International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 18, Issue 1, 2026

Original Article

"FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED-RELEASE AND EMPAGLIFLOZIN IMMEDIATE-RELEASE BILAYER TABLETS"

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Received: 16 Aug 2025, Revised and Accepted: 10 Nov 2025

ABSTRACT

Objective: The present study aimed to formulate and evaluate bilayer tablets containing sustained-release Metformin hydrochloride and immediate-release Empagliflozin for the management of Type 2 diabetes.

Methods: The wet granulation technique was employed to formulate a sustained-release Metformin HCl layer and an immediate-release Empagliflozin layer. The impact of varying concentrations of independent variables (HPMCK100M and Carbopol 971P) on drug release at different times was evaluated using a 2-factor central composite design (CCD**)**with five central replicates. The formulation was optimized using responsesurface methodology (RSM) through CCD, and optimal levels of polymers were determined using surface plots and response optimizer. *In vitro* release data observed from the optimized formulation were subjected to pre-and post-compression analysis and fitted into various drug release kinetic models.

Results: Using response surface methodology (RSM), the optimized formulation contained 17.9% HPMCK100M and 3.8% Carbopol, respectively. Various parameters were noted: hardness, 21.33 kg/cm^2; friability, 0.23%; and uniformity of content for empagliflozin (98.23%), whichwas within the limit. The assay percentages of metformin and empagliflozin were 95.27% and 96%, respectively. *In vitro* drug release at 1, 6, 10, and 12 h is 20.08%, 67.02%, 87.06%, and 97.52%, respectively, which is comparable to the predicted drug release by RSM. The optimized model accurately predicted the drug release profile, with a chi-square test (χ^2 = 0.436, df = 3) and a similarity factor (f_2) of 82.54showing no significant differences. Similarly, the drug release of the optimized formulation followed the Korsmeyer–Peppas model (R^2= 0.9986), indicating a combination of diffusion and polymer relaxation mechanisms inthe drug release process.

Conclusion: In conclusion, we developed an optimized fixed-dose bilayer formulation of sustained-release metformin HCl and immediate-release empagliflozin using a central composite design. The optimized formulation exhibited predictable release kinetics, best described by the Korsmeyer-Peppas model, confirming anomalous transport driven by both diffusion and polymer relaxation. This work presents how experimental design and mechanistic modeling can be integrated to aid in the development of bilayer tablet formulations, thereby validating the growing body of knowledge in this field. Clinically, the formulation presents a promising approach for improving glycemic control, enhancing patient compliance, and reducing healthcare costs.

Keywords: Type 2 diabetes, Sustained release, Central composite design, Metformin HCl, Empagliflozin, Response surface methodology

DOI: https://dx.doi.org/10.22159/ijap.2026v18i1.56545 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Diabetes mellitus (DM) continues to exert a significant global health challenge, affecting more than half a billion peopleworldwide, with prevalence projected torise by 46% by 2050 [1]. Type 2 diabetes mellitus (T2DM)accounts for over 90% of casesand is characterized by insulin resistance and progressive β-cell dysfunction, often associated with obesity, sedentary lifestyle, genetic predisposition, and aging. Treatment options for DM include lifestyle interventions, insulin, and oral anti-diabetic medications, which remain safe and effective treatment options. However, varying dosage requirements among patient populations and the growing demand for controlled-release formulations may aid in effective dosing, thereby optimizing therapeutic outcomes.

Metformin hydrochloridebelongs to a class of biguanide derivatives. It is the first-line therapy for T2DM due to its safety profile and unique mechanism of action, which activates protein kinase, reduces hepatic glucose production, and enhances peripheral glucose uptake [2, 3]. Another effective class of anti-diabetic drugs is the selective sodium-glucose cotransporter-2 (SGLT2) inhibitor, Empagliflozin, which acts by reducing blood glucose levels by blocking renal glucose reabsorption, leading to increased urinary glucose excretion [4, 5]. Dual therapy, combining Metformin HCl and Empagliflozin, is recommended by the American College of Endocrinology (AACE) and the Americandiabetes association (ADA) to achieve enhanced glycemic control, reduce HbA1C levels, and provide synergistic cardioprotective effects compared to monotherapy [6-9].

A fixed-dose bilayer oral tablet formulation enables the immediate release of one drug while maintaining sustained release of the other. This approach to drug dosage form design enhances patient compliance by reducing dosing frequency and controlling drug release, leading to a better therapeutic outcome that monotherapy cannot achieve [10, 11]. Therefore, this research aims to design, formulate, and evaluate a bilayer tablet comprising a sustained-release layer of metformin HCl and an immediate-release layer of empagliflozin, optimize the formulation parameters using a central composite design, and assess its *in vitro* drug release kinetics to achieve a clinically viable dosage form for improved management of T2DM.

MATERIALS AND METHODS

Materials

Metformin HCl, Empagliflozin, HPMCK100M, Carbopol 971P, Sodium CMC, PVK-90, Lactose Monohydrate, Crospovidone, Croscarmellose sodium, PVK-30, HPMC 15CPS, Microcrystalline Cellulose, Magnesium Stearate,Yellow oxide of Iron, Lactose anhydrous, Aerosil was provided by Nepal Pharmaceuticals Limited Pvt. Ltd. in Birgunj.

Methods

Active pharmaceutical ingredient (API)-excipient compatibility studies

For the API-excipient compatibility study, the API (Metformin HCl) was combined with excipients in equal weight portions and incubated in glass vials sealed with Teflon plugs and aluminum caps at 40 °C and 75% relative humidity for 6 mo. Infrared (IR) spectroscopy was used to analyze the stability of the drug in the blended mixture after 6 mo. The Fourier transform infrared spectroscopy (FTIR) spectra of API-HPMC K100M and API-Carbopol971P, stored for 6 mo at 40 °C, were compared with the spectrum of the API to assess changes in the API structure.

Design of experiment

A 2-factor, rotatable central composite design (CCD) was employed to investigate the effect of HPMCK100M and Carbopol 971P on formulation properties. Based on preliminary screening, the concentration of HPMCK100M varied between 14% and 19% w/w, and that of Carbopol 971P varied between 3% and 7% w/w. Factor levels were coded as-1 and+1 for low and high levels, respectively (table 1), with the center point set at 16.5% HPMCK100M and 5% Carbopol 971P. For the CCD, four full factorial points, four axial points at α=±1.41 were taken to estimate the curvature, and five replicates were taken at centerpoints for estimation of model fit and lack of fit. In total, 13 formulations were prepared, and the order in which they were run was randomized to minimize systematic bias, as shown in table 2.

