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PREPARATION AND OPTIMIZATION OF QUICK/SLOW-RELEASE BILAYERED TABLETS OF PRAZOSIN HCL USING DOE AND PCA

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ABSTRACT

The study aimed to develop once a day bilayer tablet of Prazosin HCl (PZH) for the effective treatment of hypertension with a quick-release layer to provide a loading dose while a slow-release layer as a maintenance dose. A statistical approach employing face-centred central composite design and principal component analysis (PCA) to develop bilayer tablets of PZH and scrutinize the critical responses was implemented. Independent factors in the study included the amount of guar gum (X1) and the amount of xanthan gum (X2). Results suggested the significant influence of independent factors on the dependent variables. Optimized formulation showed better performance with the initial first hour period giving a release burst from quick-release layer and then for the next 24 h a sustained release of drug follows. The drug release mechanism was analyzed using various mathematical models of which the optimized formulation exhibited the Higuchi Model. Accelerated stability studies of the preparation suggested no significant difference in the results even after six months. From the study, it could be concluded that a stable, once-a-day bilayer tablet preparation would be feasible in the context of patient compliance.

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Introduction

Therapeutic strategies using bilayered/multilayered technologies have long been recognized among pharmaceutical products due to the convergence of various factors viz. Patient compliance, combination therapy, modified advanced drug delivery systems etc. Such drug delivery systems are gaining importance in the treatment of chronic diseases where conventional preparations are not suitable and multiple doses are required [1-4]. Bilayer tablets are formulated to provide biphasic drug delivery with a quick-release layer and a slow-release layer. The quick-release layer will promptly release the drug and within a small period allow the achievement of high plasma whereas the slow-release layer will allow the constant and sustained drug release for a longer period to sustain the active drug concentration [5-7].

Quality by design (QbD) is pointed as a systematic approach for the development of pharmaceutical products beginning with predefined objectives. PCA and Design of experiments (DoE) have been proved as extremely utile tools for the construction of design spaces, an important component of control strategy for QbD [8-12]. Central composite design is the most frequently used design in the response surface optimization technique [13-16].

Prazosin HCl (PZH) is a sympatholytic drug used to treat high blood pressure, anxiety and post-traumatic stress disorder. It is widely used because of its selective alpha one adrenergic blocking action. PZH is a paradigm candidate for sustained drug delivery due to its short biological half-life and the requirement of frequent dosing makes [17-21].

In light of this, the goal of the investigation was the preparation of a bilayer tablet of PZH with a quick-release layer containing a super disintegrant and a slow-release layer consisting of release retardants. Loading and maintenance dose for the bilayer tablet was calculated and utilized for the formulation purpose. Different amounts of release retardants were utilized as independent variables to check the influence of dependent factors on the formulation of the sustained release layer. To find the best preparation, a multivariate regression analysis was undertaken. An optimized batch was obtained and evaluated. Further, the optimized batch was subjected to accelerated stability studies at 40 ˚C/75 % relative humidity (RH) for a period of six months.

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Materials and Methods

Materials

PZH was obtained as a gift sample from Vaibhav Laboratories, Ahmedabad, India. Crospovidone, sodium starch glycolate and croscarmellose sodium were procured from Thomas Baker, Mumbai, India. Kyron T20 was obtained from Corel Pharma, Ahmedabad, India. Guar gum, Carrageenan gum and Acacia gum were purchased from Astron chemicals, Ahmedabad, India. Xanthan gum was gifted from West coast laboratories, Mumbai, India. Di-calcium phosphate was gifted by Rankem Laboratories, New Delhi, India. Microcrystalline cellulose (MCC) was kindly donated by Sevafine Chemicals, Ahmedabad, India. Deionised-distilled water was used in this study.

Methods

Preparation of Bilayer Tablet Formulations

Formulation of Quick-Release Layer

The following equation was used in the calculation of the immediate release part of the bilayer tablet [22, 23].

