Int. J. Pharm. Investigation, 2026; 16(1):316-323.
https://www.jpionline.org

Original Article

Formulation Development of Carvedilol Phosphate and Lisinopril Hydrochloride Bilayer Tablet using QbD

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ABSTRACT

Introduction: Lisinopril HCl (LH) and Carvedilol Phosphate (CP) combination bilayer tablet to be developed for the treatment of hypertension. **Objectives:** To develop carvedilol phosphate and lisinopril hydrochloride bilayer tablet using QbD. **Materials and Methods:** Bilayer tablet technology is used for the development of the combination of LH and CP to achieve two different release profiles of each drug. LH containing layer released the drug at a much faster rate due to faster disintegration time and CP containing layer swells and releases the drug content for a longer period by forming the swellable matrix. The central composite design is used for the development and optimization of the formulation of bilayer tablets. Critical responses like disintegration time and dissolution for the LH layer and dissolution at 2 hr, 16 hr, and 24 hr for the CP layer were evaluated against factors like Maize starch, Crospovidone XL for the LH layer, and concentration of HPMC K 100M and MA Polymer for CP layer. The wet granulation method was used for the preparation of granules and further processing of bilayer tablets. **Results:** Critical responses were evaluated by response surface methodology by design expert software to verify the best-fit model for the development and optimization bilayer tablet. Responses obtained for the LH layer show that the concentration of maize starch and crospovidone XL and for the CP layer concentration of HPMC K100M and MA Polymer need to be optimized to achieve desired responses for both layers. The model selected was found to be significant as per ANOVA tables. **Conclusion:** The evaluation of results of the LH layer found that the concentration of maize starch (3%) and crospovidone XL (10%) and the CP Layer found that concentration of HPMC K100M (34%) and MA polymer (17%) were found best composition.

Keywords: Bilayer tablets, Hypertension, Central Composite Design, ANOVA, Response surface methodology.

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Received: 09-04-2025;
Revised: 24-06-2025;
Accepted: 18-08-2025.

INTRODUCTION

In recent decades, the pharmaceutical industry has actively worked on improving existing drugs by enhancing their safety, and efficacy, and minimizing side effects. This effort also aims to improve patient access to the latest treatments and foster better adherence to medical guidance (Panchal *et al.*, 2012). Innovations include developing new pharmaceutical applications, such as novel forms and administration routes, as well as more cost-effective and efficient production techniques. Combination drugs, which merge two or more active ingredients, have gained prominence (Kavitha *et al.*, 2011). These formulations are designed to improve patient tolerance, reduce adverse effects, enhance cooperation between patients and physicians, and sometimes increase drug efficacy. Research has demonstrated that such combination therapies can often be more effective than administering individual active ingredients separately (Chowdary and Balatripura, 2003). While these modifications may appear simple they require extensive research to be carried out to preserve the drug's original properties while altering its drug release which ultimately benefits patients by offering safer, more convenient medications. The advancement of sustained and controlled drug delivery systems has gained considerable momentum over the past decade (Mishra *et al.*, 2014). This is largely due to the increased focus on marketing new drug molecules, especially as combination therapies have become more prevalent in addressing multiple diseases that require varying dosage regimens (Kale *et al.*, 2011). Bilayer tablets, in particular, have emerged as a valuable tool for enhancing patient compliance. These tablets offer advantages by enabling either the sequential release of two combined drugs or the controlled release of a single drug, where one layer provides an initial dose while the other ensures a sustained maintenance dose (Deshpande *et al.*, 2011; Abdul and Poddar, 2004).

Bilayer tablets allow the integration of two distinct drugs or varying release profiles of the same drug within a single dosage

DOI: 10.5530/ijpi.20260456

form (Akhtar *et al*., 2020). This approach can be particularly advantageous in combination therapy for hypertension (high blood pressure) because it allows for more effective management of the condition, improves patient compliance, and can enhance the therapeutic outcomes. (Niranjan and Bahadur, 2023). A combination of Carvedilol Phosphate (CP) and Lisinopril (LP) clinical studies has been done to evaluate its effectiveness for reducing Blood Pressure (BP) as compared to its monotherapy in which it found that at high dose combination it helps to reduce BP compared to its monotherapy (Bakris *et al*., 2020; Saul *et al*., 2013). This combination also showed positive results for reducing BP in obese patients as compared to existing antihypertensive drug combinations (Kelly *et al*., 2012).