Table 1: Variables in factorial design

Factors	Levels used		
	Low (-1)	Medium (0)	High (+)
HPMC K100M (X_1) (%w/w)	14	16.5	19
Carbopol 971P (X_2) (%w/w)	3	5	7
Dependent variables	Target		
Drug release at 1h (Y_1)	15-25		
Drug release at 6h (Y_2)	50-70		
Drug release at 10h (Y_3)	not less than (NLT) 80		
Drug release at 12h (Y_4)	not less than (NLT) 90		

Table 2: Two-factor, rotatable central composite design (CCD) with independent variables HPMCK100M (X_1) and carbopol 971P (X_2)

Formulation	Type	Independent variables (Polymers)	
		HPMCK100 (X_1)	Carbopol 971P (X_2)
F1	Center	16.5	5
F2	Factorial	14	3
F3	Center	16.5	5
F4	Center	16.5	5
F5	Factorial	19	7
F6	Axial	16.5	7.8
F7	Axial	20.03	5
F8	Center	16.5	5
F9	Center	16.5	5
F10	Axial	12.96	5
F11	Factorial	19	3
F12	Axial	16.5	2.17
F13	Factorial	14	7

Preparation of bilayer tablet

Preparation of metformin hydrochloride part (ER Part) and empagliflozin immediate release part (IR Part)

Metformin HCl granules were prepared using wet granulation, and direct blending was used for the Empagliflozin part as described by Chinta *et al.* [12]. Thirteen different formulations were prepared, as listed in table 3 and table 4 for Metformin and Empagliflozin, respectively.

Evaluation of pre-compression parameters of metformin granules

Before compressing the granules into a bilayer tablet, several pre-compression tests were performed on the metformin granules. Parameters tested were Bulk density, Tapped density, Hausner ratio, Carr's index, and Angle of Repose.

Post compression parameters

After compressing the granules into bilayer tablets, the tablets were tested for weight variation, dimensions, hardness, and friability. Similarly, the percentage assay was calculated for both APIs, and the disintegration time of the Empagliflozin immediate-release portion was calculated.

In vitro drug release

Dissolution studies were performed, and the % release of metformin was analyzed at different time points (1 h, 6 h, 10 h, and 12 h). The experimental drug release data were fitted to a second-order polynomial model:

$$Y= \beta_0+\beta_1 X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_{11}X_1^2+\beta_{22}X_2^2+\varepsilon$$

where, Y is the measured response (%drug release at various time points) and X_1 and X_2 are the coded values of HPMCK100M and Carbopol 971P, respectively (table 1 and table 2); ε is the residual error. Using multiple regression analysis and plots, the adequacy of the models was assessed.

Formulation optimization and drug release kinetics evaluation

After the model is prepared, the optimum concentration of the independent variable required for desirable drug release is determined using a response surface plot and a desirability function and is then formulated. Different pre-and post-compression parameters are measured. Finally, the drug release kinetics isestimated by fitting the release profile into various models. The models tested werethe Zero-Order kinetics model, first-order kinetics model, Higuchi model, and Korsmeyer-Peppas model.

Table 3: Composition of metformin parts of different formulations

Ingredients/Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Metformin HCl (ER part)													
Metformin HCl	500	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K 100M	16.5	14	16.5	16.5	19	16.5	20.03	16.5	16.5	12.96	19	16.5	14
Carbopol	5	3	5	5	7	7.828	5	5	5	5	3	2.171	7
PVK-90	27	27	27	27	27	27	27	27	27	27	27	27	27
Sod. CMC	45	45	45	45	45	45	45	45	45	45	45	45	45
Mg. stearate	9	9	9	9	9	9	9	9	9	9	9	9	9
Aerosil	9	9	9	9	9	9	9	9	9	9	9	9	9
Lactose MH	288.5	293	288.5	288.5	284	285.672	284.965	288.5	288.5	292.04	288	291.329	289
Total (mg)	900	900	900	900	900	900	900	900	900	900	900	900	900

Table 4: Composition of empagliflozin immediate release part

Empagliflozin (IR part)	
Empagliflozin	5
Crospovidone	7.5
PVK-30	9
HPMC 15 CPS	9
Croscarmellose Sodium	6
Lactose anhydrous	129
MCCP	130
Mg. stearate	1.8
Aerosil	1.8
Yellow oxide of Iron	0.9
Total	300 mg

RESULTS AND DISCUSSION

Compatibility

IR spectra of the API and the API-excipient mixture were obtained under different conditions (fig. 1, 2, 3A-C). The spectrum from all the samples showed characteristic peaks at about 1100 cm^{-1} corresponding to the functional group Aromatic (C-F) stretch and 1650 cm^{-1} for (C=O) Stretch, C-H aliphatic at about 3059 – 2946 cm^{-1}, and C-N stretching at about 1350 cm^{-1}. The obtained spectra indicated that the principal IR peaks of the API were similar to those of the API-excipient mixture, confirming the compatibility of the API with various excipients. Detailed observations are provided in table 5.

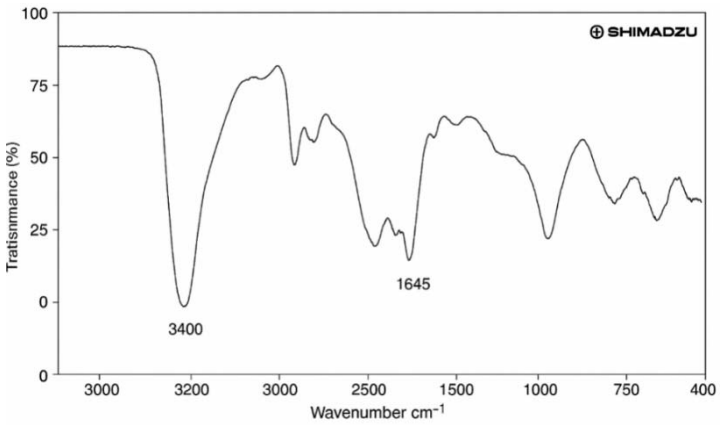

Fig. 1: Infrared (IR) spectrum of metformin HCl and carbopol at the initial stage