$$D_L = C_{max} \times \frac{V_d}{F} \quad (1)$$

$$D_{Total} = Dose\left(1 + 0.693 \times \frac{t}{t_{1/2}}\right) \quad (2)$$

D_{Total} = total dose, D_L = loading dose, $t_{1/2}$ = half life of drug (2-3 h), t = time during which sustained release is desired (24 h), V_d =Volume of distribution (42.2 L/ kg), C_{max} = maximum plasma concentration (23.01 ng/mL), F = bioavailability factor = (85%), $D_L = C_{max} \times V_d / F$, V_d = 42.2 L/ kg, C_{max} = 23.01 ng/mL, V_d = 42.2 × 1000 = 450 L = 42200 mL, $C_{max} = 23.01 \times 10^{-6}$ mg/mL, D_L = **1.14 mg**, $D_{Total} = D_L (1 + 0.693 \times t/t_{1/2})$ = **7.475 mg**, Maintenance dose = 7.475 – 1.14 = **6.33 mg**

The direct compression method was employed for the preparation of immediate-release tablets of PZH. All the ingredients were passed through sieve number 80 to produce a fine powder. Required quantities of the drug (1.14 mg) and excipients except for talc and magnesium stearate were mixed thoroughly for 5 minutes in a polybag. The addition of Talc (2 mg) and magnesium stearate (3 mg) as the respective glidant and lubricant was done and the resulting mixture was mixed for 5 minutes. Different super disintegrants (Croscarmellose sodium (IR-1), sodium starch glycolate, (IR-2) crospovidone (IR-3), and Kyron (IR-4); 5 mg) were evaluated for the performance of the immediate-release tablets. Microcrystalline cellulose (88 mg) was added as the directly compressible diluent and binder. By utilizing the using rotary tablet compression machine all the batches of tablets were prepared using a round shape flat 8 mm punch. Moreover, tablets were analyzed for multiple tablet characteristics.

Formulation of Slow-Release Layer

The wet granulation method was utilized in the preparation of PZH sustained-release tablets. Weighed quantity of drug (6.33 mg) and other excipients (di-calcium phosphate; 138 mg, methylparaben; 0.25 mg) was mixed uniformly with the help of a mortar and pestle. Different gums (Guar (SR-1), Xanthan (SR-2), Acacia (SR-3) and Carrageenan (SR-4); 100 mg) were evaluated for the performance of the slow-release layer. Damp mass was prepared by using isopropyl alcohol as the binding solvent. This damp mass was forced manually to pass through sieve number 12. A hot air oven was used to dry the obtained Granules at 40°C for half an hour and passed through sieve number 22. Talc, Magnesium stearate and the resulting granules were then mixed in a polybag for 5 min. All the tablet batches were prepared using a round shape flat 8 mm punch using a rotary tablet compression machine. Later, the combination of Guar (P) and Xanthan (Q) gum was taken at different amounts (SR-5 with 100mg of P and 40mg of Q, SR-6 with 140mg of P and 40 mg of Q, SR-6 with 100mg of P and 80mg of Q, and SR-7 with 140mg of P and 80mg of Q) and evaluated for the performance of slow-release.

Formulation of Bilayer Tablets

Formulation of the immediate-release tablets (IR-3) was constant during the bilayer tablet preparation, and the layer of the sustained-release formulation was changed. A slight compression of the die cavity after the weighed quantity of the sustained-release layer was initially added to it was done to get a uniform layer, and then the final tablet compression was done by adding an immediate layer. Tablets were analyzed for various characteristics such as drug content and drug release.

Optimization of Bilayer Systems

As part of QbD, the optimization of PZH-loaded bilayer tablet systems was done through the utilization of DoE and PCA techniques. The face-centred central composite design was applied to study the joint influence of independent variables [24, 25]; X_1 (amount of Xanthan gum) and X_2 (amount of guar gum) on critical dependent variables viz. % swelling index at 8 h, the respective % drug release at 2, 8, and 12 %. The investigation of two independent factors at three different levels (100,

120, and 140 mg for X_1 and 40, 60 and 80 mg for X_2) was done, and all the nine possible combinations were considered for the experimental trials. The observed evaluation parameters by PCA were able to produce Critical responses from the utilization of the Unscrambler X (trial version) (CAMO AS, Norway, Switzerland). This evaluator data helped in the construction of a scoring plot, loading plot, correlation plot, cluster analysis plot, and scree plot by PCA. A statistical model involving polynomial and interactive terms was taken for response assessment, $Y_i = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$, whereby b_0 is the arithmetic mean response, Y_i is the dependent variable, and bi is the projected coefficient for factor Xi. A DoE software (Version 10) (Software from Stat Ease, Inc) was utilized in the production of a 2-factor, 3-level face-centred central composite design.

