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Research Article

FORMULATION AND EVALUATION OF BILAYERED TABLET OF METFORMIN HYDROCHLORIDE AND PIOGLITAZONE HYDROCHLORIDE

SADHANA SHAHI, SHANTANU SHIVANIKAR, NITYANAND ZADBUKE*, ABHAY PADALKAR

Department of Pharmaceutics, Government College of Pharmacy, Aurangabad - 431005, Maharashtra, India.
Email: nityanandzadbuke@gmail.com

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ABSTRACT

The present work focuses on the formulation of bilayered tablet of Metformin Hydrochloride sustained release (SR) 500 mg and Pioglitazone Hydrochloride immediate release (IR) 15mg. Sustained release matrix layer of Metformin Hydrochloride were formulated using Hydroxyl propyl methyl cellulose (HPMC K100M) and Microcrystalline cellulose (MCC PH-101) in different combinations by wet granulation technique to meet Indian Pharmacopoeia (IP) 2010 specification. Immediate release layer of Pioglitazone Hydrochloride was formulated using sodium starch glycolate (SSG) as superdisintegrant. The formulated tablets were evaluated for thickness, weight variation test, hardness test, friability test and drug content. In vitro dissolution studies were carried out in 6.8 phosphate buffer as described in the IP 2010 monograph. The kinetic modeling of in vitro dissolution profiles revealed diffusion release mechanism. The stability studies revealed no significant changes in physical and chemical properties for the optimized formulation.

Keywords: Bilayered tablet, Pioglitazone Hydrochloride, Metformin Hydrochloride, HPMC K 100M, MCC PH101

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a worldwide public health challenge. The morbidity, mortality and economic consequences of T2DM are still a great burden to patients, society, health care systems and the economy. The existing treatments for glycaemic control have limitations either because of their side effects (particularly weight gain and hypoglycemia) or contraindications that limit their use. [1-4]

Thiazolidinediones such as Pioglitazone Hydrochloride is a new class of compounds to improve insulin sensitivity in T2DM. Its plasma elimination half-life ($t_{1/2}$) at steady state concentrations is 3.3-4.9 h. The metabolites of Pioglitazone Hydrochloride are active in vivo. Hence, for total Pioglitazone Hydrochloride (parent drug and metabolites) the $t_{1/2}$ is 16 to 24 h. [5-6]

Biguanide, in particular Metformin Hydrochloride, increases the sensitivity to insulin in peripheral tissues of the hosts. Metformin Hydrochloride is also involved in inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. It has an absolute oral bioavailability of 40 to 60% and gastrointestinal absorption is apparently complete within 6 h of the ingestion. An inverse relation is observed between the dose ingested and the relative absorption with the therapeutic doses of ranging from 0.5 to 1.5 gm, suggesting the involvement of active, saturable absorption process. The plasma $t_{1/2}$ of Metformin Hydrochloride is 1.5-4.9 h. Suitable dosage regimens of Metformin Hydrochloride include unit doses of 500 mg two to three times daily and can even be build up to five times daily or 850 mg once or twice daily. The large spectrum of effects of Pioglitazone Hydrochloride makes the combination of Metformin Hydrochloride and Pioglitazone Hydrochloride a promising treatment option not only for optimizing management of glycemic control but also for prevention of the cardiovascular complication.[7-10]

The present work focuses on the formulation of bilayered tablet of Metformin Hydrochloride (SR) 500 mg and Pioglitazone Hydrochloride (IR) 15mg. Sustained release matrix layer of Metformin Hydrochloride were formulated using Hydroxyl propyl methyl cellulose (HPMC K100M) and Microcrystalline cellulose (MCC PH-101) in different combinations by wet granulation technique to meet Indian Pharmacopoeia (IP) 2010 specification.[11]

MATERIALS

Metformin Hydrochloride (Ipca Laboratories Aurangabad), Pioglitazone Hydrochloride(Lupin Research Park, Aurangabad), HPMC K-100M (Colorcon Asia Pvt.Ltd. Goa), MCC PH101, MCC PH102, PVP-K30, and PVP-K90 (Signet Pharma, Mumbai). All others reagents and chemicals used were of analytical reagent grade.