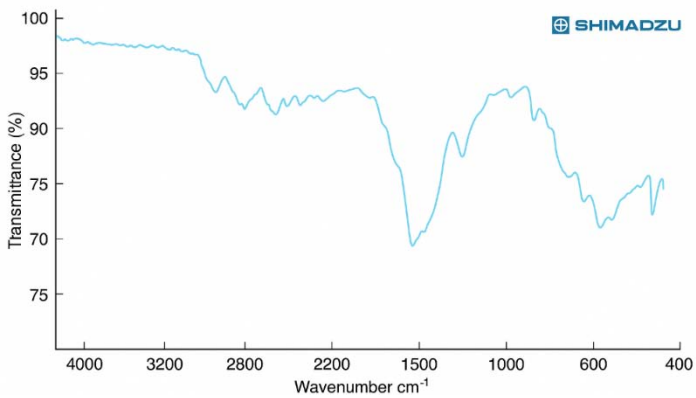

Fig. 1: IR spectrum of metformin HCl and HPMC K 100M at the initial stage

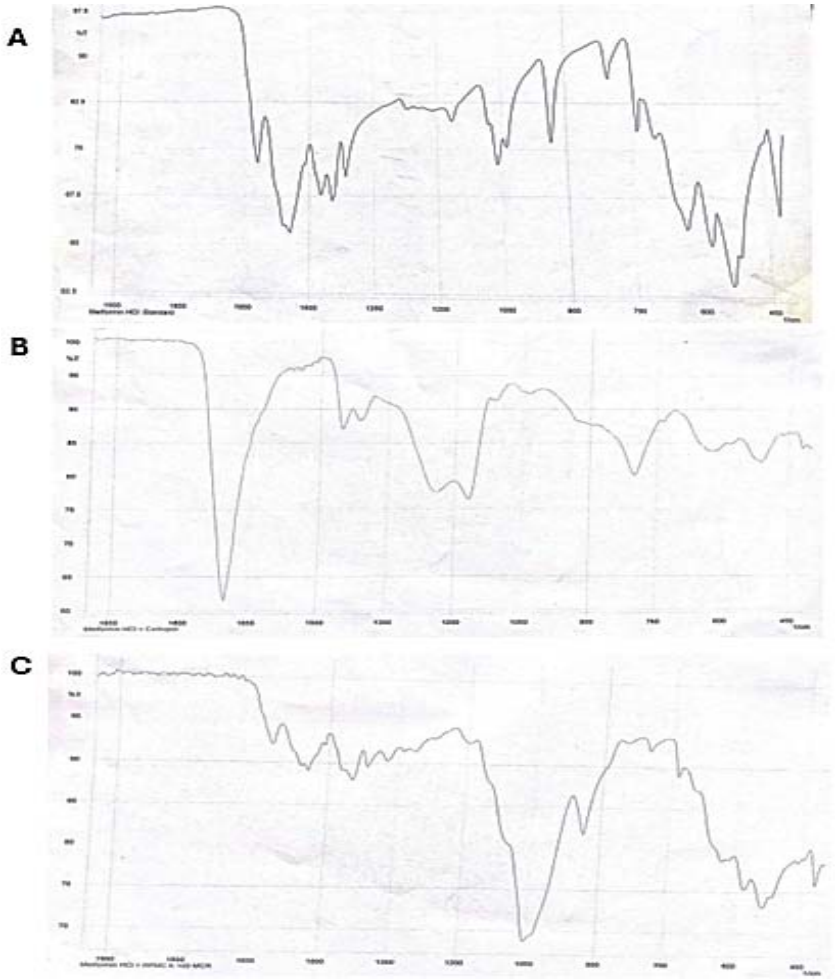

Fig. 3: IR spectra of API and API-excipient mixture after incubation for 6 mo at 40 °C and 75% relative humidity for 6 mo. A) Metformin HCl B) Metformin HCl with Carbopol971P C) metformin HCl with HPMCK100M

Table 5: Summary of IR peaks in compatibility study

Functional group	Characteristic peak (cm^{-1}) pure drug	Metformin+carbopol (cm^{-1})	Metformin+HPMC K100M (cm^{-1})	Observation
N–H stretching (biguanide)	~3360–3290	~3362 (no shift)	~3358 (no shift)	Retained – no significant shift, suggesting hydrogen bonding unchanged
N–H bending (scissoring)	~1620–1640	~1622	~1620	Retained – peak position stable
C=N stretching (biguanide group)	~1550–1570	~1552	~1551	Retained – no new peak or disappearance
C–N stretching	~1040–1070	~1041	~1043	Slight shift (<5 cm^{-1}) – not significant

Table 6: Pre-compression parameters for the metformin HCl granules

Formulations	Bulk density g/ml	Tapped density g/ml	Hausner's ratio	Carr's Index (CI)	Angle of repose (º)	Moisture content (%)
F1	0.404	0.531	1.164	14.556	30.7	3
F2	0.372	0.525	1.153	13.33	32.9	2.9
F3	0.39	0.51	1.122	10.909	35.09	2
F4	0.409	0.51	1.122	10.909	32.537	2.9
F5	0.357	0.49	1.137	12.069	31.84	2.4
F6	0.366	0.49	1.132	11.666	30.11	2
F7	0.35	0.475	1.15	13.114	32.37	2.6
F8	0.377	0.508	1.142	12.5	33.384	2
F9	0.337	0.446	1.142	12.5	30.54	2.1
F10	0.322	0.444	1.155	13.461	27	2.1
F11	0.322	0.434	1.152	13.207	29.59	2.6
F12	0.327	0.444	1.143	12.369	35.79	2.3
F13	0.312	0.416	1.166	14.285	30.96	2.5

Note. For granules, pre-compression parameters were calculated once before compression.

Pre-compression parameter results

Thirteen batches (F1 to F13) were prepared according to the experimental design for optimizing the HPMCK100M and Carbopol 971P concentrations (table 3). The granules were subjected to pre-compression parameters (table 6). Based on the observation, the bulk density ranges from 0.312 (F13) to 0.409 g/ml (F4), and the tapped density ranges from 0.416 (F13) to 0.531 g/ml (F1). Hausner's ratio ranged from 1.122 (F3 and F4) to 1.166 (F13), Carr's index ranged from 10.909 (F3 and F4) to 14.556 (F1). The angle of repose ranged from 27° (F10) to 35.79° (F12). Overall, for the metformin HCl granules, the values for Carr's index and Hausner's ratio were within the pharmacopeial limits (<16% and<1.25, respectively), indicating good flowability and compressibility. Similarly, the angle of repose was less than 40°, indicating an acceptable flow property. Finally, the moisture content was between 2% and 3% reflecting adequate drying.

Post compression parameters

The tablets were subjected to various post-compression parameters. The mean weight variation of the tablet for different formulations ranged between 1200.18±2.29 and 1203.14±1.85 mg, which was within the acceptable limit. Furthermore, the average hardness ranged from 19.583±0.705 to 23.183±0.714 kg/cm^2. The average range of dimensions of the tablet, i. e., thickness, was from 6.43±0.026 to 6.64±0.019 mm, width was from 9.51±0.018 to 9.532±0.018 mm, and length was from 21.08±0.011 to 21.113±0.048 mm. Assay was performed for Metformin and Empagliflozin. All assays for metformin in all the formulations were greater than 95%. The disintegration time for the Empagliflozin immediate-release portion was less than 7 min, and friability was less than 1%. Thus, all the formulations had acceptable post-compression parameters.

