RESEARCH PAPER

Formulation, Evaluation And Optimization Of Time-Activated Press Coated Tablet Of Nicardipine By Applying Box-Behnken Design

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ABSTRACT
The main aim of this study is to design and optimize time-activated press-coated tablets of Nicardipine (NDP) for the treatment of hypertension using the Box Behnken design approach. The fast-dispersible core tablets were prepared by using the direct compression method applying Box-Behnken design (BBD) using independent factors namely the amount of croscarmellose (X1), Avicel PH102 (X2), and magnesium stearate (X3), and disintegration time (Y1) and drug release (Y2) as dependent factors. The optimized formulation of the core tablet (B3) showed rapid disintegration and drug release (84.24% in 60 minutes). Further, the optimized dispersible core tablets were subjected to press coating by applying 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 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. The accelerated stability studies confirmed the robustness of the formulation. The study concluded that the time-dependent release of the drug can be achieved using the press-coating formulation of fast disintegrating core tablet by applying BBD.
Keywords: Chronotherapeutics, Nicardipine, Press-coated tablet, Box-Behnken design, Direct compression

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INTRODUCTION

Hypertension, or high blood pressure, is a chronic cardiovascular disease characterized by increased blood pressure and is considered one of the major causes of cardiovascular complications, such as stroke and myocardial infarction. A characteristic feature of hypertension is the presence of a circadian rhythm in blood pressure. This refers to the fact that there are fluctuations in blood pressure over a period of 24 hours[1]. In most patients, there is a fall in blood pressure during sleep, or nocturnal dip. There is a sudden rise in blood pressure in the early hours of the morning when the 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 for the "morning surge" are increased activity in the sympathetic nervous system, increased levels of cortisol, increased platelet aggregability, and changes in vascular tone[2].

The conventional immediate release dosage forms of antihypertensive drugs may not be in accordance with the circadian rhythm. When given at conventional

times, the peak plasma concentration may occur too early or too late in relation to the timing when the risk is greatest. Therefore, there may be inadequate therapeutic cover during the vulnerable period in the early morning hours. In response to the limitation, chronotherapeutic or time activated drug delivery systems have been developed to coincide with the body's natural rhythm[3].

Chronotherapeutic systems are designed to administer drugs in such a way that the maximum concentration of the drug is reached at the precise time when it is most needed. Such chronotherapeutic systems are found to be effective in diseases like hypertension, asthma, arthritis, and peptic ulcers, as the symptoms manifest at specific times during the 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].

NDP, a dihydropyridine derivative, is a calcium entry blocker used in the management of hypertension. This drug acts by blocking the entry of calcium ions into smooth muscles, resulting in vasodilatation[6]. However, the half-life of NDP is short, and multiple dosing of conventional dosage forms of NDP is required. This not only reduces patient compliance but also does not control blood pressure surges occurring in the early morning. There exists a need for a modified drug delivery system which can provide a delayed release of NDP in sync with the natural rhythm of hypertension[7].

Time-activated press-coated tablets appear to offer a promising tool for the administration of chronotherapeutic drug delivery systems. This consists of a core tablet that disintegrates quickly and contains the drug of choice[8]. The core tablet is covered by an outer coating layer that consists of hydrophilic or hydrophobic polymers. The outer coating acts as a barrier that prevents the drug from being released for a predetermined period of time. Once the outer coating erodes or ruptures due to the hydration and subsequent swelling of the polymers, the core tablet is exposed to the dissolution medium for rapid drug release[9].

The lag time is controllable by adjusting parameters such as the type and concentration of polymers and their viscosity in the coating solution. For instance, hydrophilic polymers such as hydroxypropyl methylcellulose and sodium alginate have a swelling effect in response to contact with GI fluids, resulting in a gel membrane that acts to delay drug release. It is therefore possible to adjust parameters to design a formulation that releases NDP 4-6 hours after dosing, provided that dosing is administered at bedtime, to maximize drug concentration in the early morning[10].

For the systematic optimization of such a complex formulation, statistical experimental design methodologies are utilized. Among such methodologies, the Box Behnken Design (BBD) is a popular response surface methodology that facilitates the evaluation of various formulation factors and their interactions. BBD is a powerful methodology for the evaluation of complex formulations due to the following reasons: it requires fewer experimental runs compared to the full factorial design and provides a wide range of information about the system.

In BBD, the independent variables (factors) such as polymer concentration, disintegrant content, and lubricant content are varied at three levels (low, medium, and high) and the effect of the formulation factors on the dependent variables (responses) such as disintegration time, drug release, and lag time is evaluated. The experimental design provides a wide range of experimental runs that enable the construction of a second-order polynomial equation relating the factors and the responses[11].

One of the major advantages that make BBD an important statistical tool in drug formulation is the ability to evaluate both the individual and combined effects of variables. For example, the combined effect of polymer concentration and viscosity on lag time can be studied, which is important in the formulation of press-coated tablets. Moreover, the response surface plots and contour plots obtained from BBD make it easy to visualize the effects of variables on responses, thus making optimization easy[12].

Using BBD, researchers can easily determine the optimal combination of variables in a drug formulation that can give the desired drug release profile with minimum experimentation. This makes drug formulation efficient and saves time. In the case of NDP press-coated tablets, BBD plays an important role in achieving the desired lag time and rapid drug release during the lag time, thus making it possible to achieve chronotherapeutic drug release[13].

In conclusion, the integration of chronotherapeutic concepts with advanced formulation techniques such as press coating and statistical optimization by Box Behnken design provides a promising approach in the management of hypertension. By controlling the release of the drug in accordance with the circadian rhythm of the human body, it has the potential to show significant improvement in therapeutic efficacy[14].

MATERIALS AND METHOD

Materials

NDP 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:

Preformulation was performed to determine the physicochemical characteristics of NDP and its interaction with some excipients[15]. The Shimadzu FTIR spectrophotometer was used to obtain the infrared spectra of pure drug, individual excipients and their physical mixtures. The pellet technique of sample preparation was employed with potassium bromide (KBr)[16]. The scan of the spectral range of 4000-500 cm-1 was performed on the pellets. The acquired spectra were used to determine whether there are any changes in characteristic peaks that may be due to chemical interaction with the drug and formulation excipients.

The flowability of the drug and powder mixture was measured by measuring several micromeritic parameters. The fixed funnel technique was used to determine the angle of repose to analyze the behavior of powder flowing. A tapped density apparatus was used to calculate bulk density and tapped density. Based on these values, the compressibility index of Carr and the ratio of Hausner were determined to assess the compressibility and flowability of the powder blend[17].

Formulation of NDP core tablets by direct compression

Blends of 13 different formulations of NDP (100 mg per tablet) were prepared according to the BBD design considering independent variables. All materials were sieved through Sieve Number 120, then weighed and well blended (except magnesium stearate). Further magnesium stearate was added and the powder was blended well. To avoid capping, tablets were formed on a 16-station single-roller tablet-punching machine (Cadmach) at a slow rate and with 2-3 tons compression pressures (Table 1).

Table no 1. Presentation of factors and factor levels investigated using BBD for NDP 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 NDP core tablets

The core tablets were evaluated for appearance, thickness using screw gauge, hardness using Monsanto hardness tester, friability using Roche friabilator and weight variation. The drug content was determined by triturating 20 tablets in glass mortar pestle. Further powder equivalent to 100 mg NDP was added into 250 ml volumetric flask, diluted upto 100 ml with deionized water, and sonicated for 60 minutes. The aliquots were collected filtered and subjected to UV spectrophotometric determination at 235 nm. Disintegration time was calculated using tablet disintegration test apparatus. Wetting time and wetting absorption ratio were determined using methods reported earlier. Briefly, in a glass plate containing 10 ml deionized water, a folded sheet of absorbent paper was kept. Few drops of eosin dye were added and the experimental tablet was kept, and time for the color to appear on the top most tablet layer was recorded as wetting time. Similarly, water absorption ratio was determined using equation below, by weighing the wetted tablet collected after above method. The results of these evaluation tests are given in Table no. 2.

