dependent responses in this investigation, while HPMC K4M, HPMC K100M, and sodium alginate were chosen as independent factors.

Weight variation, hardness, content homogeneity, friability, disintegration tests, and in vitro dissolving tests were assessed for the manufactured press-coated tablets. During in vitro dissolving tests utilizing the paddle method, optimized press-coated tablets of CPT batch C5 demonstrated 95% drug release. Overall, the results showed that using a combination of polymers that could delay the drug's diffusion for around seven hours, chrono-modulated press-coated tablets of CPT could give timely burst release after 450 minutes. This strategy would undoubtedly be helpful for illnesses like hypertension that worsen in the early morning.

CONFLICT OF INTEREST

The authors declare no conflict of interest

ACKNOWLEDGEMENTS

None

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