In vitro Release Studies of Bilayer Tablets

a medium of 0.1M hydrochloric acid (pH 1.2) (900 mL) at 37 ± 0.5 ºC and rotated at 50 rpm for a 2h period followed by a release in phosphate buffer (pH 6.8) as the basic media for another 22 h through the employ of USP II (paddle) dissolution apparatus (Electrolab Pvt Ltd, Mumbai, India) was used as the drug release analysis. The addition of 5 mL aqueous dispersion of 4.32 g of sodium hydroxide and 6.08 g of potassium dihydrogen phosphate to the acidic part was used to manage the media change [26-28]. At specific intervals, a 5mL sample was withdrawn. The sink conditions were maintained by the addition of the same amount of fresh media. Further, filtration of the samples was done using Whatman filter paper (0.2 µm) and examined by UV-Visible spectrophotometer (Shimadzu 1800, Japan) at 246 nm after appropriate dilutions. The average data values were tabulated after performing the study was carried out three times.

Mathematical Modelling of Release Profile

To investigate the model of release from tablets, the release data of selected formulations were analyzed with the mathematical models viz. Higuchi, First order, Zero-order, Korse-Meyer Pappas equation. The entire curve-fitting analysis was performed using Excel (Microsoft) software [29].

Accelerated Stability Studies

The sample of tablets from the optimized batch was enveloped in the aluminium foil and placed in the accelerated stability chamber (Remi Instruments, Mumbai, India) at 40 ˚C/75 % RH for six months. Samples were analyzed at predetermined time intervals of 0, 3, and 6 months for various parameters viz. *in-vitro* dissolution studies and % swelling index at 8 h.

FT-IR Analysis

FT-IR spectrophotometer was used for FT-IR (Fourier Transform Infrared) study was carried out for batch stability. A nitrogen purge was used for sweeping the sample compartment before runs, which was then filled with dry desiccant to absorb any moisture present. The mortar and pestle were used to triturate the tablet powder until fine. Then the mixture was kept in a stability chamber (Remi Instruments, Mumbai, India) at 40 ˚C/75 % relative humidity (RH) for six months. The sample mixture was then analysed using an FT-IR spectrophotometer, scanned in the region of 4000-400 cm^{-1}.

Results and Discussion

Preliminary Trials of Quick and Slow-Release Layers

The immediate-release layer was investigated for various super disintegrants like croscarmellose sodium, sodium starch glycolate, crospovidone and Kyron T20. **Table 1** exhibits the results of the quick-release layer containing various super disintegrants. Results indicated the suitability of crospovidone as a super disintegrant in the final formulations. Batch IR-3 exhibited faster disintegration with a disintegration time of 22.1 ± 0.32 sec. Thus, the IR3 batch consisting of crospovidone as a super disintegrant was selected for further development of bilayer tablets.

Table 1 showed the results of the sustained release layer from the bilayer tablet. Results of % drug release at 12 h in **Table 1** suggested that individual gums release more than 90% of the drug content. In addition, guar gum and xanthan gum were able to retard acacia and carrageenan gum. Thus, a further combination of xanthan gum and guar gum was taken and evaluated for drug release in a different amount which suggested better retardation of the drug till 12 h.

Table 1. Results of the immediate and sustained release layer

Batches	Drug Content (%)	Disintegration time (sec)	% Drug release at 12 h
IR-1	98.16 ± 0.17	28.5	-
IR-2	98.53 ± 0.95	25.2	-
IR-3	99.27 ± 0.14	22.1	-
IR-4	98.72 ± 0.34	23.2	-
SR-1	97.22 ± 0.39	-	92.33 ± 1.2
SR-2	99.87 ± 0.01	-	90.94 ± 0.95
SR-3	98.76 ± 0.57	-	98.47 ± 1.03

SR-4	99.21 ± 0.41	-	99.05 ± 1.1
SR-5	97.35 ± 0.87	-	87.7 ± 2.10
SR-6	98.17 ± 1.13	-	79.1 ± 0.34
SR-7	98.05 ± 0.94	-	78.5 ± 0.62
SR-8	99.28 ± 0.96	-	51.6 ± 0.76

Optimization of Bilayer Tablets

From the preliminary trials, crospovidone was used as a super disintegrant for the quick-release layer. Guar gum and Xanthan gum were taken in combination for optimization of the formulation. The face-centred central composite design was applied to study the influence of two factors; (X_1) amount of guar gum and (X_2) amount of xanthan gum on different responses have been summarized in **Table 2**. *In vitro* release profile **(Figure 1)** of all the 9 batches suggested the sustained release of the drug throughout 24 h. All the responses of 9 batches were analysed for critical variables by PCA using Unscrambler X.