METHODS

Formulation of Immediate Release Layer of Pioglitazone Hydrochloride

Immediate release layer of Pioglitazone Hydrochloride (P1-P3) were prepared by wet granulation technique as per composition in Table 1. Pioglitazone Hydrochloride, MCC PH101, aerosil 200, sodium starch glycolate were passed through 60#. All the above ingredients were mixed in geometric proportion for 15 minutes. Wet mass was prepared using PVP-K30 in isopropyl alcohol as binder. To binder solution coloring agent was added. Wet mass was passed through 20# sieve, dried at 60°C for 1 h to achieve a moisture content of 4–6%. The dried granules were again passed through a 60# sieve and lubricated with talc and magnesium stearate.

Table 1: Formulation of Immediate Release Layer of Pioglitazone Hydrochloride

Ingredients (mg)	P1	P2	P3
Pioglitazone Hydrochloride	15	15	15
MCC PH-101	118.68	118.68	118.68
Aerosil 200	8	8	8
SSG	10.65	14	17.04
PVP-K30	5	5	5
MCC PH-102	50	50	50
Magnesium Stearate	2	2	2
Total weight	209.33	212.68	215.72

The formulation P2 retains integrity and considered as optimized level of immediate release layer of Pioglitazone Hydrochloride for the development of bilayered tablet.

Formulation of Sustained Release Layer of Pioglitazone Hydrochloride

Sustained release layer of Metformin Hydrochloride (M1-M9) were prepared by wet granulation technique as per composition in Table 2. Metformin Hydrochloride, HPMC-K100M, MCC-101 and aerosil 200 were passed through 60#. All the above ingredients were mixed in geometric proportion for 15 minutes. Wet mass was prepared using PVP-K90 in isopropyl alcohol as binder. The sustained release layer granules were also subjected to similar processing steps as the immediate release layer granules.

Table 2: Formulation of Sustained Release Layer of Metformin Hydrochloride

Ingredients (mg)	Formulation Code								
	M1	M2	M3	M4	M5	M6	M7	M8	M9
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500
HPMC-K100M	210	230	250	210	230	250	210	230	250
MCC PH-101	60	60	60	80	80	80	100	100	100
Aerosil 200	5	5	5	5	5	5	5	5	5
PVP K-90	40	40	40	40	40	40	40	40	40
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
Total	830	850	870	850	870	890	870	890	910

Characterization of Granules

Prior to compression granules were evaluated for the flow properties, such as bulk density, tapped density, carr's index, Hausner ratio and angle of repose.

Formulation of Bilayered Tablet

Final bilayered tablets (F1-F9) were compressed as one layer for Metformin Hydrochloride (M1-M9) and second layer for Pioglitazone Hydrochloride (P2) using 14 mm concave punch in 12 station tablet compression machine (Cip tablet machine).The tablets were compressed as bilayered using granules of Metformin Hydrochloride and Pioglitazone Hydrochloride granules. Metformin Hydrochloride granules were first introduced into the die cavity and a slight precompression was made, over it second layer of Pioglitazone Hydrochloride granules were added. Final compression was made. The composition of F1-F9 formulations are summarized in Table 3.

Table 3: Formulation of Bilayered Tablet

Ingredients (mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500
HPMC-K100M	210	230	250	210	230	250	210	230	250
MCC PH-101	60	60	60	80	80	80	100	100	100
Aerosil 200	5	5	5	5	5	5	5	5	5
PVP K-90	40	40	40	40	40	40	40	40	40
Magnesium Stearate	5	5	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10	10	10
P2 Layer	212.68	212.68	212.68	212.68	212.68	212.68	212.68	212.68	212.68
Total	1042.68	1062.68	1082.68	1062.68	1082.68	1102.68	1082.68	1102.68	1122.68

Evaluation of Bilayered Tablet

The prepared matrix tablets were evaluated as per standard procedure for hardness (n=3), weight variation (n=20), thickness (n=20), friability and drug content. Hardness of the tablets was tested using a Strong-Monsanto tablet hardness tester. Friability test was conducted using Roche friabilator. The thickness of the tablets was measured by digital vernier caliper. Drug content was analyzed by measuring the absorbance of standard and samples at λmax 233.2 nm (Metformin Hydrochloride) and 269.2 nm (Pioglitazone Hydrochloride) using UV/Visible spectrophotometer (Shimadzu UV-1700).