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

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 NDP

Batch	Weight Variation (%)	Thickness (mm)	Hardess (kg/cm²)	Friablity (%)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio	Content Uniformity (%)
B1	195.68±1.12	3.44±0.04	4.20±0.52	0.89±0.02	70.4± 0.66	10.22±1.10	96.23±0.43	99.25 ±0.36

B2	235.69±1.10	3.54±0.06	3.99±0.44	0.81±0.01	68.30±0.58	10.39±1.01	95.42±0.49	94.25 ±0.30
B3	235.96±1.23	3.60±0.05	4.25±0.39	0.90±0.02	67.10±0.61	10.27±1.13	96.36±0.56	98.80 ±0.42
B4	276.03±1.11	3.36±0.03	3.77±0.41	0.79±0.01	63.42±0.55	9.88±1.14	97.96±0.43	95.25 ±0.22
B5	212.73±1.45	3.44±0.07	3.81±0.36	0.71±0.02	59.35±0.63	9.75±1.29	97.23±0.39	99.85 ±0.33
B6	218..99±1.12	3.56±0.05	3.54±0.42	0.72±0.01	57.20±0.47	9.85±1.09	99.86±0.43	94.25 ±0.46
B7	254.35±1.22	3.43±0.04	3.96±0.38	0.81±0.02	65.15±0.54	10.06±1.03	97.66±0.29	97.30 ±0.29
B8	257.66±1.21	3.40±0.06	4.12±0.35	0.83±0.01	54.62±0.68	9.22±1.13	99.61±0.36	93.25 ±0.26
B9	213.67±1.13	3.44±0.05	3.47±0.31	0.73±0.02	61.90±0.71	9.34±1.09	99.75±0.82	99.42 ±0.35
B10	217.62±1.11	3.34±0.03	3.39±0.37	0.70±0.01	70.85±0.59	9.05±1.06	99.53±0.49	92.25 ±0.16
B11	253.66±1.21	3.28±0.04	4.12±0.40	0.75±0.02	59.40±0.46	9.35±1.12	98.88±0.26	99.55 ±0.31
B12	258.92±1.11	3.12±0.07	3.25±0.33	0.69±0.01	53.72±0.63	9.09±1.14	99.43±0.41	92.25 ±0.22
B13	234.29±1.31	3.20±0.05	3.62±0.45	0.73±0.02	65.10±0.52	10.03±1.12	98.15±0.49	98.95 ±0.25

In-vitro dissolution of NDP core tablets

The USP dissolution test apparatus type II was employed for investigation tablet dissolution profile. The tablet was introduced in the vessel containing 900 ml of dissolution medium pH 6.8 buffer, with a paddle type assembly at a speed 100 rpm, and was maintained at 37 ± 5ºC. After periodic intervals fixed aliquots were withdrawn, and replenished with equal amount of buffer. The samples collected were subjected to spectrophotometric analysis at respective wavelengths of NDP. The process for individual tablet was performed in triplicate.

Formulation of press coated tablets of NDP using BBD:

The amount of HPMC K4 M in coating (X1, mg), HPMC K100 (X2, mg), and the amount of sodium alginate (X3, mg) were chosen as independent variables, while the lag time (Y1, minutes) and the amount of drug released in 450 minutes (Y2, percent) was chosen as dependent variables (Table no.).

Table No. 3: Three-factor, two-level full factorial experimental design of NDP 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 NDP for factor levels for the Box–Behnken design

Code	Coded level			Polymer concentration (in mg)		
	X1	X2	X3	HPMC K4	HPMC K100	Sodium Alginate
N1	-1	-1	0	130	90	100
N2	-1	1	0	120	120	250
N3	1	-1	0	140	120	250
N4	1	1	0	130	90	400
N5	-1	0	-1	140	105	400
N6	-1	0	1	140	90	250
N7	1	0	-1	120	105	100
N8	1	0	1	130	120	100
N9	0	-1	-1	140	105	100
N10	0	-1	1	130	120	400
N11	0	1	-1	120	90	250
N12	0	1	1	120	105	400
N13	0	0	0	130	105	250

Evaluation of press coating powder blend:

The powder blend was evaluated similarly as given in the previous section for powder blend evaluation of core tablet. Parameters evaluated were bulk and taped density, Hausner's ratio, Carr's index and angle of repose.

Press-coating of optimized NDP core tablets:

The powder blend recommended by BBD was used to prepare the press-coated tablet. The optimized core tablet of NDP (Batch B3) were used for compression

coating. The respective core tablet was carefully coated from the top and bottom by adding a blend of coating polymers into a 10 mm die cavity of the tableting machine. The tablets were punched using a hydraulic mechanism at pressures ranging from 3 to 4 tons.

The prepared tablets were screened for the following evaluation parameters, as described in the earlier sections of core tablets; 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 NDP:

Each batch of tablets was subjected to in vitro dissolution testing in an acidic solution (pH 1.2) for first 2 hrs and in phosphate buffer (pH 6.8) thereafter, to observe the impact of different viscosity grades of HPMC and Sodium Alginate on release behavior. The dissolution testing was performed using paddle type dissolution apparatus, at 100rpm paddle speed and 37 ± 5°C, in pH 1.2 and 6.8. Sink condition was maintained throughout the experiment.

Lag time:

The dissolution profile shows lag time in the dissolution of formulations. NDP press coated tablets were added in 900 ml of buffer 6.8 pH and agitated at 75 rpm at 37 ± 0.5°C. The lag time is characterized by the point where the extended straight line of the dissolution curve meets and intersects the time axis. The length of time it took for the external coat to burst was measured and recorded as delay time. Lag time of press coated formulations shown in the Table no.

RESULTS AND DISCUSSION

Circadian rhythms regulate many aspects of the human body's activities, including metabolic rate, pathophysiology, sleep, and hormone production. The body functions dependence on circadian rhythms is well known in some disease states and mainly influenced by genetics. The brain releases many hormones in the morning and others during sleep. Blood pressure and heart rate increases quickly in the early morning and falls steadily in the late evening. Organisms can use these challenges to anticipate and prepare for changes in their environment. The body's immune system can be affected by many external factors, including exposure to sunlight and the use of certain medications (such as coffee). Circadian rhythms variation symptoms occur during the 2.00 am to 8.00 am and the peak period for attack is 4.00 am. To overcome this situation pulsatile drug delivery system requires delivering drug in chronological order throughout the night.[18] The present investigation aims to formulate, optimize and evaluate press coated tablet comprising fast disintegrating tablet of NDP using hydrophilic polymers through successful application of BBD.

Preformulation studies:

NDP 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 NDP and the other excipients.[19] Physical mixture of drug with excipients confirmed no interactions among the functional group of the drug (Figure 1).

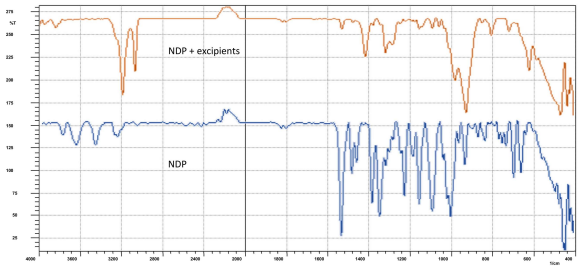


Figure 1: FT-IR spectra of NDP alone and with excipients

Investigations of the powder blend of NDP core tablets:

Direct compression, is widely regarded as the most reliable and widely used method for tablet formulation. According to standard references, it improves powder flow, compressibility, and content uniformity. In agreement with these findings, direct compression was selected in the present study as the most suitable method for the preparation of core tablets of NDP. The method provided better blending, improved flow properties, and enhanced compressibility, leading to the formation of tablets with desirable physical characteristics. All tablet blends showed satisfactory micromeritic properties.[20] The findings are indicated in table no. 5.

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

Batch	Angle of Repose (θ)	Flowability	Bulk Density (g/cc)	Tapped Density	Carr's Index (%)	Hausner Ratio

				(g/cc)		
B1	22.38 ± 0.6	Good	0.51 ± 0.02	0.54 ± 0.01	5.49 ±0.62	1.03 ±0.03
B2	22.18 ± 0.6	Excellent	0.52 ± 0.03	0.57 ± 0.03	5.56 ± 0.64	1.03 ±0.01
B3	26.63 ±0.47	Good	0.48 ± 0.02	0.58 ± 0.02	5.7 ± 0.76	1.06 ±0.02
B4	25.09 ±0.38	Excellent	0.51 ± 0.03	0.52 ± 0.03	6.3 ± 0.53	1.0 ± 0.02
B5	22.44 ±0.32	Good	0.51 ± 0.01	0.53 ± 0.03	9.81 ± 0.84	1.04 ±0.03
B6	25.55 ±0.55	Good	0.48 ± 0.03	0.55 ± 0.02	9.75 ± 0.82	1.1 ± 0.03
B7	25.18 ±0.66	Excellent	0.48 ± 0.03	0.54 ± 0.02	5.18 ± 0.68	1.03 ±0.02
B8	26.13 ± 0.6	Good	0.53 ± 0.02	0.55 ± 0.01	9.83 ± 0.74	1.01 ±0.02
B9	23.09 ±0.41	Good	0.52 ± 0.02	0.6 ± 0.02	5.05 ± 0.87	1.02 ±0.02
B10	23.55 ±0.46	Excellent	0.54 ± 0.02	0.57 ± 0.02	8.33 ± 0.95	1.08 ±0.01
B11	23.11 ±0.46	Good	0.51 ± 0.01	0.52 ± 0.02	8.15 ± 0.65	1.1 ± 0.02
B12	24.23 ±0.35	Excellent	0.48 ± 0.01	0.54 ± 0.02	5.49 ± 0.77	1.01 ±0.02
B13	24.06 ±0.55	Excellent	0.45 ± 0.02	0.54 ± 0.03	7.05 ± 0.79	1.06 ±0.01

Formulation of core tablets of NDP by direct compression:

The formulation of dispersible tablets requires careful selection of excipients and processing conditions to ensure rapid disintegration and effective drug release.