Table 2. Responses of design batches

Batches	% Swelling index at 8 h	% Drug release at 2 h	% Drug release at 4 h	% Drug release at 6 h	% Drug release at 8 h	% Drug release at 12 h	% Drug release at 24 h
BL-1	76.2 ± 0.99	21.9 ± 0.80	44.1 ± 0.31	60.1 ± 1.20	69.9 ± 1.12	87.7 ± 2.10	100.87 ± 1.20
BL-2	80.0 ± 0.54	17.2 ± 0.98	35.1 ± 0.92	56.97 ± 0.96	65.6 ± 0.99	79.1 ± 0.34	99.3 ± 0.96
BL-3	79.23 ± 0.18	18.9 ± 1.01	37.9 ± 0.99	57.1 ± 0.86	64.7 ± 1.18	78.5 ± 0.62	99.3 ± 1.10
BL-4	84.90 ± 0.59	5.9 ± 0.71	18.89 ± 1.12	29.13 ± 0.31	36.8 ± 0.18	51.6 ± 0.76	82.4 ± 0.89
BL-5	77.15 ± 0.57	20.6 ± 0.97	40.9 ± 1.02	58.38 ± 0.38	67.5 ± 1.20	85.6 ± 0.19	99.98 ± 1.22
BL-6	82.7 ± 0.01	8.6 ± 0.26	22.38 ± 1.19	34.95 ± 0.23	40.3 ± 0.51	58.3 ± 1.92	87.2 ± 1.40
BL-7	76.03 ± 0.84	19.9 ± 1.10	41.72 ± 0.60	59.0 ± 0.11	66.8 ± 0.32	84.4 ± 0.39	99.53 ± 0.70
BL-8	81.24 ± 0.88	9.9 ± 1.09	24.29 ± 0.98	36.10 ± 0.91	41.1 ± 0.43	59.9 ± 1.83	89.01 ± 0.29
BL-9	79.1 ± 0.11	17.3 ± 0.83	36.82 ± 1.03	57.04 ± 0.41	65.9 ± 0.59	77.9 ± 0.31	99.91 ± 0.65

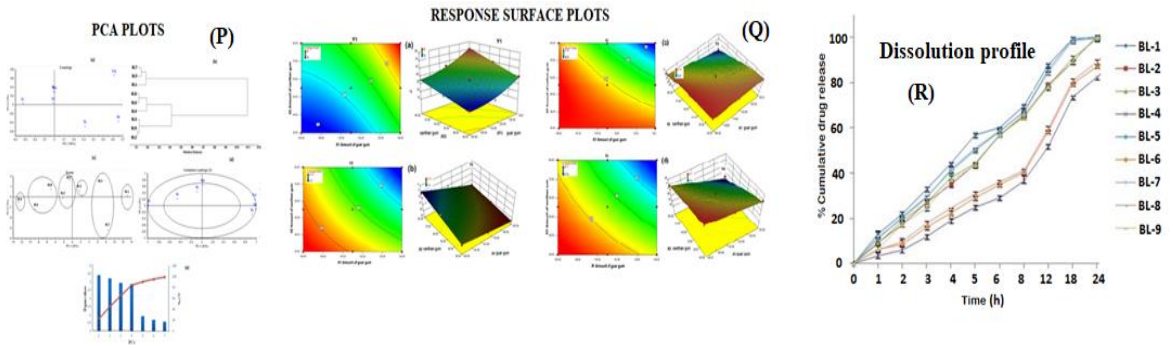


Figure 1. Graphs of (P) PCA plots of design batches (a) Loading plot (b) Dendrogram (c) Score Plot (d) Correlation loading plot € Scree plot and (Q) Response surface and contour plots of design batches of PZH bilayer tablets (a) Influence of X_1 and X_2 on Y_1 (b) Influence of X_1 and X_2 on Y_2 (c) Influence of X_1 and X_2 on Y_3 and (d) Influence of X_1 and X_2 on Y_4 and (R) *In vitro* release study (Dissolution profile)