In vitro Drug Release Study

Drug release studies were conducted using the USP Apparatus 2 (Paddle) (Labindia 2000, Mumbai, India) at the speed of 100 rpm at 37±0.5°C. The dissolution media used were 1000 mL of pH 6.8 phosphate buffer solutions for 10 h. Sink condition was maintained for the whole experiment. Samples (5 mL) were withdrawn at regular intervals 1,3,5,7 and 10 h for Metformin Hydrochloride and for 15, 30, 45 and 60 minutes and the same volume of prewarmed (37±0.5°C) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.5 µ membrane filter and the drug content in each sample was analyzed by UV spectrophotometer after suitable dilution at 233.2nm for Metformin Hydrochloride and 269.2nm for Pioglitazone Hydrochloride.[12]

RESULTS AND DISCUSSION

Characterization of Granules

Bulk and tapped density observed for all formulations (M1-M9, P2) was in the range 0.282 – 0.384gm/ml and 0.342-0.416 gm/ml respectively. The angle of repose was observed in the range 27.2º - 33.69º. The compressibility indices for all formulation are below 21% and Hausner ratio in the range 1.08 -1.26 (Table 4).

Evaluation of Bilayered Tablet

Bilayered tablets were evaluated for hardness, friability, thickness and drug content (Table 5).

In vitro Drug Release

All the formulation except F1 and F2 achieved IP 2010 specification for Metformin Hydrochloride for 1,3,10 h. Dissolution profile significantly revealed the retardant effect of HPMC K100M compare to that of the MCC-101. Immediate release layer shows the desired release within 1h. The formulation F4 gives release as per IP 2010 specification (Fig. 1, 2 and 3).

Release Kinetics

To describe the kinetics of drug release from matrix tablets, release data was analyzed according to Kosmeyer et al. equation as

$M_t / M_\infty = Kt^n$

Where, $Mt/M\infty$ = fraction solute release; t = release time; K = kinetic constant characteristic of the drug/ polymer system; n = exponent that characterizes the mechanism of release of traces.

Based on various mathematical models, the magnitude of the release exponent "n" indicates the release mechanism (i.e. Fickian diffusion, case II transport, or anomalous transport). In the present study n < 0.5 which indicate fickian diffusion mechanism.[13]

In the present study n<0.5 this indicates fickian diffusion mechanism. All the formulations revealed Korsmeyer peppas model for the drug release (Table 6).

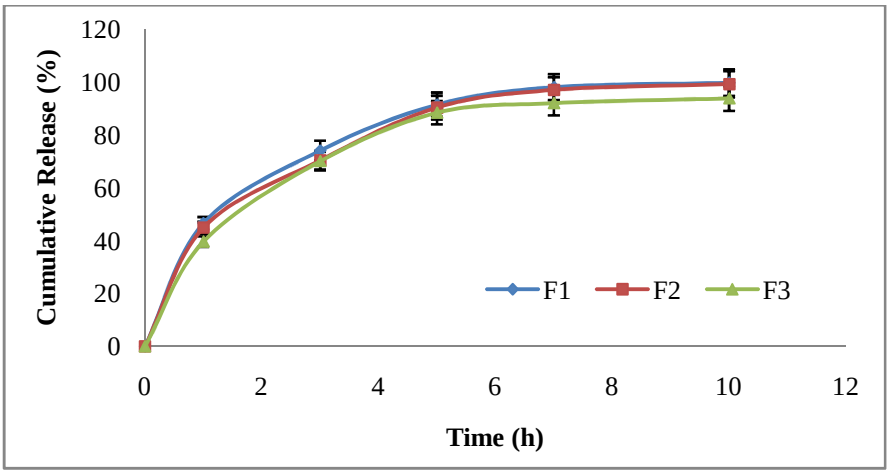
Table 4: Characterization of Granules

Parameter	Formulation Code									
	M1	M2	M3	M4	M5	M6	M7	M8	M9	P2
Bulk Density (gm/ml)	0.282±0.004	0.289±0.012	0.296±0.014	0.287±0.012	0.311±0.008	0.313±0.006	0.307±0.013	0.328±0.007	0.321±0.012	0.384±0.012
Tapped Density (gm/ml)	0.342±0.007	0.357±0.006	0.367±0.015	0.345±0.011	0.374±0.036	0.397±0.005	0.375±0.013	0.396±0.028	0.384±0.011	0.416±0.005
Carr's Index (%)	18.01±1.83	19.14±3.13	19.09±5.13	16.85±3.35	16.31±10.81	20.94±2.73	17.83±6.51	16.83±4.25	17.81±2.18	7.681±0.004
Hausner Ratio	1.22± 0.02	1.23± 0.04	1.23± 0.08	1.20± 0.04	1.20± 0.14	1.26± 0.04	1.22± 0.04	1.20± 0.06	1.23± 0.03	1.083± 0.55
Angle of Repose (θ)	27.30±1.04	29.52±1.02	28.20±1.40	30.81±1.09	29.52±1.23	28.57±1.12	30.19±1.45	29.35±1.04	29.18±1.19	33.69±1.34