In the present study, thirteen different formulations of NDP tablets were prepared using the direct compression method. The procedure followed was in accordance with standard methods reported in the literature, including sieving of all ingredients through sieve number 120 to ensure uniform particle size distribution, followed by proper blending of drug and excipients. Magnesium stearate was excluded during initial mixing to prevent interference with powder blend.

The dried powder mixture was further sized and lubricated before compression. Tablet compression was carried out using a multi-tooling lab-scale punching machine under controlled conditions to avoid defects such as capping and lamination. The slow compression speed and optimization of compression pressure ensured uniform tablet formation. The results obtained from this process indicated that direct compression method produced satisfactory tablets.

Evaluation of core tablets of NDP:

Uniform appearance without defects such as cracking, chipping, or mottling indicates good formulation and compression characteristics. In the present study, all formulations of NDP tablets showed uniform appearance with no visible defects, indicating proper mixing and compression of ingredients. [21,22]

In the present study, the thickness of NDP tablets was in the range of 3.12 ± 0.07 to 3.60 ± 0.05 mm, as presented in Table no. 6. The low variation in thickness values indicates uniform compression and proper die filling for all batches. These results are in agreement with pharmacopoeial standards.

In the present study, the weight of NDP tablets ranged from 92.74 ± 2.11 to 107.14 ± 2.22 %, 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 NDP tablets ranged from 3.25 ± 0.33 to 4.25 ± 0.52 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 NDP tablets ranged from 0.68 ± 0.01 to 0.90 ± 0.02%, as shown in Table no. 6. All formulations showed friability values below 1%, indicating excellent mechanical resistance.[26]

In the present study, NDP tablets showed drug content uniformity values between 97.30 ± 0.29 to 99.85 ± 0.33%, 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 NDP tablets ranged from 9.05 ± 1.11 to 10.55 ± 1.18 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, NDP tablets showed water absorption ratios between 97.40 ± 0.41 and 99.70 ± 0.28%, with formulation B12 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, NDP tablets showed disintegration time values between 53.72 ± 0.63 to 70.85 ± 0.59 seconds, as presented in Table no.6. Among all formulations, B12 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 NDP

Batch	Weight Variation (%)	Thickness (mm)	Hardness (kg/cm²)	Friability (%)	Disintegration Time (sec)	Wetting Time (sec)	Water Absorption Ratio	Content Uniformity (%)
B1	195.68±1.12	3.44±0.04	4.20±0.52	0.89±0.02	70.4± 0.66	10.22±1.10	96.23±0.43	99.25 ±0.36
B2	235.69±1.10	3.54±0.06	3.99±0.44	0.81±0.01	68.30±0.58	10.39±1.01	95.42±0.49	94.25 ±0.30
B3	235.96±1.23	3.60±0.05	4.25±0.39	0.90±0.02	67.10±0.61	10.27±1.13	96.36±0.56	98.80 ±0.42
B4	276.03±1.11	3.36±0.03	3.77±0.41	0.79±0.01	63.42±0.55	9.88±1.14	97.96±0.43	95.25 ±0.22
B5	212.73±1.45	3.44±0.07	3.81±0.36	0.71±0.02	59.35±0.63	9.75±1.29	97.23±0.39	99.85 ±0.33
B6	218..99±1.12	3.56±0.05	3.54±0.42	0.72±0.01	57.20±0.47	9.85±1.09	99.86±0.43	94.25 ±0.46
B7	254.35±1.22	3.43±0.04	3.96±0.38	0.81±02	65.15±0.54	10.06±1.03	97.66±0.29	97.30 ±0.29
B8	257.66±1.21	3.40±0.06	4.12±0.35	0.83±0.01	54.62±0.68	9.22±1.13	99.61±0.36	93.25 ±0.26
B9	213.67±1.13	3.44±0.05	3.47±0.31	0.73±0.02	61.90±0.71	9.34±1.09	99.75±0.82	99.42 ±0.35
B10	217.62±1.11	3.34±0.03	3.39±0.37	0.70±0.01	70.85±0.59	9.05±1.06	99.53±0.49	92.25 ±0.16
B11	253.66±1.21	3.28±0.04	4.12±0.40	0.75±0.02	59.40±0.46	9.35±1.12	98.88±0.26	99.55 ±0.31
B12	258.92±1.11	3.12±0.07	3.25±.33	0.69±0.01	53.72±0.63	9.09±1.14	99.43±0.41	92.25 ±0.22
B13	234.29±1.31	3.20±0.05	3.62±0.45	0.73±0.02	65.10±0.52	10.03±1.12	98.15±0.49	98.95 ±0.25

In vitro dissolution profile of NDP core tablets:

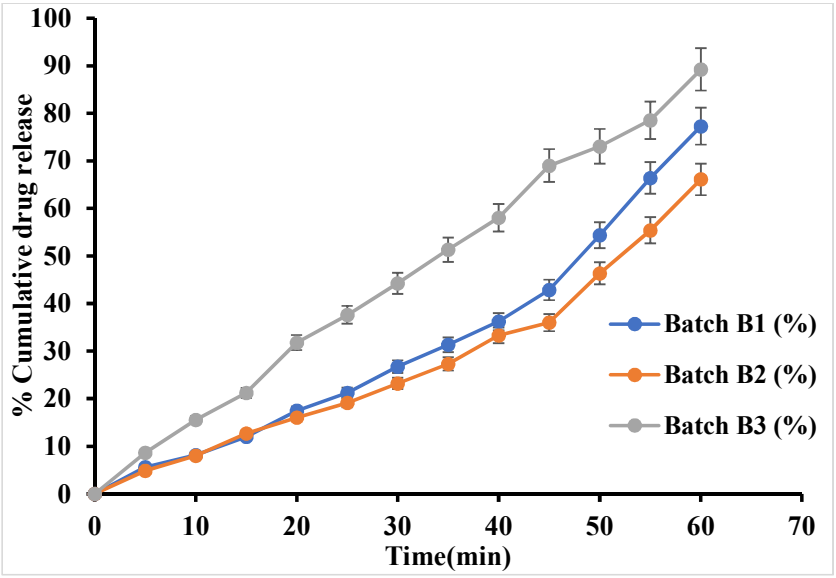
In vitro drug release study is a critical parameter for evaluating the performance of dispersible tablets, as it indicates the rate and extent of drug availability for absorption. According to standard dissolution principles, fast dispersible tablets should exhibit rapid drug release due to quick disintegration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

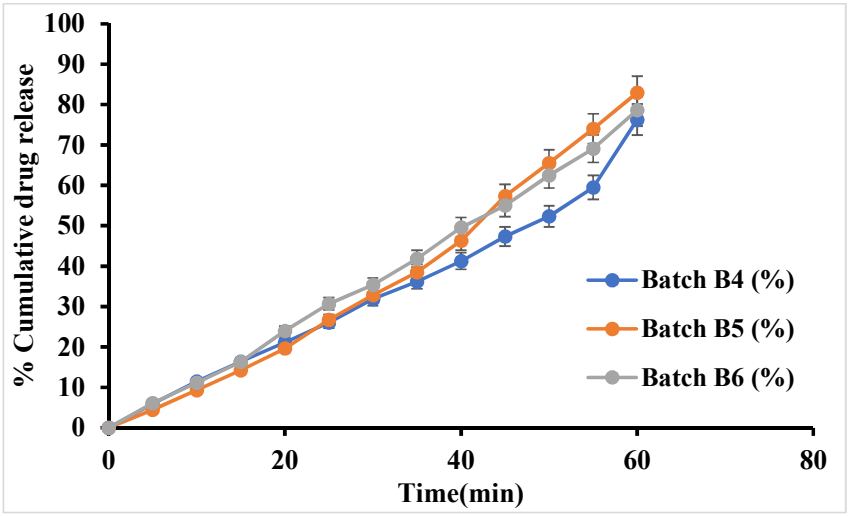
In the present study, all batches of NDP (B1–B13) tablets were subjected to dissolution studies under simulated physiological conditions. The results demonstrated that all formulations showed rapid drug release, which is characteristic of dispersible tablet formulations. However, slight variations in release profiles were observed among different batches due to variation in excipient concentrations, particularly crosscarmellose sodium and Avicel.