***In vitro* drug release**

Data analysis and model validation

The response data (Y) fitted into the experimental design (table 8). After fitting the response data, the results were analyzed using ANOVA for various statistical parameters. Table 9 represents the ANOVA results and R^2values for each response. value with $p<0.05$ are considered significant. The mean release values for empagliflozin across formulations ranged from 83% to 95%, as confirmed in table 8, indicating the rapid dissolution of the IR layer. For the empagliflozin immediate release tablet, not less than 75% of the drug is released in 45 min. These results, together with the disintegration time (<7 min) and assay (>95%), provide strong evidence that the empagliflozin portion of the bilayer tablet meets the requirements of an immediate-release formulation.

Table 7: Post-compression parameters for bilayer tablets

Formulations	Weight variation (n=20)		Hardness (n=6)		Thickness (n=6)		Width (n=6)		Length (n=6)		Assay		Friability	Disintegration
	Mean (mg)	SD	Mean (kg)	SD	Mean (mm)	SD	Mean (mm)	SD	Mean (mm)	SD	MET (%)	EMPA (%)	(%)	EMPA (min)
F1	1201.01	2.55	22.967	0.843	6.63	0.036	9.523	0.012	21.113	0.048	95.671	96.523	0.071	6.16
F2	1200.747	2.4	21.833	1.274	6.64	0.019	9.517	0.01	21.1	0.017	99.652	98.325	0.098	6.45
F3	1202.765	1.61	20.867	1.201	6.5	0.03	9.51	0.018	21.092	0.017	101.07	102.4	0.042	6.39
F4	1200.18	2.29	22.767	0.689	6.49	0.052	9.518	0.016	21.085	0.012	97.169	96.865	0.013	6.31
F5	1203.14	1.68	19.583	0.705	6.54	0.026	9.525	0.008	21.09	0.023	98.93	100.4	0.001	6.09
F6	1201.06	2.4	23.183	0.714	6.5	0.024	9.53	0.011	21.087	0.015	95.864	96.646	0.02	6.13
F7	1202.193	3.16	22.1	1.173	6.46	0.024	9.532	0.018	21.08	0.011	96.279	95.409	0.015	6.03
F8	1203.14	1.85	20.867	1.467	6.43	0.026	9.525	0.008	21.095	0.019	96.142	95.973	0.021	6.16
F9	1201.193	2.87	21.133	1.628	6.49	0.025	9.52	0.017	21.085	0.022	96.32	101.51	0.076	6.34
F10	1202.193	3.16	22.783	0.9	6.51	0.032	9.518	0.016	21.095	0.018	97.65	94.663	0.043	6.47
F11	1200.747	2.4	21.867	1.329	6.5	0.029	9.52	0.009	21.088	0.017	96.978	95.31	0.006	6.01
F12	1202.765	1.61	21	1.23	6.53	0.028	9.528	0.012	21.09	0.011	98.215	94.304	0.026	6.06
F13	1201.102	2.64	22.783	0.643	6.52	0.027	9.525	0.019	21.095	0.014	97.231	96.652	0.041	6.28

Note. For weight variation, the number of replicates (n)=20, for other post-compression parameters, n=6. Data format: mean of SD

Table 8: Observed responses in 2-Level factorial (Full factorial): Central composite design (CCD)and % release of empagliflozin in different formulations

Formulation	Type	Independent variables (Polymers)		Mean % drug release (Metformin HCl)				Mean % drug release (Empagliflozin)
		HPMCK100 X_1	Carbopol 971P X_2	1sth (Y_1)	6thh (Y_2)	10thh (Y_3)	12thh (Y_4)	(60 min)
F1	Center	16.5	5	23.94	65.21	87.59	98.45	89.25
F2	Factorial	14	3	16.66	66.95	84.7	95.44	85.55
F3	Center	16.5	5	22.46	63.96	86.58	99.15	87.04
F4	Center	16.5	5	24.32	68.96	89.11	98.86	83.25
F5	Factorial	19	7	24.59	66.89	88.89	95.43	86.71
F6	Axial	16.5	7.8	24.88	64.29	89.47	95	89.33
F7	Axial	20.03	5	20.05	62.05	85.4	92.35	91.34
F8	Center	16.5	5	22.41	66.25	88.1	96.93	83.11
F9	Center	16.5	5	21.76	68.22	87.97	96.96	92.16
F10	Axial	12.96	5	16.85	63.44	89.38	98.25	95.13
F11	Factorial	19	3	16.29	62.98	81.35	91.47	85.86
F12	Axial	16.5	2.17	15.8	63.85	80.02	92.09	84.24
F13	Factorial	14	7	20.89	61.61	85.99	93.54	84.24

Note. n = 6 samples were analyzed from every formulation in this study and mean % drug release is tabulated.

For the drug release responses (Y), the R^2,Adjusted R^2, and Predicted R^2values were 0.9632, 0.9369, and 0.9312(Y_1), 0.6607, 0.4183, and 0.0612(Y_2), 0.9220,0.8320, and0.4737(Y_3), and 0.8808, 0.7957, and 0.4390 (Y_4). These results showed that the created models were statistically sufficient to predict the formulation responses. The Model for Y_2 demonstrated moderate fit, accounting for 0.6607 variance; however, the models for Y1, Y3, and Y4 showed excellent predictive accuracy (R^2>0.85).

Table 9: ANOVA result for prediction of % drug release employing HPMCK100M and carbopol 971P as polymers