Table 5: Evaluation of Bilayered Tablet

Formulation Code	Hardness (Kg/cm²)	Friability (%)	Thickness (mm)	Drug Content(M)* (%)	Drug Content(P)** (%)
F1	5.16±0.28	0.44	6.52±0.32	100.25±0.09	98.25±1.12
F2	5.25±0.05	0.35	6.61±0.32	101.69±0.98	99.01±1.10
F3	5.36±0.28	0.37	6.87±0.30	101.15±1.92	98.97±1.23
F4	5.62±0.28	0.46	6.67±0.21	101.34±1.52	99.19±0.90
F5	5.33±0.28	0.37	6.85±0.19	101.58±1.52	98.26±0.78
F6	5.36±0.51	0.42	6.92±0.08	100.52±1.41	98.78±0.86
F7	5.27±0.28	0.39	6.85±0.25	101.99±0.61	98.69±1.13
F8	5.18±0.50	0.37	7.16±0.20	101.10±1.54	99.26±0.95
F9	5.23±0.23	0.46	7.23±0.26	101.24±1.45	98.36±1.19

* Metformin Hydrochloride, ** Pioglitazone Hydrochloride



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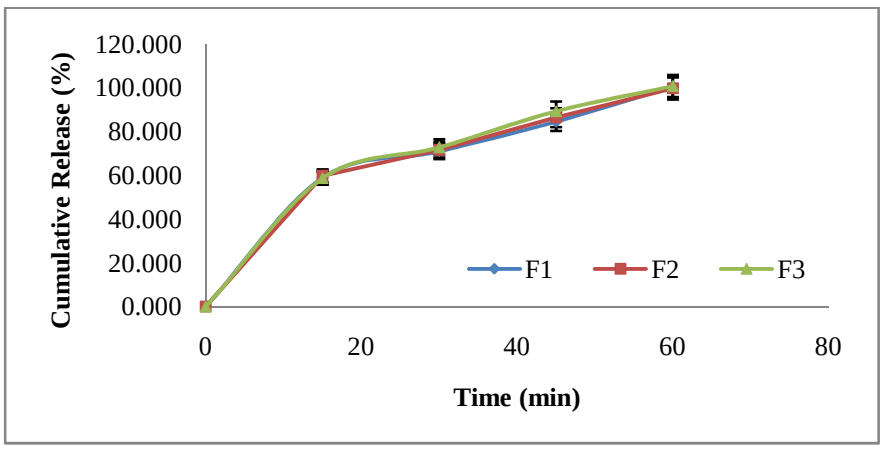
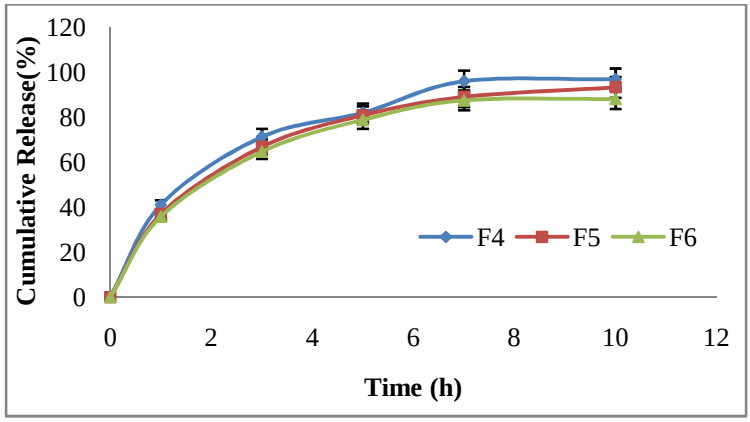


(b)

Fig. 1: Comparative Cumulative Release (%) of Formulations F1-F3 (a) Metformin Hydrochloride, (b) Pioglitazone Hydrochloride