The plot of loading **Figure 1a** indicates PC1's overall variation effect at 94% of the data set, with the remainder being a result of PC2. A cluster analysis was performed for all the 9 batches, whose results are shown as a dendrogram **(Figure 1b)**. Sixprimary groups were revealed by the dendrogram of the batches: group I (BL2, BL9), group II (BL4), group III (BL8 and BL6), group IV (BL1), group V (BL5 and BL7), and group VI (BL5 and BL7) (BL3). Furthermore, an indication of the subtle differences among all the five groups as they are likely somewhat far apart, demonstrating data variation. In **Figure 1c**, a PCA score plot depicted a similar formulation for all clusters. A correlation loading plot **(Figure 1d)** was created to determine the prime factors for further optimization. The Swelling index and medication release were evaluated as important reactions at 2h, 8h, and 12h based on their retention between two eclipses [10, 30]. Other variables that were drawn close to the origin were not discussed. The scree plot in **Figure 1e** shows a decrease in eigenvalues from the first to the last component. The eigenvalues of PC1, PC2, PC3, and PC4, as well as the others, indicated a significant difference, showing the importance of these four components.

A central composite statistical experimental design with two factors and three levels was used. From all the 9 batches the selected dependent variables; % swelling index at 8 h (Y_1), % drug release at 2 h (Y_2), % drug release at 8 h (Y_3) and % drug release at 12 h (Y_4) exhibited wide variation **(Table 2 and Figure 1)**. The statistics revealed that certain parameters (X1 and

X2) had a major impact on responses (Y1, Y2, Y3 and Y4). The observations were evaluated using a stepwise multivariate linear regression. The number of coefficients and mathematical signs was considered, and the results were drawn using the fitted polynomial equation. For all responses, % Swelling index at 8 h (Y_1), % Drug release at 2 h (Y_2), % Drug release at 8 h (Y_3, and % Drug release at 12 h (Y_4) coefficients X_1 and X_2 were found to be significant. The findings of the analysis of variance are shown in **Table 3**. (ANOVA). A significant p-value at p 0.05 of the quadratic model, hence no further reductions were developed in the model design.

Table 3. ANOVA studies

Source	Sum of squares	Degrees of freedom	Mean square	F Value	P-Value	R^2
% Swelling index						
Regression	47.30952	5	9.461905	99.35	0.0081	0.995
Residual	0.190476	2	0.095238			
Total	47.5	7				
% Cumulative drug release at 2 h						
Regression	219.513	5	43.902	8.271	0.011	0.953
Residual	10.615	2	5.307			
Total	230.128	7				
% Cumulative drug release at 8 h						
Regression	116.274	5	232.454	2.452	0.031	0.985
Residual	189.555	2	94.777			
Total	1351.829	7				
% Cumulative drug release at 12 h						
Regression	1160.061	5	232.012	8.237	0.0111	0.953
Residual	56.327	2	28.163			
Total	1216.389	7				

Multilinear regression analysis of the % swelling index at 8 h (Y_1) was carried out. Results showed coefficients X_1 and X_2 were found to be positive suggesting an increase in the value of % swelling index with the increase in the amount of guar gum and amount of xanthan gum. This might be attributed to the better water-absorbing properties of natural gums [31]. Results of multi-linear regression analysis of % drug release at 2 h, % drug release at 8 h and % drug release at 12 h with negative coefficients, X_1 and X_2 indicated a decrease in drug release at 2 h (Y_2), 8 h (Y_3) and 12 h (Y_4) respectively, with an increase in the amount of guar gum and amount of xanthan gum which might be attributed to viscous nature of natural gums [32-35].

$$Y_1 = 78.90 + 2.69X_1 + 2.36X_2 + 0.286X_1X_2 + 0.643X_1^2 - 0.357X_2^2 \quad (3)$$

$$Y_2 = 15.29 - 5.45X_1 - 4.55X_2 - 1.33X_1X_2 + 0.338\,X_1^2 + 0.614\,X_2^2 \quad (4)$$

$$Y_3 = 57.42 - 11.08X_1 - 11.13X_2 - 4.13X_1X_2 + 0.714\,X_1^2 + 0.764\,X_2^2 \quad (5)$$

$$Y_4 = 73.35 - 11.95X_1 - 11.68X_2 - 2.36X_1X_2 + 0.878\,X_1^2 + 1.078\,X_2^2 \quad (6)$$

The checkpoint batch was selected arbitrarily based on the criteria as maximum % swelling index and minimum % drug release. The observed values as depicted in **Table 4** were found to be in close agreement with the theoretical values obtained. The non-significant difference was confirmed based on lower values of % relative error between experimental and theoretical data suggesting the suitability of the applied design.