Source	Adjusted sum of squares	df	Adjusted mean square	F value	Pvalue
1sth Drug release Y_1(%)					
Model	133.081	5	26.6163	36.66	<0.0001
Linear	88.175	2	44.0875	60.73	<0.0001
X_1	7.714	1	7.7136	10.62	0.014
X_2	80.461	1	80.4613	110.83	<0.0001
Square	40.765	2	20.3827	28.08	<0.0001
$X1^2$	34.003	1	34.0033	46.84	<0.0001
X_2^2	11.147	1	11.1474	15.35	0.006
2-Way Interaction	4.141	1	4.1412	5.7	0.048
X1* X_2	4.141	1	4.1412	5.7	0.048
Error	5.082	7	0.726		
Lack-of-Fit	0.281	3	0.0937	0.08	0.969
Pure Error	4.801	4	1.2002		
Total	138.163	12			
Regression equation of the fitted Model: Y_1=-78.9+11.05 X_1+1.39 X_2-0.3537 X_1^2-0.3165 X_2^2+0.2035 X_1* X_2					
R^2=0.9632Adjusted R^2 = 0.9369, Predicated R^2 = 0.9312					
6th h Drug release Y_2 (%)					
Model	42.7051	5	8.541	2.73	0.112
Linear	0.1353	2	0.0677	0.02	0.979
X_1	0.0538	1	0.0538	0.02	0.899
X_2	0.0816	1	0.0816	0.03	0.876
Square	21.1792	2	10.5896	3.38	0.094
$X1^2$	17.5315	1	17.5315	5.59	0.05
X_2^2	5.9522	1	5.9522	1.9	0.211
2-Way Interaction	21.3906	1	21.3906	6.83	0.035
X1* X_2	21.3906	1	21.3906	6.83	0.035
Error	21.934	7	3.1334		
Lack-of-Fit	4.7478	3	1.5826	0.37	0.781
Pure Error	17.1862	4	4.2965		
Total	64.6391	12			
Regression equation of the fitted Model:					
Y_2= 30.5+6.04 X_1-5.37 X_2-0.254 X_1^2-0.231 X_2^2+0.463 X_1* X_2					
R^2=0.6607Adjusted R^2 = 0.4183, Predicated R^2 = 0.0612					
10th h Drug release Y_3 (%)					
Model	98.118	5	19.6236	12.89	0.002
Linear	66.192	2	33.096	21.73	0.001
X_1	4.619	1	4.6186	3.03	0.125
X_2	61.573	1	61.5735	40.43	0
Square	22.16	2	11.0802	7.28	0.02
$X1^2$	1.401	1	1.4009	0.92	0.369
X_2^2	21.825	1	21.8249	14.33	0.007
2-Way Interaction	9.766	1	9.7656	6.41	0.039
X1* X_2	9.766	1	9.7656	6.41	0.039
Error	10.66	7	1.5228		
Lack-of-Fit	7.317	3	2.4389	2.92	0.164
Pure Error	3.343	4	0.8357		
Total	108.778	12			
Regression equation of the fitted Model:					
Y_3= 81.1+0.5 X_1+0.66 X_2-0.0718 X_1^2-0.443 X_2^2+0.313 X_1* X_2					
R^2=0.9020Adjusted R^2 = 0.8320, Predicated R^2 = 0.4737					
12th h Drug release Y_4 (%)					
Model	76.186	5	15.237	10.35	0.004
Linear	18.349	2	9.174	6.23	0.028
X_1	13.582	1	13.582	9.22	0.019
X_2	4.767	1	4.767	3.24	0.115
Square	49.252	2	24.626	16.72	0.002
$X1^2$	15.613	1	15.613	10.6	0.014
X_2^2	39.26	1	39.26	26.66	0.001
2-Way Interaction	8.585	1	8.585	5.83	0.046
X1* X_2	8.585	1	8.585	5.83	0.046
Error	10.309	7	1.473		
Lack-of-Fit	5.842	3	1.947	1.74	0.296
Pure Error	4.467	4	1.117		
Total	86.495	12			
Regression equation of the fitted Model:					
Y_4= 48.5+5.92 X_1+1.49 X_2-0.2397 X_1^2-0.594 X_2^2+0.293 X_1* X_2					
R^2=0.8808Adjusted R^2 = 0.7957, Predicated R^2 = 0.4390					

Note: All regression models are presented in coded units for X_1 (HPMC K100M) and X_2 (Carbopol 971P). The coefficients are thus dimensionless, while the response (Y) remains expressed as % drug release. Y_1: %Drug release at 1 h, Y_2: %Drug release at 6 h, Y_3: %Drug release at 10 h, Y_4: %Drug release at 12 h, X_1:HPMCK100M, X_2: Carbopol 971P

Data analysis of 1st h (Y_1)

The mathematical relationships for the measured responses derived from the statistical design in the form of polynomial equationsare:

Y_1=-78.9+11.05 X_1+1.39 X_2-0.3537 X_1^2-0.3165 X_2^2+0.2035 X_1*X_2

where, Y_1 (%): %Drug release at 1 h, X_1:HPMCK100M, X_2: Carbopol 971P

According to the regression equation for the 1st hour, both HPMCK100M (X1) and Carbopol 971P (X2) have a positive impact on drug release. Compared to Carbopol 971P (1.39), HPMCK100M exhibits a more substantial linear effect (11.05). The negative quadratic terms imply that release is decreased when either polymer is increased past a particular point. A synergistic effect between the two polymers is shown by a positive interaction (+0.2035). Similarly, drug release is effectively enhanced when both excipients are in an ideal balance. According to surface regression analysis(table 9), Carbopol 971P had the most significant impact ($p<0.0001$), while HPMC K100 M's linear effect was relatively weaker despite being significant ($p = 0.014$). At higher polymer concentrations, non-linear and combined effects were indicated by the significant quadratic terms (X_1^2: $p<0.0001$; X_2^2: $p = 0.006$) and the interaction term (X_1X_2:$p = 0.048$). Similar results were obtained by Acharya *et al.* (2014) and Vueba *et al.*, where Carbopol showed stronger gel matrices and had a greater impact on early drug release, whereas high-viscosity HPMC grades, such as K100M, delayed early release [13, 14].

The contour plot revealed that both HPMC and Carbopol 971P polymers positively affect drug release within the first hour, with drug release increasing as the concentration of both polymers rises (fig. 4A). Carbopol 971P plays a dominant role in enhancing 1st h drug release, while HPMC K100M contributes up to an optimal concentration.

Pareto Chart of the Standardized Effects at 1st h (fig. 4B) showedthat Carbopol 971P has the most potent effect on the 1st h release as its standardized effect is above the red line (critical t-value = 2.36), indicating statistical significance. AA (quadratic term of HPMC K 100M) and BB (quadratic term of Carbopol 971P) also have a moderate effect. HPMCK100M and AB (interaction between A and B) have a minor or insignificant impact (below the red line). Thus, at 1st h, formulations containing Carbopol exhibited a noticeable effect on drug release, likely due to its rapid swelling and viscosity-building behavior. In contrast, HPMC K100M did not significantly influence release at this stage, which may be attributed to its delayed gel formation characteristics. These findings align with the known swelling kinetics of Carbopoland the time-dependent matrix behavior of HPMC. Thus, the regression and Pareto outcomes are fully supported by physical matrix behavior observed in controlled-release formulations.