CP is given as an extended-release dosage and LP is given once daily as monotherapy (Davar and Ghosh, 2010), but to achieve its combined effect these two drugs should be combined in a single dosage unit; hence tablet dosage has to be designed in which one layer releases the CP for an extended period to achieve therapeutic concentration for a longer period and lisinopril will release immediately after administration. Achieving these two different release profiles of the two drugs in a single stable tablet dosage will give the defined therapeutic effect as well as provide patient compliance by avoiding the use of two pills. Hence bilayer tablet would be the appropriate option to combine these two drugs in a single tablet with a predefined release profile and due to separating drugs into two different layers, it will also avoid drug-drug interaction.

The Design of Experiments (DoE) approach is extensively employed in implementing Quality by Design (QbD) in both research and industrial applications (Nyavanandi *et al*., 2024). Among the various DoE methodologies, CCD incorporates center points, enhanced with a set of axial points, which allows for the estimation of curvature (Beg and Rahman, 2021). This design is particularly effective in sequential experimentation, enabling researchers to work on various experiments (Willden and Jensen, 2020). Formulation or process optimization focuses on determining the ideal composition or operating parameters. The key objective is to systematically evaluate the influence of different factors on response variables. Depending on the number of factors, levels, and their possible interactions, suitable experimental designs are chosen.

The main aim of this study is to formulate a bilayer tablet comprising an Immediate-Release (IR) layer of Lisinopril HCL and an Extended-Release (ER) layer of Carvedilol Phosphate. Utilizing the CCD, the investigation evaluates the impact of selected factors on the response variables. In this study, for the IR part, the concentration of Binder and Disintegrant were considered as factors, and response variables were evaluated as disintegration time and % drug release by dissolution and for ER part the concentrations of Hydroxy Propyl Methyl Cellulose (HPMC), and methacrylic acid-ethyl acrylate copolymer (MA Polymer) were considered as factors, while the response variables included drug release at 2 hr, 16 hr, and 24 hr.

MATERIALS AND METHODS

Materials

Carvedilol Phosphate was gifted by Viatris India Pvt. Ltd., Lisinopril HCl was gifted by Vasudha Chemicals Pvt. Ltd., Microcrystalline Cellulose, Maize Starch, Crospovidone XL, Mannitol, Sucralose, Magnesium stearate, Iron oxide red, Povidone K30, Sodium Laural Sulphate, colloidal Silicon dioxide (Aerosil), HPMC K100M, MA Polymer received from Shalina laboratories as gift samples.

Methods

Selection of Design for formulation development

Before initiating the experimental trials, an assessment of different challenges was done for the IR and ER layers of bilayer tablets. Challenges identified for the IR layer were disintegration time and drug release in 15 min. Challenges for the XR layer were dissolution rate at longer periods i.e. at 2 hr, 14 hr, and 24 hr.

A feasibility trial was conducted for bilayer tablet formulation having different release profiles of each layer and some critical factors were identified as concentration of Maize starch (1-5% w/w) and Crospovidone XL (7-13% w/w) for the IR layer, concentration of HPMC K100M (29-39% w/w) & MA Polymer (MA POLYMER) (13-21% w/w) for XR layer considered for optimization of formulation using CCD. Design Expert Version 7.0.0 software was used for designing an optimization trial plan by considering identified different critical factors of the IR layer and ER layer of the bilayer Tablet 2 factors and 3 level (-1, 0, +1) design was applied by considering 3 mid-point for optimization of both layers which design 11 trials (Tables 1 and 2) for each layer.

Manufacturing of bilayer tablet

To make bilayer tablet IR layer granules and ER layer granules prepared using wet granulation. The procedure for making IR and ER layer granules is as follows:

Manufacturing of IR layer granules

Lisinopril, MCC, and Sucralose sift through sieve 30#, iron oxide red through sieve 80# then mixed into the pneumatic mixer for 5 min. Dry mixed blend then granulated with maize starch paste. Granulated material was dried at 60 to 65°C to achieve dried granules. Then dried granules pass through 30#. Then it was mixed with Crosspovidone XL for 10 min and then it was mixed with Magnesium stearate for 5 min.