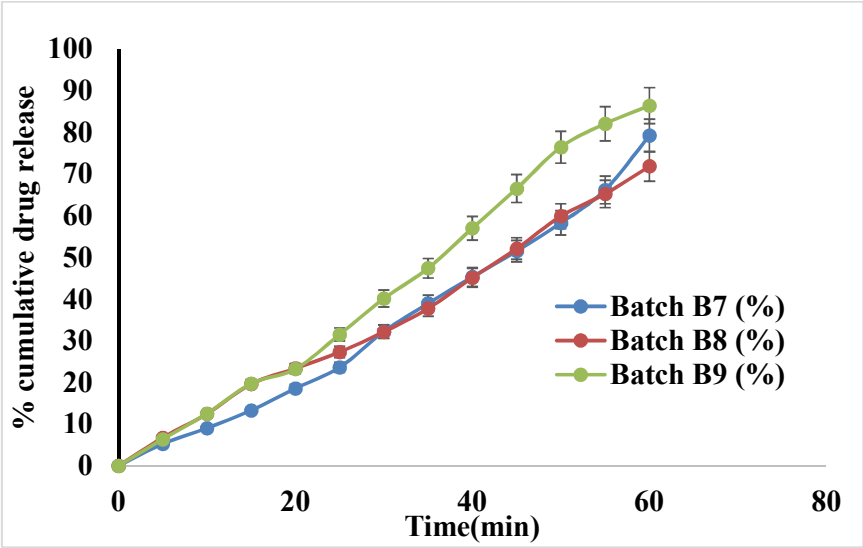
NDP formulations, batches B1, B2, and B3 exhibited comparatively slower drug release, likely due to lower superdisintegrant concentration and reduced wettability. As the formulation variables were optimized in batches B4 to B7, drug release improved gradually. Batches B8, B9, B10, B11, B12, and B13 demonstrated rapid drug release profiles, with B3 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.







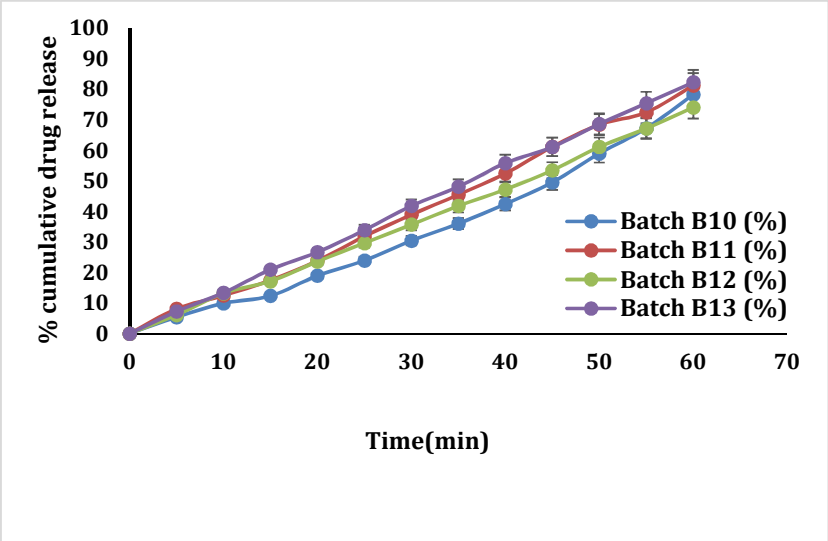


Figure no. 1. In vitro dissolution profile of NDP core tablets

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

The time required for formulation disintegration is a significant parameter that ultimately modulates drug dissolution. The time a tablet takes to disintegrate is primarily influenced by the concentration and interactions among the formulation variables used in its preparation. The quantum of drug solubilized is a significant parameter that ultimately modulates the drug's availability in the bloodstream. The extent of drug dissolution is primarily influenced by the concentrations and interactions among the formulation variables used in its preparation.

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

$Y_1 = 65.10 + 0.7875X_1 + 0.8438X_2 + 2.79X_3 - 4.91X_1X_2 - 4.23X_1X_3 + 0.3950X_2X_3 - 0.4725X_1^2 - 3.16X_2^2 - 0.0850X_3^2$

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:

$Y_2 = 79.91 - 0.3637X_1 + 1.64X_2 + 2.24X_3 + 1.10X_1X_2 - 2.54X_1X_3 - 2.14X_2X_3 + 0.7062X_1^2 + 0.5412X_2^2 + 4.60X_3^2$

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

Optimization using BBD for NDP core tablets:

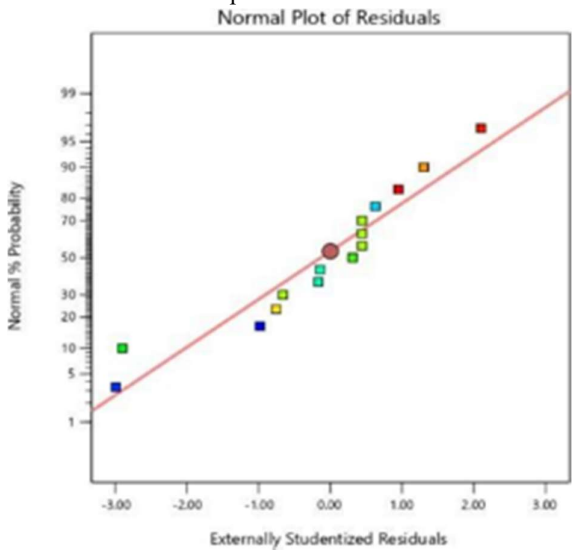
BBD approach was applied to NDP core formulations to evaluate the influence of formulation variables on disintegration time and drug release.

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.

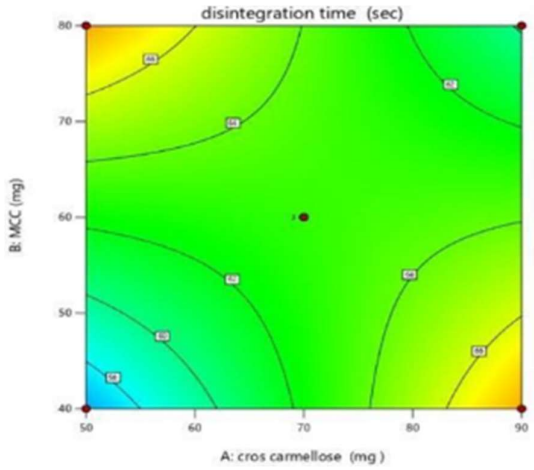
The response surface and 3D plots shown in Figure no. 2, demonstrate that disintegration time is significantly affected by the interaction between crosscarmellose sodium and MCC. The plots suggest that moderate concentrations of these variables result in optimum disintegration performance.

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.