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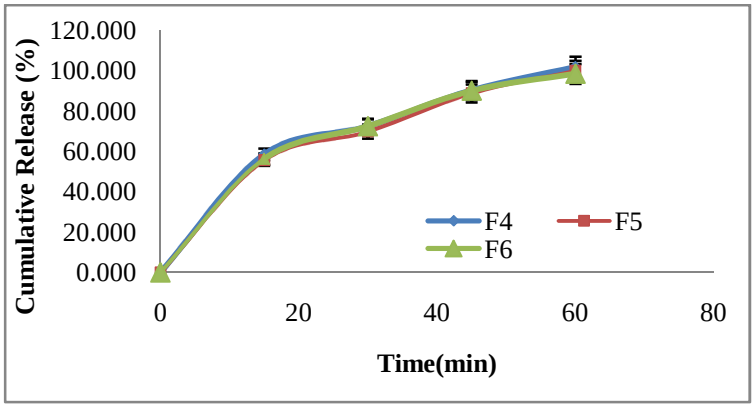
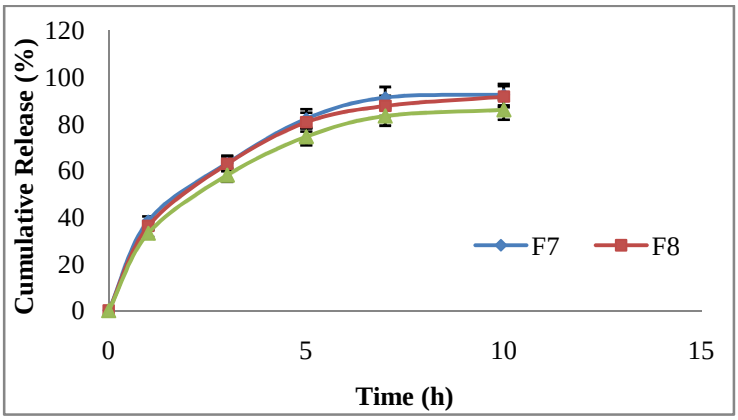
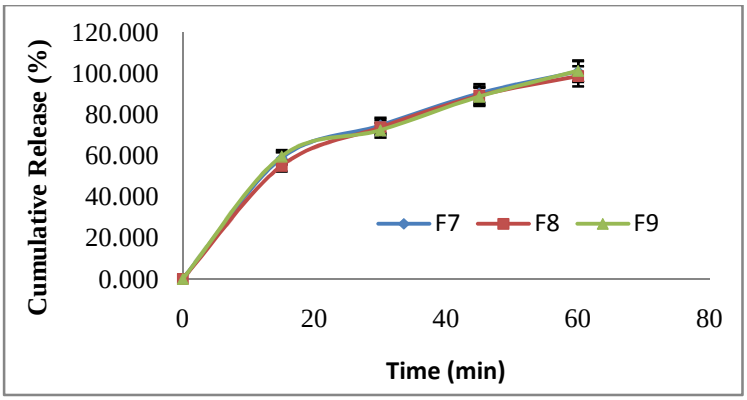


(b)

Fig. 2: Comparative Cumulative Release (%) of Formulations F4-F6 (a) Metformin Hydrochloride, (b) Pioglitazone Hydrochloride



(a)



(b)

Fig. 3: Comparative Cumulative Release (%) of Formulations F7-F9 (a) Metformin Hydrochloride, (b) Pioglitazone Hydrochloride

Table 6: Kinetics of Drug Release for Formulation Batches

Formulation Code	R^2					n	k
	Zero Order	1st order	Matrix	Peppas	Hixson Crowell		
F1	0.6850	0.9903	0.9621	0.9802	0.9711	0.3485	48.7073
F2	0.7371	0.9846	0.9749	0.9914	0.9724	0.3585	46.0090
F3	0.7318	0.9705	0.9719	0.9795	0.9224	0.3866	42.0358
F4	0.7209	0.9711	0.9669	0.9728	0.9238	0.3942	43.6509
F5	0.7631	0.9825	0.9783	0.9818	0.9360	0.4151	39.1861
F6	0.7441	0.9392	0.9725	0.9761	0.8936	0.4103	38.1819
F7	0.7650	0.9659	0.9778	0.9847	0.9259	0.4057	39.8355
F8	0.7757	0.9753	0.9804	0.9846	0.4057	0.4213	37.9704
F9	0.8063	0.9752	0.9868	0.9895	39.8355	0.4408	34.5457