Manufacturing of ER layer granules

CP, MCC, HPMC K100M, MA Polymer, SLS sift through a sieve 40# and mix into the pneumatic mixer for 5 min. Dry mixed blend

then granulated with PVP K 30 aqueous solution. Granulated material was dried at 60 to 65°C to achieve dried granules. Then dried granules pass through 30#. Then it was mixed with aerosil 200 for 10 min and then it was mixed with Magnesium stearate for 5 min. IR and ER layer granules ready for compression were then compressed into bilayer tablets using the Karnavati bilayer Tablet compression Press.

Bilayer tablets were manufactured using the above procedure for all trials set, obtained from CCD using design expert software. All trials were analyzed for physicochemical parameters and their respective response. After evaluation individual trial responses were studied with the ANOVA parameter, Curvature graph. This response obtained after the statistical evaluation was then fed into design expert software to conclude the design space from which optimized formulation parameters catch out.

Precompression Parameters

Bulk Density (BD)

The granules were weighed and added to a 50 mL measuring cylinder volume was noted down and BD was calculated using the following formula (Panda and Suryawanshi, 2023).

$$BD = \frac{\text{Granule weight (g)}}{\text{volume (ml)}}$$

Tapped Density (TD)

The granules were weighed and added to a 50 mL measuring cylinder and the initial volume was noted down and followed by tapping till no volume was changed. The tapped volume was noted down and TD was calculated (Panda and Suryawanshi, 2023).

Compressibility Index (CI)

CI was calculated using this formula (Panda and Suryawanshi, 2023).

$$CI = \frac{TD - BD}{TD} X\ 100$$

Hausner's Ratio (HR)

HR was calculated using this formula (Panda and Suryawanshi, 2023).

$$HR = \frac{TD}{BD}$$

Angle of Repose (AR)

This is a simple method used to assess the resistance of particles to movement. AR represents the maximum angle formed between the surface of a powder heap and the horizontal plane (Panda and Suryawanshi, 2023).

$$\text{Tan } \theta = h/r,\ \theta = \tan\text{-}1h/r$$

Post compression Parameters

Physical Parameters.

Weight variation

As per IP 20 tablets were selected randomly from each batch and weighed separately. The average weight and standard deviation were calculated (Panda and Suryawanshi, 2023).

Thickness

The thickness of randomly selected tablets (n=5) was determined by using a vernier caliper.

Hardness

It was determined on 5 tablets from each batch and determined on Monsanto tablet hardness tester and expressed in Kg/cm^2 (Gupta *et al.*, 2023).

Friability

Randomly selected 20 tablets were placed in a friabilator and 100 rotations were performed. The weight of the tablets was noted down. Considering initial weight and final weight, weight loss was determined (Patel *et al.*, 2011).

Chemical Parameters

Drug content/Assay

Twenty tablets were weighed, and the average weight was determined. The tablets were then crushed using a mortar and pestle, and the resulting powder was uniformly mixed on butter paper. A portion of the powdered material, equivalent to 20 mg of Lisinopril and 80 mg of Carvedilol phosphate (400 mg total), was accurately weighed and transferred into a clean, dry 100 mL volumetric flask. Approximately 70-75 mL of methanol was added, and the mixture was sonicated for 15 min with intermittent shaking. Finally, the volume was adjusted to 100 mL with methanol. The solution was filtered through a suitable 0.45 µ syringe filter discarding 3-5 mL of filtrate. Further diluted 2 mL of filtrate to 20 mL with mobile phase (20 PPM of Lisinopril and 80 PPM of Carvedilol phosphate).

Assay by HPLC

The samples analyzed by using these chromatographic conditions: Column: Agilent ZORBAX SB-Phenyl Column Dimension: (250 mm×4.6 mm i.d.) 5µm, Column oven temp: 40°C, Detector: U.V. Detector, Wavelength: 216 nm, Flow Rate: 1.0 mL/min, Mobile phase: Methanol: 0.1% OPA (60:40), Injection Volume: 20 µL.