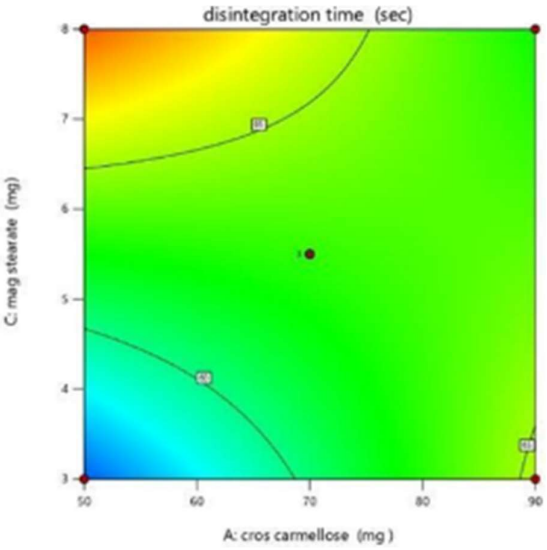
The normal probability plot confirms the adequacy of the model, indicating that the experimental data fits well with the predicted model. Overall, the factorial design study for NDP demonstrates that formulation variables significantly influence both disintegration time and drug release, and optimization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



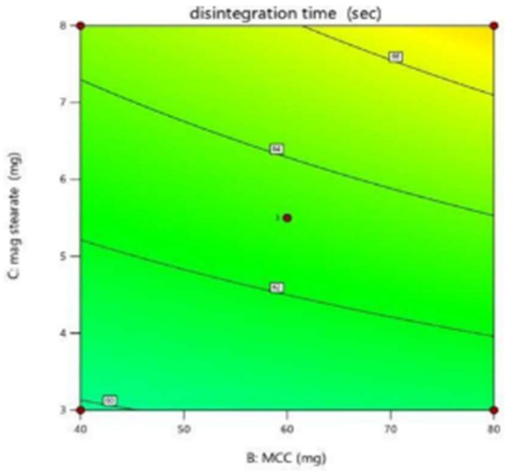
Normal Plot of Residuals of NDP core tablets



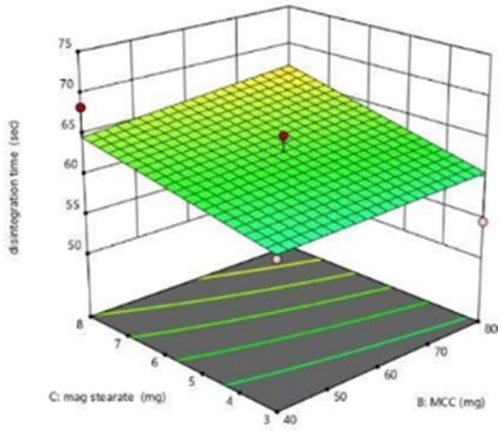
Contour plot of effect of Croscarmellose and Avicel on Disintegration Time of NDP core tablets



Contour plot of effect of Croscarmellose and Mag. stearate on Disintegration Time of NDP core tablets



Contour plot of effect of Avicel and Mag. stearate on disintegration time of NDP core tablets



3D plot of effect of Avicel and Mag. stearate on Disintegration Time of NDP core tablets

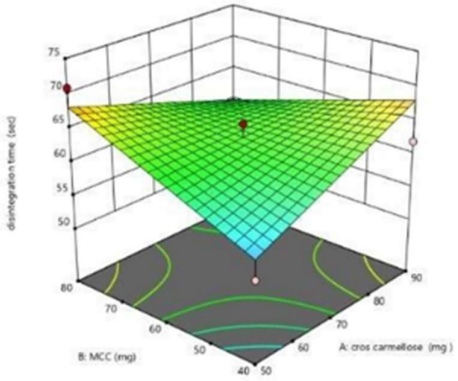
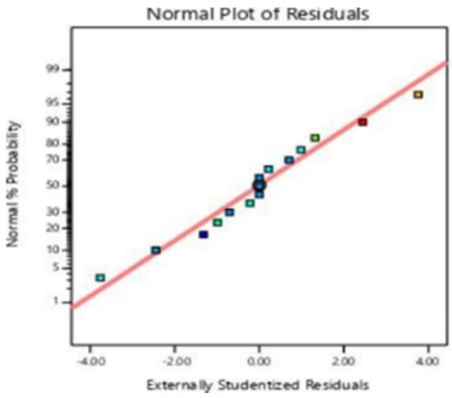


Figure 46: 3D plot of effect of Croscarmellose and Avicel on Disintegration Time of NDP core tablets



Normal Plot of Residuals of NDP core tablets

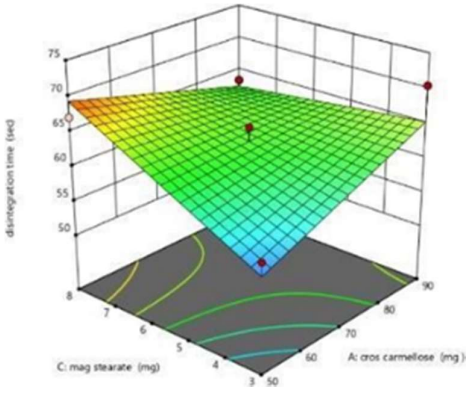
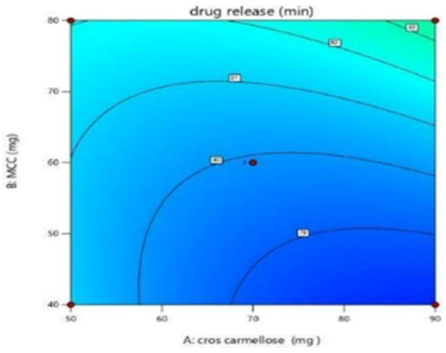
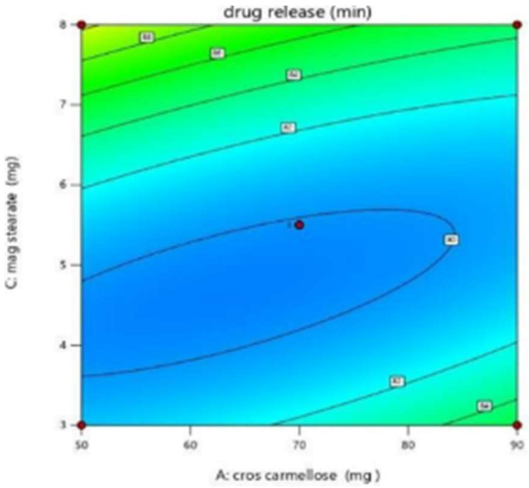


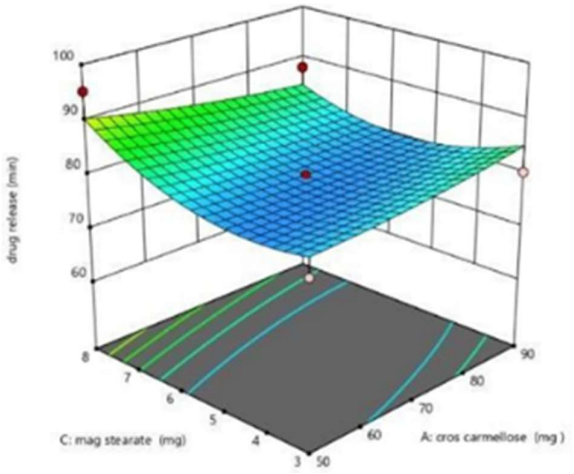
Figure 47:3D plot of effect of Croscarmellose and Mag. stearate on Disintegration Time of NDP core tablets



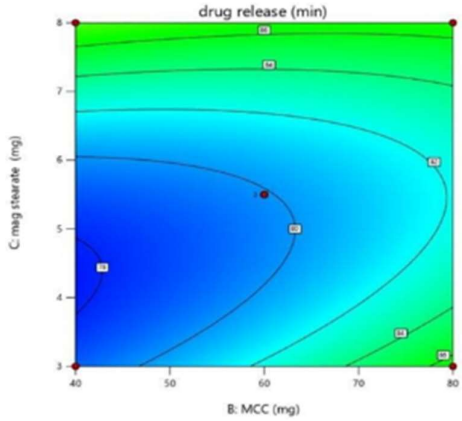
Contour plot of effect of Croscarmellose and Avicel on drug release of NDP core tablets



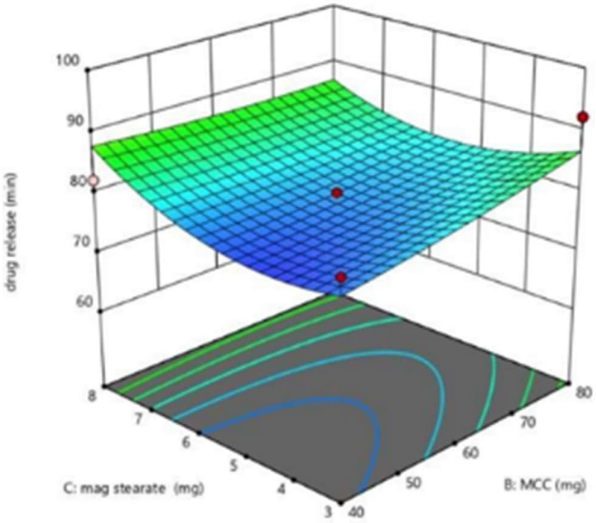
Contour plot of effect of Croscarmellose and Mag. Stearate on drug release of NDP core tablets