Data analysis of 6th h (Y_2)

The fitted model's equation is:

$$Y_2= 30.5+6.04\ X_1-5.37\ X_2-0.254\ X_1^2-0.231\ X_2^2+0.463\ X_1*\ X_2$$

where, Y_2 (%): %Drug release at 6 h, X_1:HPMCK100M, X_2: Carbopol 971P

Following time-dependent gel strength and interaction effects, Carbopol 971P had a greater impact at the 1st h, but HPMC's contribution increased over time. Contour Plot of 6 h vs. Carbopol 971P and HPMC K 100M (fig. 4C) showed that HPMC K100M has a more substantialsustained release effect compared to Carbopol at 6 h.

The Pareto Chart (fig. 4D) showed that the interaction between HPMCK100M (A) and Carbopol is a substantial and sustained statistically significant factor (critical t-value 2.365). The quadratic terms AA and BB have a moderate influence but arenot statistically significant. The main effects of A (HPMC K 100M) and B (Carbopol) are minimal and insignificant. Thus, at the 6thh, a synergistic interaction between HPMC K100M and Carbopol appears to influence the drug release behavior. Such a drug release profile can be attributed to the complete hydration and gel formation of both polymers, resulting in a more cohesive and retentive matrix structure, which leads to a more sustained and controlled release compared to individual polymers alone. Similar findings were obtained by Li *et al.*, in which the authors showed that the interactions between Carbopol and HPMC dramatically alter the swelling and release kinetics in hydrophilic matrix tablets [15].

It should be noted that, based on the regression model for the 6-h release, the coefficient of determination (R^2 = 0.6607) is lower, which is not statistically significant ($p = 0.112$). This is a major limitation of the article. Similarly, it should be noted that the regressionmodel for Y_2 was weaker, with only the interaction term reaching significance ($p = 0.035$) and the X_1^2 term on the borderline of significance ($p = 0.05$). However, we retained this time point, considering the clinical relevance of the 6 h drug release of the Metformin sustained-release formulation. Similarly, the lack-of-fit test (table 9) was not significant ($p = 0.781$), indicating that, despite the low predictive power, the observed data did not deviate significantly from the model. Finally, the multi-response integration includes all four points, which diminishes the overall effect of any single point.

Data analysis for 10th h (Y_3)

The fitted model's equation for the 10th h drug release is:

$$Y_3= 81.1+0.5\ X_1+0.66\ X_2-0.0718\ X_1^2-0.443\ X_2^2+0.313\ X_1*\ X_2$$

where, Y_3 (%): %Drug release at 10 h, X_1:HPMCK100M, X_2: Carbopol 971P

The Contour Plot of drug release at the 10th h vs. Carbopol and HPMC K 100M (fig. 4E) showed that both HPMC K100M and Carbopol contribute to sustained drug release at this time. However, HPMC K100M shows a more consistent enhancing effect, while Carbopol's effect is optimal at moderate levels.

Pareto Chart (fig. 4F) showedthat Carbopol has the highest and statistically significant effect (critical t-value: 2.365). BB (the Quadratic term of Carbopol) and AB (the interaction of HPMC and Carbopol) also showed a moderate impact but were not statistically significant. A (HPMC K 100M) and AA (Quadratic of HPMC) have minimal effects. At 10 h, Carbopol concentration alone (B) is the most dominant factor in controlling drug release. These findings are consistent with optimization experiments by Roy *et al.* [16] on Metformin HCl matrix tablets, where the gel strength of Carbopol considerably inhibited drug diffusion at later time points, supporting the notion that it was predominant at 10 h.

Data analysis of 12th h (Y_4)

The fitted model's equation for 12th h drug release is:

$$Y_4= 48.5+5.92\ X_1+1.49\ X_2-0.2397\ X_1^2-0.594\ X_2^2+0.293\ X_1*\ X_2$$

where, Y_4 (%): %Drug release at 12 h, X_1:HPMCK100M, X_2: Carbopol 971P

The contour plot (fig. 4G) illustrates that the combined concentrations of HPMC K100M and Carbopol significantly influenced drug release at the 12th h. A maximal release (>97.5%) was observed in the central region of the plot, specifically where HPMC ranged from 15% to 16% and Carbopol ranged from 4.5% to6%. Beyond these optimal ranges, either an excess of HPMC or a deficiency in Carbopol resulted in suboptimal release (<90%).

The release at the 12th h is most influenced by the non-linear effect of Carbopol, followed by the non-linear and linear effects of HPMC K100M. The quadratic effect of Carbopol (BB) had the most substantial influence on 12th h drug release, followed by the quadratic and linear effects of HPMC K100M (AA and A, respectively) (fig. 4H). While HPMC showed both linear and non-linear contributions, Carbopol's linear effect (B) was not statistically significant. The interaction between HPMC and Carbopol (AB) also did not significantly affect the release profile. Similar results were obtained by Deb *et al.* [17]. In the study, higher Carbopol concentrations significantly retardedthe early release of drug from Metformin-loaded microspheres, while increasing HPMC concentration produced a more subtle delay [18].