In vitro Drug Release (Dissolution Study)

The drug release profile pattern of lisinopril and carvedilol phosphate is different i.e. Lisinopril is immediate release and carvedilol phosphate is extended-release. To evaluate its release profile dissolution test was carried out at the following conditions:

For lisinopril (Immediate release layer)

Dissolution study Parameters

Simulated saliva pH 6.8, Media volume: 300 mL, Apparatus: USP type II (Paddle), RPM:100, Temperature: 37°C, Time points: 15 min and 30 min. Withdraw the aliquot and analyze it at 210 nm using a UV spectrophotometer.

For Carvedilol Phosphate (Extended-release Layer)

Dissolution study parameters

Apparatus: USP type II (Paddle), RPM:100, Temperature: 37°C, Media volume: 900 mL of 0.1M hydrochloric acid (gastric simulated fluid, pH 1.2) as a dissolution medium for the first 2 hr and in intestinal simulated fluid (900 mL, pH 6.8) for the next 22 hr. Timepoint: 2 hr, 16 hr and 24 hr. Withdraw the aliquot and analyze it at 242nm using a UV spectrophotometer.

RESULTS

Precompression parameters

IR layer granules for compression

Lisinopril layer blend evaluated before compression for various flow properties. It was found that the concentration of maize starch and crospovidone has an impact physical characteristics of the powder. The angle of repose was found to be in the range 21.80° to 28.20° which indicates good flow property. The HR (1.12 to 1.20) and compressibility index (10.2 to 15.3) were calculated and indicated good to excellent flowability.

ER layer granules for compression

The concentration of the binder was kept constant for all batches hence physical properties like angle of repose, CI, and HR were found similar for all batches. The pre-compression evaluation data for the IR (F) and ER (M) layer granules indicate variations in flow properties. For the IR layer, the angle of repose ranges from 25.1 to 42.2, Carr's Index (CI) varies between 7.1 and 22.1, and the Hausner Ratio (HR) spans 1.02 to 1.27, suggesting that some formulations exhibit better flow than others. The angle of repose ranged from 21.8 to 28.2, CI between 10.2 and 15.3, and HR from 1.11 to 1.20, indicating relatively better compressibility and flow properties.

Post Compression Parameters

The weight variation was within ±3% of the average tablet weight (400 mg). The thickness was uniform, and the hardness ranged from 7.0 to 11.0 kg/cm^2. The friability percentage was found to be between 0.10% and 0.20%. Assay of both drugs found between a range of 95% to 105%.

Disintegration Time and Dissolution rate evaluation of IR layer

Formulation trials of the IR layer were carried out as per Table 1 and its DT & %DR data mentioned in Table 3. In the present study the DT of F1-F11 were observed in the acceptable limit. 3D plots (three dimensional) of Response Surface Methodology (RSM) of disintegration as shown in Figure 1. indicated that the use of maize starch (binder) (X1) (1 to 5%) and Crospovidone XL (superdisintegrant) (X2) (7 to 10%) resulted in acceptable values of disintegration time.

A dissolution study was carried out to evaluate the % drug release rate. A faster dissolution rate is expected to have immediate absorption and a faster therapeutic effect (Vidiyala *et al*., 2025). Hence trial no F1 to F11 evaluated for % DR and its statistical evaluation was done as per ANOVA and 3Dsurface graph (Figure 2) using Response Surface methodology. In the dissolution study, it was found that maize starch and crosspovidone XL have a combined effect on %DR. From trials F1, F5, F6, and F9, it was observed that an increase in maize starch concentration as a binder led to a reduction in %DR. Additionally, in trial F7, a lower concentration of both maize starch and crospovidone XL resulted in a further decrease in % DR. Response variables like DT and %DR ANOVA data mentioned in Table 4.

Table 1: Composition of IR layer of bilayer tablet using CCD.