Table 4. Comparative results of checkpoint batches with theoretical values

Response variable	Optimized batch		% Relative error
	Theoretical value	Experimental value	
Y_1 (%)	78.74	80.12	-1.75
Y_2 (%)	15.46	14.89	3.68
Y_3 (%)	60.74	61.22	-0.79
Y_4 (%)	73.95	72.73	1.64

Mathematical Modelling of Release Profile

The checkpoint batch's dissolution profiles were fitted to a variety of mathematical kinetic models, and the release data was examined using the Zero order, First order, Higuchi kinetics, Korsmeyer Peppas, and Hixson-Crowell equations. The following

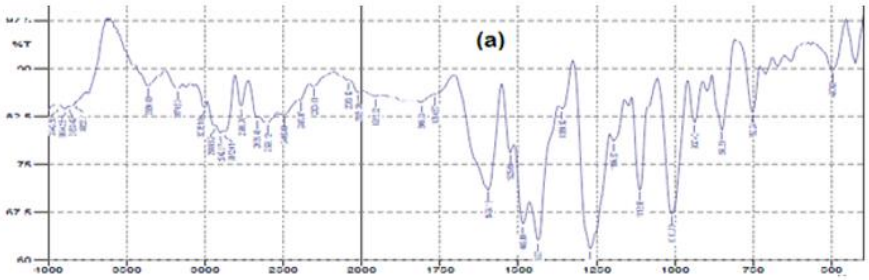
graphs were created: cumulative percentage drug release vs time (Zero order kinetic model); log cumulative of percentage drug remaining vs time (First order kinetic model); cumulative percentage drug release vs square root of time (Higuchi model); log cumulative percentage drug release vs log time (Korsmeyer model); and cube root of drug percentage remaining in matrix vs time (Hixson-Crowell cube root law). The fit accuracy was assessed using correlation coefficients (R2). Diffusion was determined as the most important drug release influence mechanism, according to the Higuchi model, which had an R2 value of 0.97.

Accelerated Stability Studies

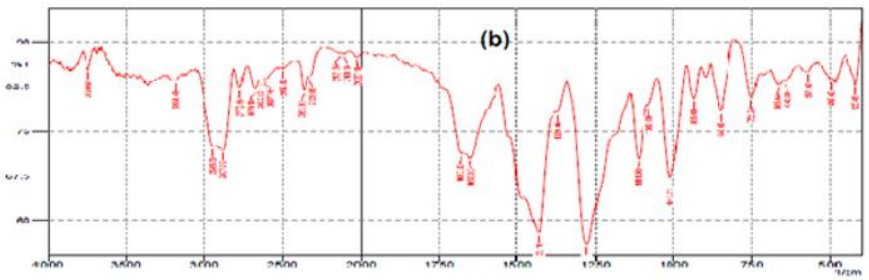
The accelerated stability experiment **(Table 5 and Figure 2)** of the optimised batch demonstrated that no significant changes in the parameters were identified while held at 40° C/75 % RH for 6 months, confirming stability.

Table 5. Accelerated stability studies of optimized batches of a bilayer tablet of PZH

Responses	Batches	Initial 0 day	3 month	6 month
			40ºC/ ± 75% RH	**40ºC/ ± 75% RH**
Y_1 (%)	**O1**	80.12 ± 0.78	79.22±0.98	78.21±0.62
Y_2 (%)	**O1**	12.89 ± 0.05	12.29±0.57	12.09±0.92
Y_3 (%)	**O1**	61.87 ± 1.01	60.45±1.01	59.12±1.01
Y_4 (%)	**O1**	74.29 ± 0.05	74.12±1.10	72.51±1.00



a)



b)

Figure 2. FT-IR spectra of (a) PZH bilayer tablet at 0 days and (b) PZH bilayer tablet at 6 month

Conclusion

The current study found that a bilayer tablet of Prazosin HCl can be successfully prepared as a once-a-day oral-controlled drug delivery system, with an initial burst release from the quick-release layer to provide the loading dose and then sustained release from the slow-release layer to release drug for almost 24 hours. The current study, which was based on a design of experiment and principal component analysis, revealed that the response was reliant on independent variables. To get an in vitro-in vivo correlation of the efficacy of the improved formulation, more in vivo investigations are required. However, the current study's in-vitro findings suggest that the Prazosin HCl bilayer tablet could be a viable alternative to the currently available established tablet dosage form.