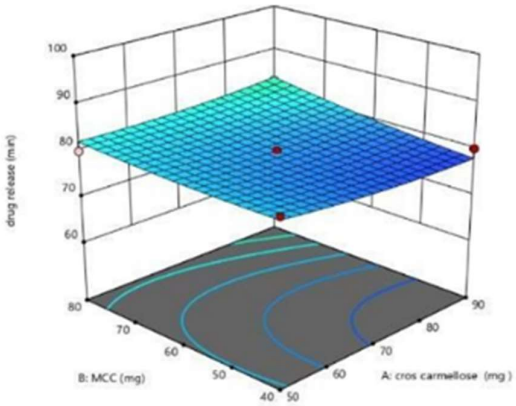
3D plot of effect of Croscarmellose and Mag. Stearate on drug release of NDP core tablets



Contour plot of effect of Avicel and Mag. Stearate on drug release of NDP core tablets



3D plot of effect of Avicel and Mag. Stearate on drug release of NDP core tablets



3D plot of effect of Croscarmellose and Avicel on drug release of NDP core tablets

Figure no. 2: Residual, response surface and 3D contour plots generated by BBD for NDP core tablets

Preparation of powder blends for press coated tablets using BBD:

Powder blends for NDP 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. The 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 NDP

Batch code	Bulk density (gm/cc)	Tapped density (gm/cc)	Hausner's ratio	Compressibility index	Angle of repose
N1	0.428±0.008	0.508±0.005	1.19 ±0.021	15.95± 1.480	29.40± 1.02
N2	0.437±0.015	0.514±0.008	1.18 ± 0.025	15.40± 1.900	29.60± 0.71
N3	0.442±0.018	0.526±0.006	1.20 ± 0.045	16.10± 3.300	29.95± 0.85
N4	0.478±0.010	0.572±0.019	1.20 ± 0.040	16.80± 2.900	29.00± 1.10
N5	0.455±0.017	0.542±0.030	1.20 ± 0.080	16.10± 5.800	29.80± 0.65
N6	0.430±0.006	0.509±0.008	1.19 ± 0.005	15.70± 0.360	29.70± 1.50
N7	0.452±0.022	0.538±0.021	1.20 ± 0.038	16.40± 2.800	29.45± 1.05
N8	0.443±0.011	0.528±0.018	1.20 ± 0.027	16.30± 2.000	29.20± 1.08
N9	0.454±0.021	0.538±0.029	1.19 ± 0.007	15.90±0.450	29.10± 0.82
N10	0.439±0.013	0.520±0.007	1.19 ± 0.050	15.70± 3.600	30.00± 1.65
N11	0.460±0.014	0.545±0.010	1.18 ± 0.009	15.85± 1.200	28.95± 0.90
N12	0.470±0.016	0.560±0.015	1.19 ±0.030	16.20± 2.100	29.30± 1.00
N13	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 NDP:

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 NDP core tablets. The evaluation parameters of press coated tablets are given in table no. 8.

The thickness ranged of NDP 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 NDP from 0.62 ± 0.01 to 0.88 ± 0.02%, confirming good mechanical resistance and durability of tablets (Table No. 8).

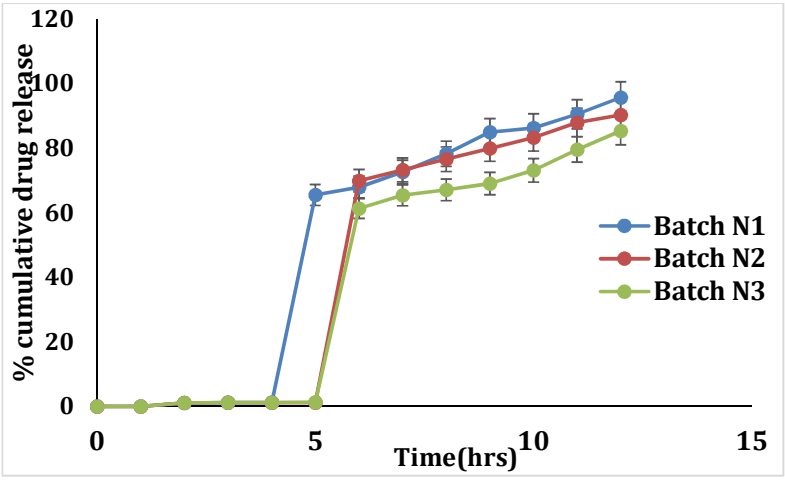
Drug content of NDP press coated tablets ranged from 96.36 ± 0.53 to 99.85 ± 0.63%, indicating uniform distribution of drug throughout the formulation. Wetting time of NDP press coated tablets ranged from 9.28 ± 1.04 to 10.42 ± 1.05 sec, indicating rapid wetting, which facilitates faster hydration and disintegration. Water absorption ratio indicates the swelling capacity of polymers. Higher values indicate better swelling. In the present study, water absorption ratio ranged from NDP tablets ranged from 90.10 ± 0.36 to 99.85 ± 0.48%, with higher values indicating greater swelling ability due to polymer content (Table No. 8).

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

Batch	Weight Variation (in mg)	Thickness (mm)	Hardness (kg/m^2)	Friability (%)	Wetting Time (sec)	Water Absorption Ratio (%)	Content uniformity (%)
N1	556.12±0.84	3.22±0.04	4.23±0.52	0.87±0.02	10.30±1.10	99.85±0.48	98.25±0.66

N2	726.02±0.66	2.99±0.06	3.99±0.44	0.82±0.01	10.42±1.05	96.40±0.41	96.36±0.53
N3	745.92±0.39	3.95±0.05	4.35±0.39	0.76±0.02	10.35±1.18	90.10±0.36	98.75±0.45
N4	855.29±0.92	3.56±0.03	4.12±0.41	0.79±0.01	9.68± 1.12	91.62±0.44	98.78±0.39
N5	881.03±0.75	4.25±0.07	4.61±0.36	0.83±0.02	10.55±1.20	99.55±0.39	99.62±0.55
N6	716.32±0.68	4.16±0.05	4.45±0.42	0.78±0.01	10.15±1.08	92.10±0.33	98.96±0.36
N7	560.26±0.32	3.95±0.04	3.35±0.38	0.73±0.02	10.10±1.09	94.85±0.52	97.69±0.45
N8	586.12±0.58	4.02±0.06	4.16±0.35	0.84±0.01	9.42± 1.16	97.26±0.29	99.78±0.38
N9	571.33±0.39	3.70±0.05	3.12±0.31	0.63±0.02	9.40± 1.13	96.40±0.25	99.82±0.25
N10	885.22±0.51	4.91±0.03	4.32±0.37	0.66±0.01	9.28± 1.04	97.55±0.31	99.23±0.85
N11	616.06±0.39	4.23±0.04	3.10±0.40	0.72±0.02	9.95± 1.15	91.38±0.41	99.39±0.86
N12	860.09±0.51	4.72±0.07	3.56±0.33	0.69±0.01	10.05±1.11	92.33±0.29	99.22±0.53
N13	721.09±0.95	4.20±0.05	3.86±0.45	0.74±0.02	10.22±1.17	97.69±0.71	99.85±0.63

In vitro drug release study of press coated NDP 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 NDP press coated exhibited a lag phase followed by rapid drug release. Among all batches, NDP batch N1 showed optimized performance with 95.66% drug release at 12 hours, indicating effective controlled release behavior (Figure no. 3). In the present study, NDP press coated tablet Batch N1 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.