Trial no.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Lisinopril	20	20	20	20	20	20	20	20	20	20	20
Mannitol	25	25	25	25	25	25	25	25	25	25	25
MCC	33.97	35.97	32.97	35.97	38.97	36.97	40.97	34.97	30.97	37.97	35.97
maize starch	5	3	3	3	3	5	1	1	5	1	3
Crospovidone XL	10	10	13	10	7	7	7	13	13	10	10
Sucralose	5	5	5	5	5	5	5	5	5	5	5
Iron oxide red	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Mg stearate	1	1	1	1	1	1	1	1	1	1	1
Layer 1 wt. (mg)	100	100	100	100	100	100	100	100	100	100	100

All values in mg.

Table 2: Composition of ER layer of bilayer tablet using CCD.

Trial no.	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11
Carvedilol Phosphate	80	80	80	80	80	80	80	80	80	80	80
Mmicrocrystalline Cellulose	61	31	43	13	52	22	46	28	37	37	37
HPMC K100M	87	117	87	117	87	117	102	102	102	102	102
MA Polymer	42	42	60	60	51	51	42	60	51	51	51
PVP K30	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
SLS	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Aerosil 200	6	6	6	6	6	6	6	6	6	6	6
Magnesium Stearate	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Layer 2 wt. (mg)	300	300	300	300	300	300	300	300	300	300	300

All values in mg.

Table 3: Disintegration time and % Drug release of IR and ER layer.

Trial No.	DT (Seconds)	% DR (IR layer)		Trial No.	% DR (ER layer)		
		15 min	30 min		2 hr	14 hr	24 hr
F1	80	58.71	98.06	M1	22	76	98
F2	30	92.93	97.83	M2	18	71	96
F3	30	94.85	99.44	M3	19	70	95
F4	30	87.85	99.2	M4	13	56	91
F5	70	57.91	97.91	M5	18	71	97
F6	120	51.18	98.3	M6	16	62	95
F7	60	59.81	97.32	M7	18	70	96
F8	10	98.32	101.9	M8	15	58	93
F9	100	55.36	99.16	M9	15	66	95
F10	10	90.25	100.17	M10	14	64	98
F11	30	91.15	100.14	M11	18	67	96

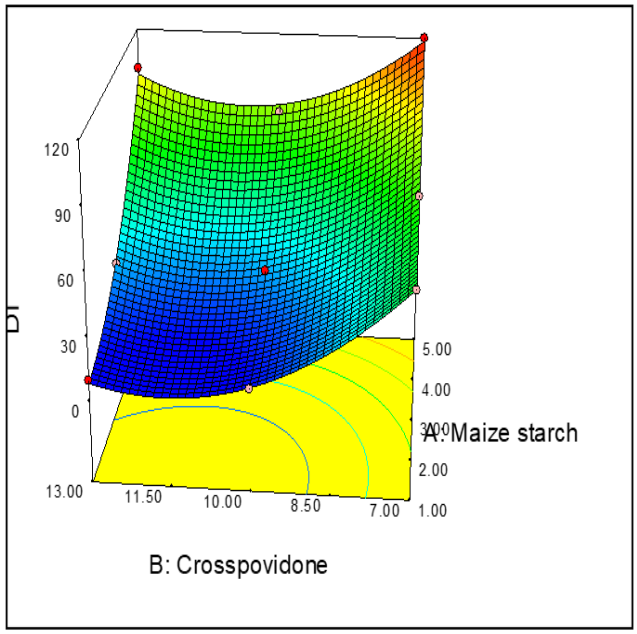

Figure 1: 3D surface graph of Disintegration Time of IR layer.

Dissolution rate evaluation of ER layer

The cumulative drug release at 2, 14, and 24 hr are presented in Table . Trial no M1, M3, and M5 have low concentrations of HPMC combined with low, high, and optimum concentrations of MA POLYMER respectively, which shows the result that at 2hr it retard the dissolution but at 14 hr it could able to sustain the release, and drug release found more than 70%. Trial no M2, M4 and M6 has a high concentration of HPMC K100M combined with high, low, and optimum concentrations of MA POLYMER which shows the result that at 12 hr it releases the drug faster rate but at high and optimum concentrations of MA POLYMER it retard the drug release less than 65% and at low concentration MA POLYMER it releases content very fast. Trail M7, M8, and M9 have optimum concentrations of HPMC K100M combined with low, high, and optimum concentrations of MA POLYMER. ANOVA results are presented in Table . At a 5% significance level, the model is considered significant if the *p*-value is less than 0.05. 3D surface plots of responses i.e. 2 hr, 14 hr, and 24 hr release represented in Figures 3 and 4.