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Conflict of interest: None

Financial support: None

Ethics statement: None

References

1. Abbas J, Bashir S, Samie M, Laghari S, Aman N, Jan HU, et al. Formulation and evaluation of a bilayer tablet comprising of diclofenac potassium as orodispersible layer and diclofenac sodium as sustained release core. Marmara Pharm J. 2017;21(3):707-16.
2. Abebe A, Akseli I, Sprockel O, Kottala N, Cuitiño AM. Review of bilayer tablet technology. Int J Pharm. 2014;461(1-2):549-58.
3. Cheng L, Li T, Dong L, Wang X, Huo Q, Wang H, et al. Design and Evaluation of Bilayer Pump Tablet of Flurbiprofen Solid Dispersion for Zero-Order Controlled Delivery. J Pharm Sci. 2018;107(5):1434-42.
4. Dey S, Mahanti B, Khila S, Mazumder B, Gupta SD. Formulation development and optimization of bilayer tablets of aceclofenac. Expert Opin Drug Deliv. 2012;9(9):1041-50.
5. Kottala N, Abebe A, Sprockel O, Bergum J, Nikfar F, Cuitiño AM. Evaluation of the performance characteristics of bilayer tablets: Part I. Impact of material properties and process parameters on the strength of bilayer tablets. AAPS PharmSciTech. 2012;13(4):1236-42.
6. Mahapatra AK, Sameeraja NH, Murthy PN. Development of modified-release tablets of zolpidem tartrate by biphasic quick/slow delivery system. AAPS PharmSciTech. 2015;16(3):579-88.
7. Qiang F, Xiaonan S, Yanxian H, Mo L, Jingru L, Jin S, et al. Once-daily amoxicillin immediate- and extended-release bilayer tablets. Powder Technol. 2016;301:405-11.
8. Tak JW, Gupta B, Thapa RK, Woo KB, Kim SY, Go TG, et al. Preparation and Optimization of Immediate Release/Sustained Release Bilayered Tablets of Loxoprofen Using Box-Behnken Design. AAPS PharmSciTech. 2017;18(4):1125-34.
9. Beg S, Saini S, Bandopadhyay S, Katare OP, Singh B. QbD-driven development and evaluation of nanostructured lipid carriers (NLCs) of Olmesartan medoxomil employing multivariate statistical techniques. Drug Dev Ind Pharm. 2018;44(3):407-20.
10. Parmar K, Patel J, Sheth N. Formulation and development of embelin liquisolid systems using quality by design approach. J Pharm Investig. 2016;46(6):547-56.
11. Simonoska CM, Dimitrovska A, Sibinovska N, Mladenovska K, Slavevska RR, Glavas Dodov M. Implementation of quality by design principles in the development of microsponges as drug delivery carriers: Identification and optimization of critical factors using multivariate statistical analyses and design of experiments studies. Int J Pharm. 2015;489(1-2):58-72.
12. Aboushady D, Parr MK, Hanafi RS. Quality-by-Design Is a Tool for Quality Assurance in the Assessment of Enantioseparation of a Model Active Pharmaceutical Ingredient. Pharmaceuticals (Basel). 2020;13(11):364.
13. Luo Q, Yang J, Xu H, Shi J, Liang Z, Zhang R, et al. Sorafenib-loaded nanostructured lipid carriers for topical ocular therapy of corneal neovascularization: development, in-vitro and in vivo study. Drug Deliv. 2022;29(1):837-55.
14. Fares AR, ElMeshad AN, Kassem MAA. Enhancement of dissolution and oral bioavailability of lacidipine via pluronic P123/F127 mixed polymeric micelles: formulation, optimization using central composite design and in vivo bioavailability study. Drug Deliv. 2018;25(1):132-42.
15. Hosny KM, Sindi AM, Ali S, Alharbi WS, Hajjaj MS, Bukhary HA, et al. Development, optimization, and evaluation of a nanostructured lipid carrier of sesame oil loaded with miconazole for the treatment of oral candidiasis. Drug Deliv. 2022;29(1):254-62.
16. Geng D, Li Y, Wang C, Ren B, Wang H, Wu C, et al. Optimization, and in vitro and in vivo evaluation of etomidate intravenous lipid emulsion. Drug Deliv. 2021;28(1):873-83.
17. Fourtillan JB, Brisson AM, Couet W. Pharmacokinetics of prazosin administered as gastro-intestinal-therapeutic-systems to 24 healthy volunteers. Therapie. 1993;48(2):115-8.
18. Jaillon P. Clinical pharmacokinetics of prazosin. Clin Pharmacokinet. 1980;5(4):365-76.
19. Kondi V, Alluri R. In Vitro and In Vivo Evaluation of Floating Microspheres of Prazosin Hydrochloride. Asian J Pharm Tech. 2016;6(4):202-6.
20. Liu L, Wang J, Zhu S. Delivery of Prazosin Hydrochloride from Osmotic Pump System Prepared by Coating the Core Tablet with an Indentation. Drug Deliv. 2007;14(4):219-24.
21. Omre VP, Goswami N, Pathak AK. Optimization and evaluation of Prazosin hydrochloride floating tablets. MIT Int J Pharm Sci. 2017;3(1):34-9.
22. Dholariya YN, Bansod YB, Vora RM, Mittal SS, Shirsat AE, Bhingare CL. Design and optimization of bilayered tablet of Hydrochlorothiazide using the Quality-by-Design approach. Int J Pharm Investig. 2014;4(2):93-101.
23. Momin MM, Kane S, Abhang P. Formulation and evaluation of bilayer tablet for bimodal release of venlafaxine hydrochloride. Front Pharmacol. 2015;6:144. doi:10.3389/fphar.2015.00144
24. Choudhury P, Deb P, Dash S. Formulation and statistical optimization of bilayer sublingual tablets of levocetirizine hydrochloride and ambroxol hydrochloride. Asian J Pharm Clin Res. 2016;9(5):228-34.