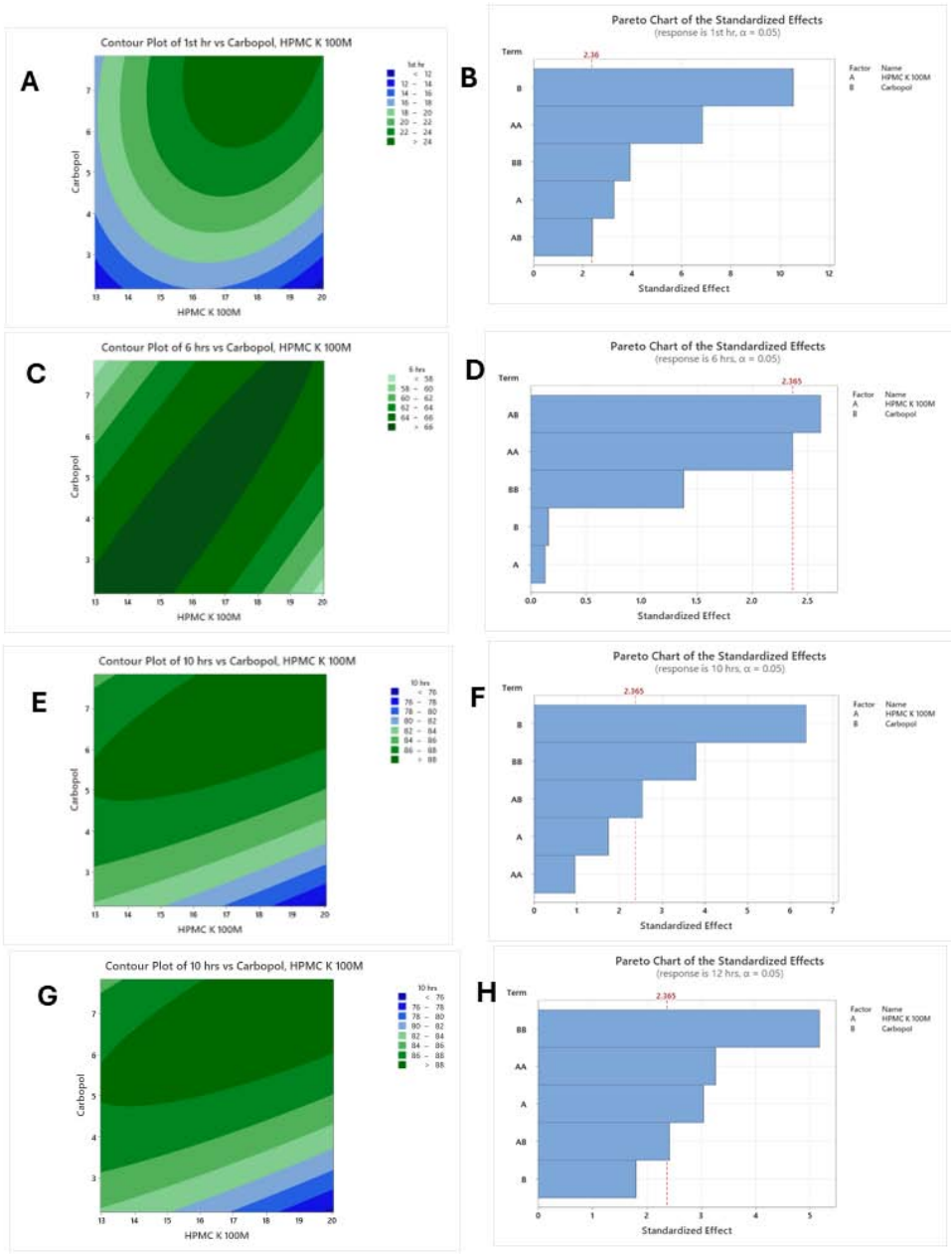

Fig. 4: A, C, E, G contour plot for drug release v/s Polymer concentration at 1,6,10, and 12 h, respectively. B, D, F, H pareto chart for % drug release v/s Polymer concentrations at 1, 6, 10, and 12 h, respectively

In line with earlier factorial design investigations in sustained-release formulations, the contour plots clearly show the interactive influence of HPMC K100M and Carbopol 971P concentrations on drug release duration [18].

HPMC K100M has the greatest impact on the release profile, above the statistical threshold, according to Pareto charts, which is consistent with RSM-based optimization studies [19].

Formulation optimization

For formulation optimization, the influence of each dependent variable on the response was investigated. A desirability function was simultaneously optimized for all four responses (Y_1-Y_4). The goal was set for each response: Y_1:15-25%, Y_2:50-70%, Y_3:80-90% and Y_4:90-100%. The final optimized formula was established using response surface methodology (fig. 5), and the concentration of polymer for the desired response is tabulated in table 10.

Pre-compression and post-compression properties of optimized formulation

The optimized formulation was subjected to the same pre-and post-compression parameters as mentioned previously for the different formulations.

Table 10: Polymer concentration in optimized formulation

Factor	Low	High	Optimum
HPMC K100M	12.96	20.03	17.9
Carbopol 971P	2.17	7.28	3.8

The Optimized tablet was prepared using the optimum concentrations of the polymer. The physicochemical parameters and assay were evaluated.

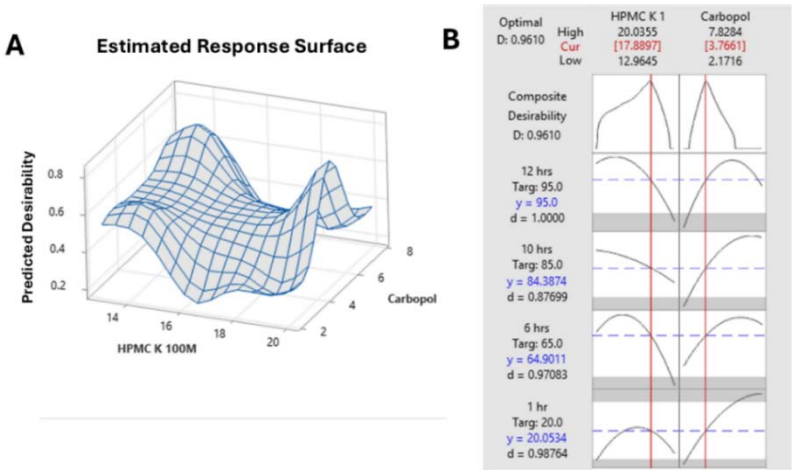

Fig. 5: A) Response surface Plot. B) Response optimization: 12, 10, 6, and 1st h drug release

Table 11: Pre-compression and post-compression properties of optimized formulation

Precompression parameters									
Optimized formulation		**Bulk density (g/ml)**			**Tapped density (g/ml)**		**Moisture content (%)**		
FO		**0.58**±0.13			**0.62**±0.11		2.16±0.84		
Post-compression parameters									
Optimized formulation	Wt. variation (mg) n=20	Hardness (kg) n=6	Thickness (mm) n=6	Width (mm) n=6	Length (mm) n=6	Friability (%) n=8	Disintegration time (min) n=6	Assay (%) n=20	Content uniformity (%) n=10
FO	1200.73	21.33	6.43	9.53	21.08	0.23	6.26	MET: 95.27 EMPA: 96.00	98.23

Note. For precompression parameters were analyzed once before compression. For post compression parameters weight variation was done in 20 tablets. (n=20), For hardness, thickness, dimensions and disintegration time; 6 tablets were used.(n=6). For the Assay calculation, 20 tablets and for content uniformity 10 tablets are used.

In vitro drug release study of optimized formulation

The *in vitro* drug release study of the optimized formulation was conducted (fig. 6) and compared with the predicted average percentage of drug release from the CCD (table 12).

The optimized drug release and the observed values of the improved formulation were compared statistically using the Chi-Square test. The chi-square goodness of fit test was conducted to compare the average percentage with the predicted average release of the optimized formulation. Since the calculated value (χ^2 = 0.436, df=3) is less than the critical value (χ^2 critical = 7.815) at a 5% level of significance, we accept the null hypothesis. This indicates that there is no statistically significant difference between the observed and predicted release values. Consequently, it suggests that the optimized formulation closely follows the predicted release profile, thereby validating the predictive model utilized. The predicted errors were within acceptable bounds when compared to the observed values from the optimized batch. The optimized drug release and the observed values of the improved formulation were compared for similarity factors using the following equation.

$$\text{Similarity factor } (f_2) = 50.\log\left(\left[1+\frac{1}{n}\sum_{t=1}^{n}(O-E)^2\right]^{-2}X100\right),$$

where n=4

According to these findings,the calculated similarity factor was 82.54 (between 50 and 100), indicating that the observed and predicted dissolution profiles are similar. Thus, the drug release behavior of the extended-release formulation could be expected both statistically and practically using the response surface methodology (RSM) employed for optimization.