Table 4: ANOVA for DT.

Factor	Sum of squares	Df	Mean Squares	F-Value	*p*-value Prob > F	Comments
ANOVA for DT						
Model	13511.443	5	2702.289	258.875	< 0.0001	Significant
A-Maize starch	8066.6667	1	8066.667	772.773	< 0.0001	
B-Crosspovidone	2016.6667	1	2016.667	193.193	< 0.0001	
ANOVA for Dissolution (%DR)						
Model	4175.49	5	835.1	29.21	0.001	Significant
A-Maize starch	1152.87	1	1152.87	40.33	0.0014	
B-Crosspovidone	1531.2	1	1531.2	53.56	0.0007	
ANOVA for Dissolution at 2 hr of ER layer						
Model	44.17	2	22.08	7.77	0.0133	Significant
A-HPMC K100 M	24.00	1	24.00	8.44	0.0197	
B-MAcoplymer	20.17	1	20.17	7.09	0.0287	
ANOVA for Dissolution at 14 hr of ER layer						
Model	312.17	2	156.08	23.76	0.0004	Significant
A-HPMC K100 M	130.67	1	130.67	19.89	0.0021	
B-MAcoplymer	181.50	1	181.50	27.63	0.0008	
ANOVA for Dissolution at 24 hr of ER layer						
Model	30.83	2	15.42	10.37	0.0060	Significant
A-HPMC K100 M	10.67	1	10.67	7.17	0.0280	
B-MAcoplymer	20.17	1	20.17	13.56	0.0062	

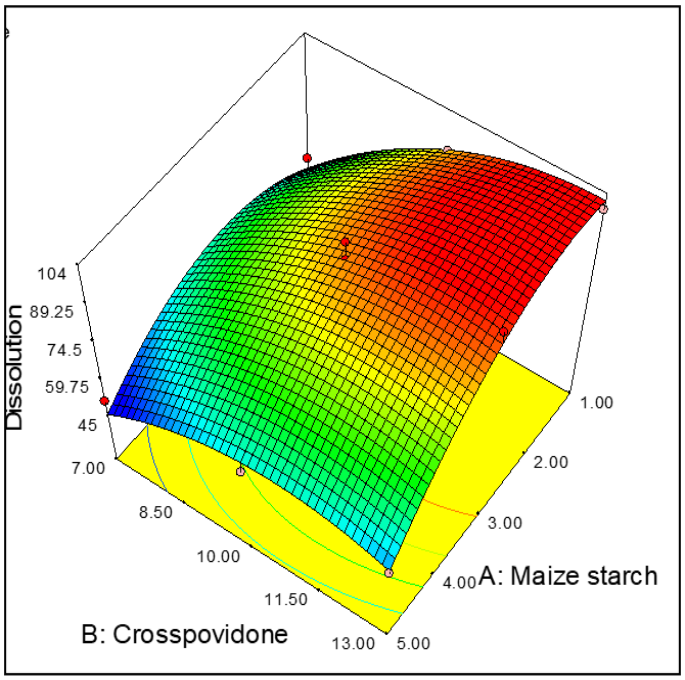

Figure 2: 3D surface graph of % Dissolution rate of IR layer.