25. Rajawat J, Ranawat M, Kamble RK. Formulation and development of Atorvastatin Calcium and Ramipril bilayer tablet. J Chem Pharm Res. 2015;7(2):979-89.
26. Dinakaran S, Kumar S, Banji D, Avasarala H, Rao V. Formulation and evaluation of bi-layer floating tablets of ziprasidone HCl and trihexyphenidyl HCl. Braz J Pharm Sci. 2011;47(3):545-53.
27. Gupta B, Debnath R, Ghosh S, Chakraborty M, Biswas A. Formulation development studies of bilayer tablet glipizide: a novel and evolutionary approach in the treatment of diabetes. Asian J Pharm Clin Res. 2013;6(4):131-7.
28. Patel MM, Soniwala MM. Influence of release enhancer of venlafaxine HCl from glyceryl behenate matrix tablet. Indian Drugs. 2008;45(2):98-104.
29. Abdul AS, Sailaja PB, Ashwin M. Formulation, Evaluation and Mathematical Modelling of Clopidogrel Bisulphate & Aspirin Immediate Release Bilayer Tablets. Pharmaceut Anal Acta. 2012;3(9):194. doi:10.4172/2153-2435.1000194
30. Dhingani A, Patel J, Garala K, Dharamsi A. Design and Development of Microemulsion Based Transdermal Gel of Lercanidipine Hydrochloride by Assimilation of Rotatable Central Composite Design and Principal Component Analysis. Pharm Nanotechnol. 2013;1(4):290-305.
31. Wang W, Wang A. Preparation, Swelling and Water-retention Properties of Crosslinked Superabsorbent Hydrogels Based on Guar Gum. Adv Mat Res. 2010;96:177-82.
32. Mughal MA, Iqbal Z, Neau SH. Guar Gum, Xanthan Gum, and HPMC Can Define Release Mechanisms and Sustain Release of Propranolol Hydrochloride. AAPS PharmSciTech. 2011;12(1):77-87.
33. Prabaharan M. Prospective of guar gum and its derivatives as controlled drug delivery systems. Int J Biol Macromol. 2011;49(2):117-24.
34. Ramasamy T, Kandhasami UDS, Ruttala H, Shanmugam S. Formulation and evaluation of xanthan gum based aceclofenac tablets for colon targeted drug delivery. Braz J Pharm Sci. 2011;47:299-311.
35. Ali A, Iqbal M, Akhtar N, Khan HM, Ullah A, Uddin M, et al. Assessment of xanthan gum based sustained release matrix tablets containing highly water-soluble propranolol HCl. Acta Pol Pharm. 2013;70(2):283-9.