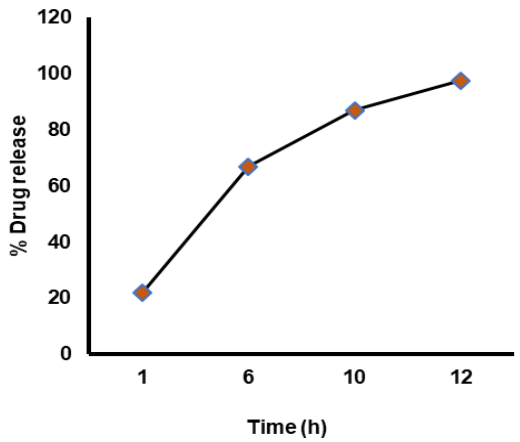

Fig. 6: *In vitro* drug release of optimized formulation

Table 12: Comparison of predicted and observed responses

Time interval (hour)	Avg. release of optimized formulation % (O)	Predicted avg. release % (E)	O-E	$(O-E)^2$	$(O-E)^2/E$	Similarity (f2)
1	22.08	20.04	2.04	4.1616	0.207	
6	67.02	64.9	2.12	4.4944	0.069	
10	87.06	84.378	2.682	7.194	0.085	82.54
12	97.52	97.863	-0.343	0.1176	0.074	
				$\sum(O-E)2 = 15.96$	χ^2=0.436	

Table 13: Correlation coefficients for release data of metformin HCl after fitting into different release kinetic models

Formulations	Zero order (R^2)	First order (R^2)	Higuchi model (R^2)	Peppas model (R^2)
F1	0.8921	0.9855	0.984	0.9985
F2	0.8204	0.978	0.996	0.9988
F3	0.8666	0.9667	0.9916	0.9997
F4	0.896	0.9645	0.9847	0.999
F5	0.9087	0.9941	0.9716	0.9935
F6	0.835	0.9772	0.995	0.9991
F7	0.8672	0.9802	0.9906	0.9994
F8	0.9416	0.9738	0.9642	0.9981
F9	0.906	0.992	0.9674	0.9896
F10	0.8948	0.9789	0.9844	0.9991
F11	0.8576	0.9869	0.9892	0.997
F12	0.9008	0.9912	0.9696	0.9901
F13	0.8359	0.9673	0.9927	0.9969
FO	0.8671	0.9813	0.9897	0.9986

The release data of the optimized formulations were fitted into four different mathematical models: zero-order, first-order, Higuchi model, and Peppas model. The curve-fitting data for different formulations, including zero-order, first-order, Higuchi, and Peppas models, are shown in table 13. Several kinetic models were used to examine the *in vitro* drug release data of the optimized Metformin HCl extended-release tablet. Out of all of them, the Korsmeyer–Peppas model showed the best correlation (R^2 = 0.998), suggesting a combination process of drug diffusion and polymer matrix relaxation. This indicates that the drug release followed anomalous (non-Fickian) transport.

Diffusion plays a significantrole in the release process, as supported by the good fit of the Higuchi model (R^2 = 0.9897) and the First-order model (R^2 = 0.9813). On the other hand, the Zero-order model (R^2 = 0.8671) was the least appropriate, suggesting that the release fluctuated with time (table 14).

Table 14: Release kinetic parameters of optimized formulation

Model	Parameters
Zero order	K0 (h-1) = 0.2087, R^2=0.8671
First order	K1 (h-1) = 0.248, R^2=0.9813
Higuchi	KH (h-1/2) = 27.56, R^2=0.9897
Korsemeyer-Peppas	Kkp (hn)= 23.16, n=0.5791, R^2=0.998

As matrix-forming agents, HPMC K100M and Carbopol 971P were used to alter the release profile of metformin HCl. Water causes HPMC K100M, a hydrophilic polymer, to swell and create a gel layer that functions as a diffusion barrier, regulating the rate at which the medicine is released through the hydrated matrix. In addition to improving matrix integrity, the cross-linked polyacrylic acid polymer Carbopol 971P also influences the dynamics of erosion and swelling in the tablet system. Simultaneous drug diffusion, polymer swelling, and water penetration define the complex release environment produced by the combined use of these polymers. The assumptions of the Korsmeyer–Peppas model, which is ideal for examining drug release from systems displaying non-Fickian (anomalous) transport behavior, align with this complex mechanism [20].

CONCLUSION

To effectively control type 2 diabetes mellitus (T2DM), the current study focuses on the development and assessment of a bilayer tablet comprising Empagliflozin immediate-release (IR) and Metformin HCl extended-release (ER). Carbopol 971P and HPMC K 100M were used to create an extended-release matrix tablet containing metformin HCl. Using response surface methods, the formulations' dependent variables, the amounts of HPMC K 100M and Carbopol 971P, were tuned to achieve predetermined drug release at predetermined time intervals. The wet granulation method was employed to formulate the Metformin HCl extended-release layer, which incorporated hydrophilic polymers such as HPMC K100M and Carbopol to control the drug's release over 12 h. Conversely, the direct compression approach was used to manufacture the Empagliflozin immediate release layer, ensuring immediate drug availability upon administration. No signs of a chemical interaction between the excipients and the API were found. The pre-compression and post-compression parameters of the bilayer were measured. With a high correlation coefficient (R^2 = 0.9986), the Korsmeyer–Peppas model provided the best fit to the metformin HCl release kinetics data. For cylindrical matrix systems, a release exponent (n) value ranging from 0.45 to 0.89 indicates anomalous transport, suggesting a combination of drug diffusion through the hydrated matrix and polymer relaxation or erosion mechanisms. Thus, a non-Fickian transport was indicated by the release exponent (n), which was determined to be 0.5791. The Korsmeyer–Peppas constant (Kkp = 23.16%/h^n) serves as a scaling factor dependent on both the extent of drug release and the exponent n.

Thus, we successfully prepared a bilayer tablet forsustained-release metformin and immediate-release empagliflozin. This work presents how experimental design and mechanistic modeling can be

integrated to aid in the development of bilayer tablet formulations, contributing to the existing pool of knowledge in this field.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

B. B. experimented and conceived the original idea. B. B. and P. S. wrote the manuscript with support from A. S. A. L. supervised the project. A. L. also conceived the original idea, providing oversight throughout.

CONFLICT OF INTERESTS

Declared none

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