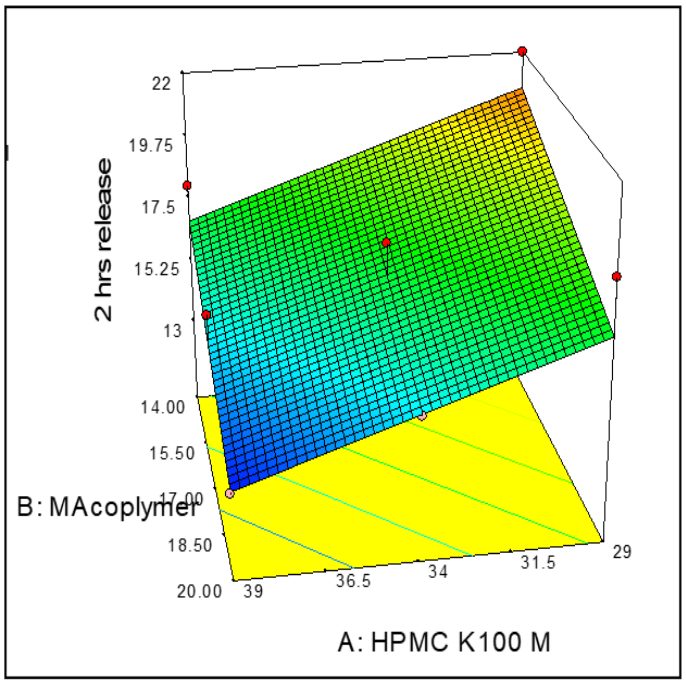

Figure 3: 3D surface graph of 2 hr Dissolution (%DR) of ER layer.

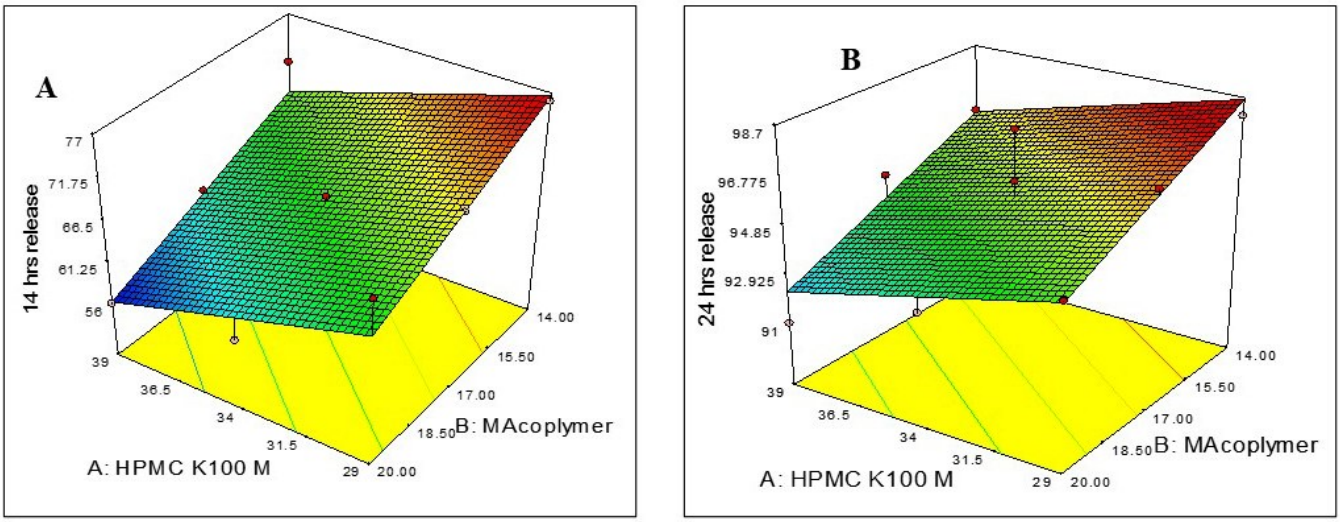

Figure 4: 3D surface graph of (A):14 hr Dissolution (%DR) of ER layer; (B): 24 hr Dissolution (%DR) of ER layer.

DISCUSSION

The study design was developed by analyzing data from all formulations using Design Expert software (version 7.0.0). The best-fit model was selected based on statistical constraints provided by the software. ANOVA was conducted to assess the significance of factors affecting the response regression coefficients. Additionally, contour plots were generated to illustrate the relationship between dependent and independent variables. A graphical optimization system incorporating contour plots was utilized to create innovative formulations with desired responses. Bilayer tablet formulation was then evaluated for their respective response of the IR layer and ER layer to validate theoretical predictions. The Relative Errors (RE) (%) between the predicted and experimental results for each response were calculated.