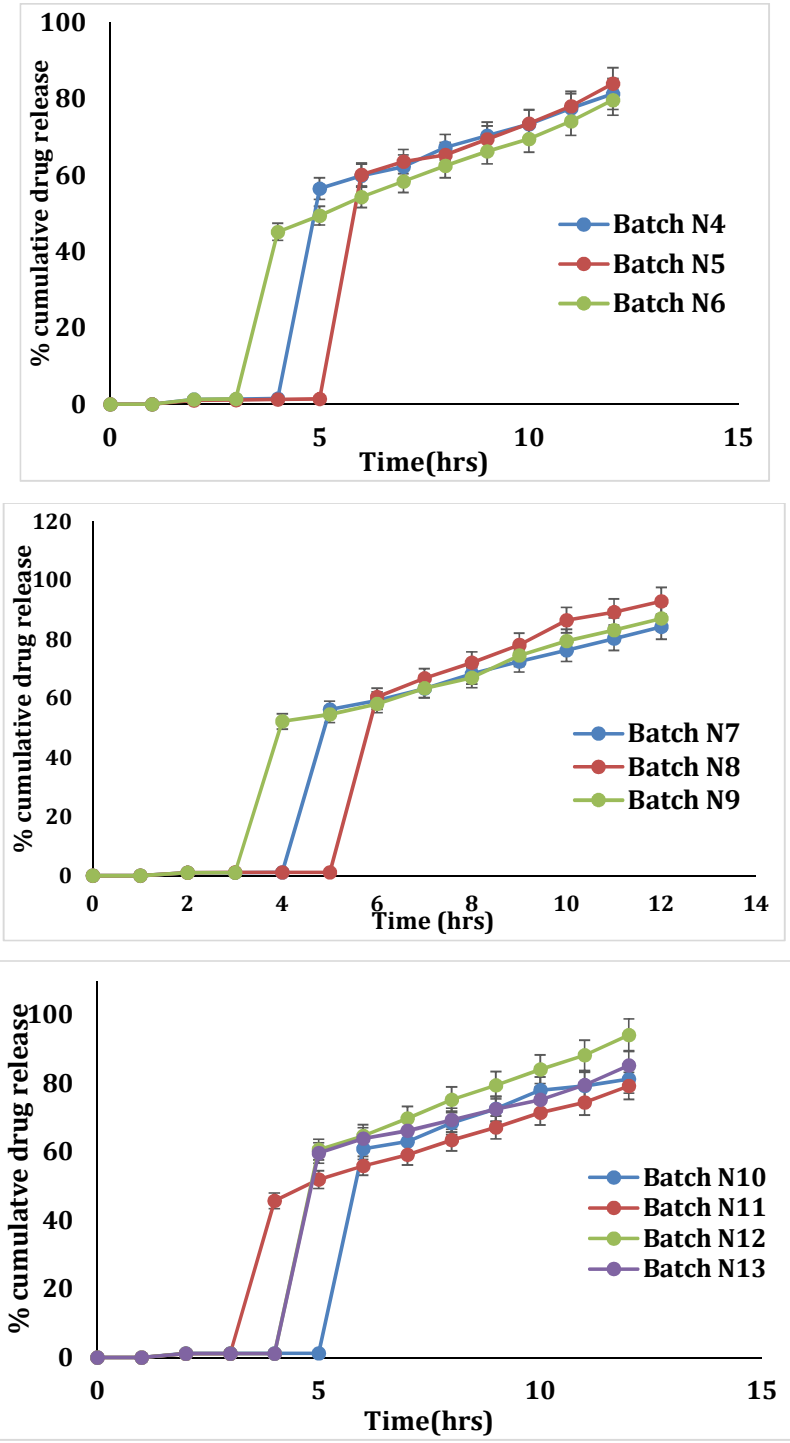


Figure no. 3. In vitro release profile of various press coated tablets of NDP

Lag time of press coated NDP tablets:

Lag time is an important parameter in pulsatile drug delivery. In the present study, lag time ranged from 4 to 7 hours. Formulations N1 showed highest lag time indicating strong influence of polymer concentration.in the Findings revealed higher polymer concentration increased lag time due to delayed erosion of coating (Table No. 9). The results indicated that increasing polymer concentration increased lag time due to

delayed erosion of the coating layer. Interaction between variables also significantly affected lag time. Increase in polymer concentration reduced drug release rate due to increased diffusion barrier and decreased permeability of coating.

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

Formulations	Lag Time (Hours)
N1	7
N2	6
N3	6
N4	5
N5	6
N6	4
N7	5
N8	6
N9	4
N10	6
N11	4
N12	5
N13	5

Optimization of press coated tablets of NDP using BBD:

For polynomial analysis validation, optimal design and quadratic expressions were chosen in the experimental design. A mathematical model created for optimum preparation was used to forecast concentration values for HPMC K4M, HPMC, and Sodium Alginate. The % bias was computed after comparing the experimental data to the projected values Experiments were performed to ascertain the mathematical relationship between the system's interacting elements and its reaction. To establish the optimum levels of HPMC K4M, HPMC, and Sodium Alginate to be released from press-coated tablets, statistical evaluation of the findings was performed using Design Expert.

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

Y_1 (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 = HPMC K100, 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:

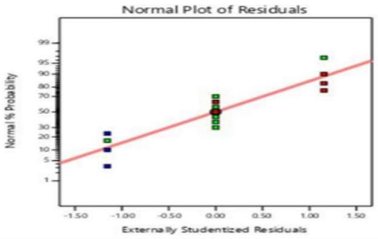
Y_2 (% Drug Release at 450 min) $=94.54 + 0.3875X_1 + 4.78X_2 - 4.19X_3 + 3.87X_1X_2 + 4.58X_1X_3 + 7.20X_2X_3 - 6.53X_1^2 - 2.53X_2^2 - 7.51X_3^2$

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

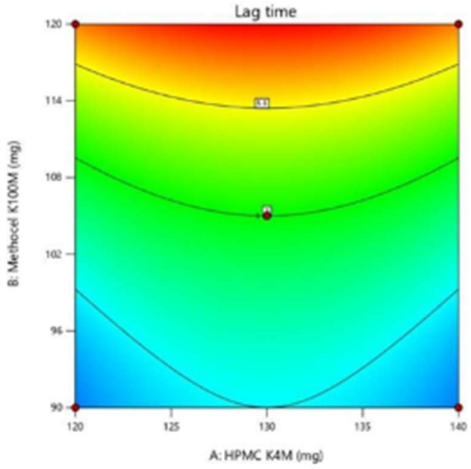
Effect of various formulation variables according to BBD:

BBD was applied to evaluate the effect of formulation variables on lag time and drug release. In the present study, HPMC K4M, Methocel K100M, and Sodium Alginate were selected as independent variables, while lag time and drug release were considered as dependent responses. The polynomial equation generated for lag time (Y_1) indicated that the concentration of coating polymers had a significant effect on lag time. It was observed that increasing polymer concentration increased lag time due to the formation of a thicker gel barrier, which delayed penetration of the dissolution medium. The interaction between variables also contributed significantly to lag time variation.

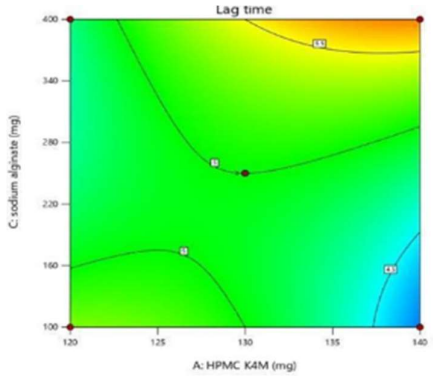
Similarly, the polynomial equation for drug release (Y_2) showed that polymer concentration significantly affected drug release behavior. An increase in polymer concentration retarded drug release due to increased diffusion path length and decreased permeability of the coating layer. The interaction effects of formulation variables further influenced the release profile. These observations were supported by residual, response surface and 3D plots (Figure No. 4), which clearly demonstrated the effect of formulation variables on lag time and drug release.



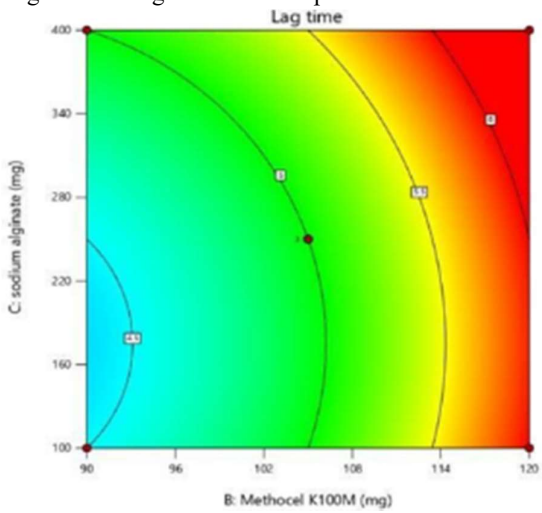
Normal Plot of Residuals of NDP press coated tablet



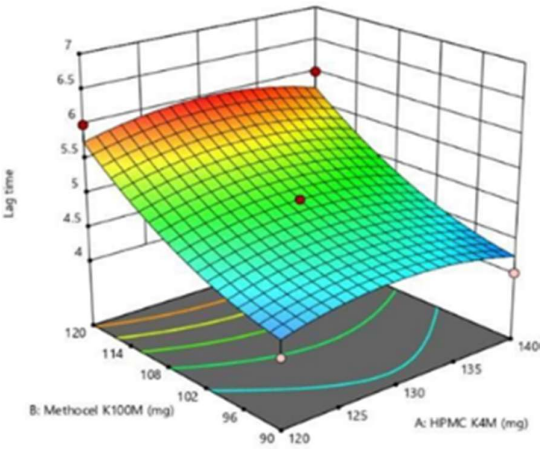
Contour plot of effect of HPMC K4M and HPMC K100M on Lag Time of NDP press coated tablet