In case of IR granules it ahs been observed that by increasing the maize starch concentration it produced free-flowing granules which leads to improvisation flow property of powder. Hence optimum to high concentration of maize starch trial batches shows good flow properties. In case of ER layer granules it demonstrated a more consistent flow behavior. The post compression parameters results indicate a good correlation with the pharmacopeial limits for all the lisinopril carvedilol phosphate combinations.

For the IR layer critical response considered was disintegration time and dissolution rate. Because the IR layer is supposed to be disintegrated in a fraction of a second based on which its further absorption into systemic circulation will take place. Hence DT & % DR were evaluated by ANOVA and 3D (three-dimensional) plots using response surface methodology.

The maize starch and crospovidone XL have a combined effect on the disintegration time of the IR layer. An increase in the concentration of crospovidone XL reduces the DT, but at 10 to 13% of crospovidone XL concentration of maize starch concentration increase it will increase DT. Also, it was observed that at high concentrations of Crospovidone XL and Maize starch DT is reduced due to the dominating effect of binder. Hence optimum Dt i.e 20 to 40 sec obtained at optimum concentration of maize starch and crospovidone XL trial no F2, F4, F11.

At optimum to low concentration of maize starch and optimum to high concentration of Crospovidone XL %DR found more than 85% in 15 min. Hence the interactive concentration of maize starch and crospovidone XL was optimized to achieve the desired DT and %DR.

DT and %DR exhibit strong regression coefficients and a reasonable closeness between R- R-predicted and R-adjusted values, indicating the design's suitability. Additionally, the percentage Coefficient of Variation (CV) and adequate precision values fall within acceptable limits. The model F-ratios being less than 0.05 suggest that the models are significant for all response variables. Furthermore, all formulation variables demonstrated interactions in quadratic terms.

HPMC K100M and Methyl methacrylate and ethyl methacrylate copolymer Type A (MA POLYMER) were found to be critical for controlling drug release for an extended period.

In this study it has been observed that low and high concentrations of MA POLYMER release rate of drugs at fast and low rates. At optimum concentration release the rate at found to be 66%. Hence its further 2 more trials were repeated which found a similar range of release rate.

In ANOVA, all response variables (Dissolution rate at 2 hr, 14 hr and 24 hr) exhibit strong regression coefficients and a close agreement between predicted and observed values, confirming the design's suitability. Additionally, the percentage Coefficient of Variation (CV) and adequate precision values fall within acceptable limits. The model F-ratios 0.0133, 0.0004, and 0.006

indicate that the models are statistically significant for all response variables.

From these plots, it is observed that HPMC and MA polymer are responsible for controlling the dissolution rate for a longer period. A high concentration of HPMC K100M caused control of the dissolution at the initial stage i.e 2 hr but at 14 hr its most crucial stage of controlling the release at this time point combined effect of HPMC K100M and MA polymer concentration successfully controlled the drug release at optimum concentration i.e 34% HPMC K100M and 17% MA Polymer.

CONCLUSION

The bilayer tablet of Lisinopril HCl (LH) and Carvedilol Phosphate (CP) was designed to deliver lisinopril HCl at a faster rate and Carvedilol phosphate at an extended-release rate for a longer period. The formulation was optimized by applying Central Composite Design (CCD) using Design Expert software. All critical responses were evaluated using response surface methodology and ANOVA. The data demonstrated that the investigational plan was effectively implemented to achieve immediate release of LH and Extended release of CP. Hence by the QbD Approach using CCD, the development of formulation can be done with minimum no. of trials with reasonable accuracy. It also shortens the development period.

ACKNOWLEDGEMENT

The authors would like to thank all faculty members and management of the MET's Bhujbal Knowledge city, Institute of Pharmacy, Adgaon, Nashik, India for providing all necessary technical supports and motivating me at every stage.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

BD: Bulk Density; **TD:** Tapped Density; **CI:** Carr's Index; **CCD:** Central Composite Design; **(θ):** Angle of Repose; **LH:** Lisinopril HCl; **CP:** Carvedilol Phosphate.

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Cite this article: Kulkarni K, Deokar G. Formulation Development of Carvedilol Phosphate and Lisinopril Hydrochloride Bilayer Tablet using QbD. Int. J. Pharm. Investigation. 2026;16(1):316-23.