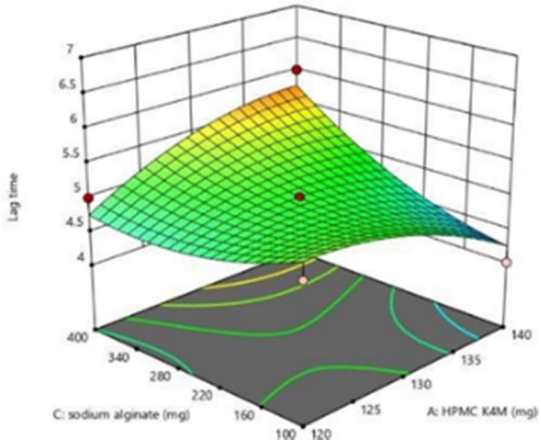
Contour plot of effect of HPMC K4M and Sodium Alginate on Lag Time of NDP press coated tablet



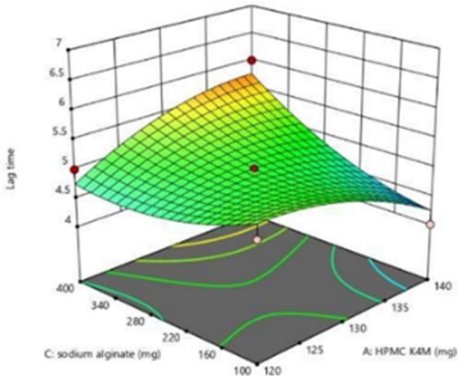
Contour plot of effect of HPMC K100M and Sodium Alginate on Lag Time of NDP press coated tablet



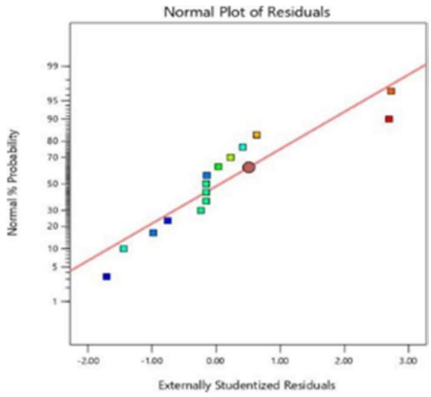
3D plot of effect of HPMC K4Mand
HPMC K100M on Lag Time of NDP press coated tablet



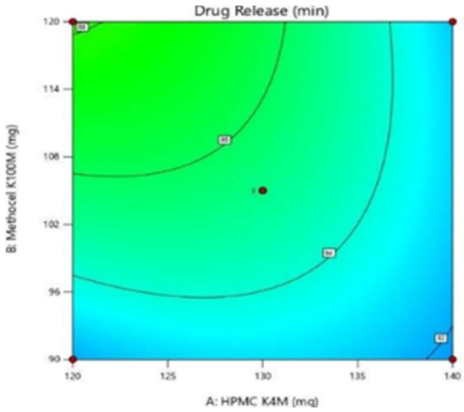
3D plot of effect of HPMC K4M and Sodium Alginate on Lag Time of NDP press coated tablet



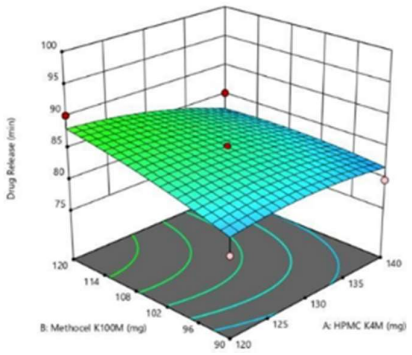
3D plot of effect of HPMC K100Mand Sodium Alginate on Lag Time of NDP press coated tablet



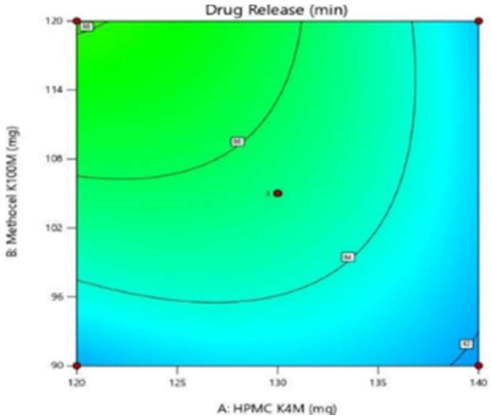
Normal Plot of Residuals of NDP press coated tablet



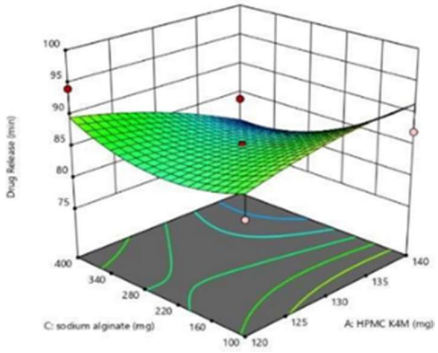
Contour plot of effect of HPMC K4M and HPMC K100M on % drug release of NDP press coated tablet



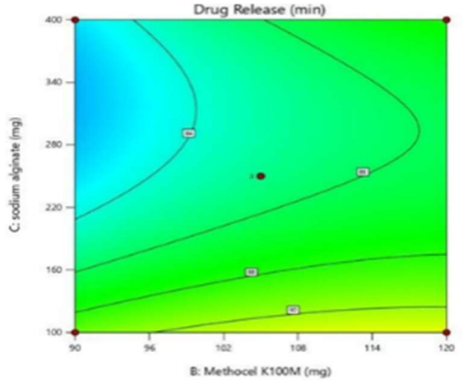
3D plot of effect of HPMC K4M and HPMC K100M on drug release of NDP press coated tablet



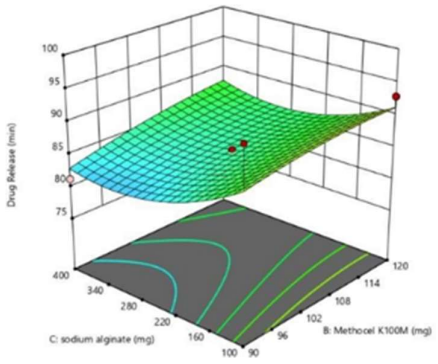
Contour plot of effect of HPMC K4M and Sodium Alginate on drug release of NDP press coated tablet



3D plot of effect of HPMC K4M and Sodium Alginate on drug release of NDP press coated tablet



Contour plot of effect of HPMC K100M and Sodium Alginate on drug release of NDP press coated tablet



3D plot of effect of HPMC K100M and Sodium Alginate on drug release of NDP press coated tablet

Figure no. 4: Residual, response surface and 3D contour plots generated by BBD for NDP press coated tablets

CONCLUSION

The investigation aims to formulate time-activated press coated tablet of NDP for effective and timely management of hypertension. Press-coated tablets are specifically designed to achieve time-dependent drug release by applying an outer polymeric coat that controls lag time prior to drug release. In the present study, BBD was employed to optimize the formulation of NDP dispersible core tablets. The independent variables selected were crosscarmellose sodium, Avicel, and magnesium stearate, which are known to significantly influence tablet properties such as disintegration, hardness, and flowability. Tablet blends were evaluated for various density and flow related properties. The results obtained from these formulations demonstrated that changes in the concentration of crosscarmellose sodium significantly affected the disintegration time, while MCC influenced tablet hardness and compressibility. The compressed tablets were screened for various evaluation parameters such as appearance, weight variation, drug content uniformity, weight variation, friability, hardness, water absorption ratio, wetting time, disintegration time and in vitro dissolution profile. The experimental designs suggests that 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. Further, press coated tablets of optimized NDP batch was prepared, using factorial design to evaluate the effect of formulation variables on lag time and drug release. In the present study, HPMC K4M, HPMC K100M, and Sodium Alginate were selected as independent variables, while lag time and drug release were considered as dependent responses. The prepared press coated tablets were evaluated for weight variation, hardness, content uniformity, friability, disintegration tests and in vitro dissolution tests. Optimized press coated tablets of NDP batch N1 showed 95 % drug release during in vitro dissolution studies using paddle method. Overall, the findings concluded that chrono-modulated press coated tablets of NDP developed could provide timely burst release after 450 minutes, utilizing a blend of polymers that could retard the drug diffusion for around 7 hrs. This approach surely would be useful for medical conditions such as hypertension that triggers during early morning hours.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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None

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