Statistical Analysis

The 3^2 factorial design was selected to study the effect of independent variables HPMC-K100M (X_1) and MCC101 (X_2) on dependent variables Q_1, Q_3 and Q_{10}.The fitted regression equations relating the responses Q_1, Q_3 and Q_{10} are shown in the following equations respectively,

Q_1 = 38.07-2.91*HPMC K100M-3.89*MCC101+0.42*HPMC K100M *MCC101-0.21*HPMC K100M*HPMC K100M+1.90*MCC101* MCC101 ……. (1)

Q_3=68.33-2.95*HPMC K100M-6.23*MCC101-0.24*HPMC K100M* MCC101-1.11*HPMC K100M*HPMC K100M+0.030*MCC101*MCC101 ……. (2)

Q_{10} = 94.05-3.53*HPMC K100M-3.74*MCC101-0.11*HPMC K100M *MCC101-1.87*HPMC K100M*HPMC K100M+1.04*MCC101*MCC101 ……. (3)

The Q_1, Q_3, Q_{10} response for the nine batches (F1-F9) showed a wide variation (i.e., 33.17-46.61, 58.10-76.13, 86.07-99.79 respectively). The coefficients of HPMC K100M and MCC-101were found to be significant at $p<0.05$, hence confirmed the significant effect of both the variables on the selected responses.

Response Surface Plot

The response surface plots were generated using Design Expert 7.1.4 software to observe the effect of independent variables on the response studied such as Q_1, Q_3 and Q_{10}, respectively. The response surface plots revealed that various combinations of independent variables HPMC-K100M (X_1) and MCC101 (X_2) may satisfy any specific requirement (i.e. release as per IP 2010 specification) while taking into consideration of various factors involved in dosage form (Fig. 4, 5 and 6).

Grid Analysis

The grid analysis was performed for selection of the optimized level for Q_1, Q_3 and Q_{10}. The best results for Q_1, Q_3 and Q_{10} was obtained at the lower level concentration of HPMC K100M and middle level concentration of MCC PH-101 which revealed the release profile (Q_1, Q_3 and Q_{10}) as per the IP 2010 specification acceptance criteria. The formulation F4 was selected as optimized formulation.

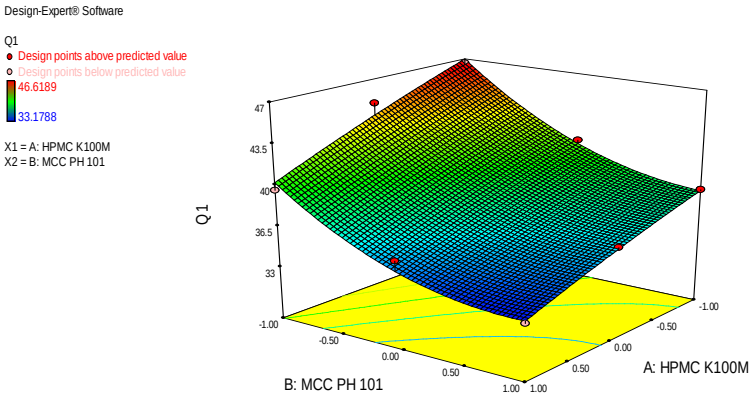


Fig. 4: Response surface plot of Q_1 (Metformin hydrochloride)

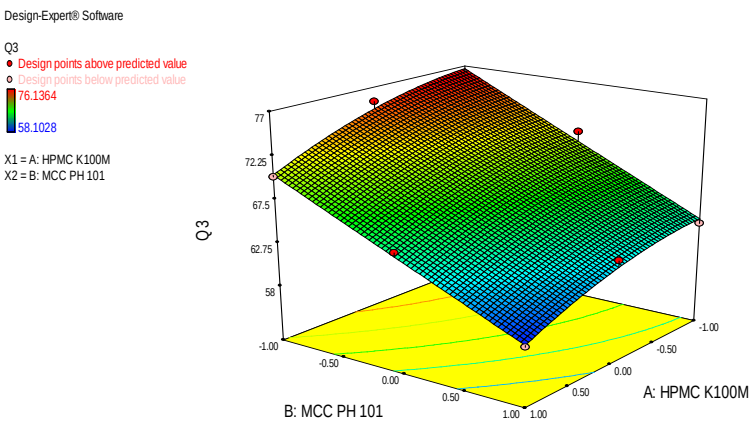


Fig. 5: Response surface plot of Q_3 (Metformin Hydrochloride)

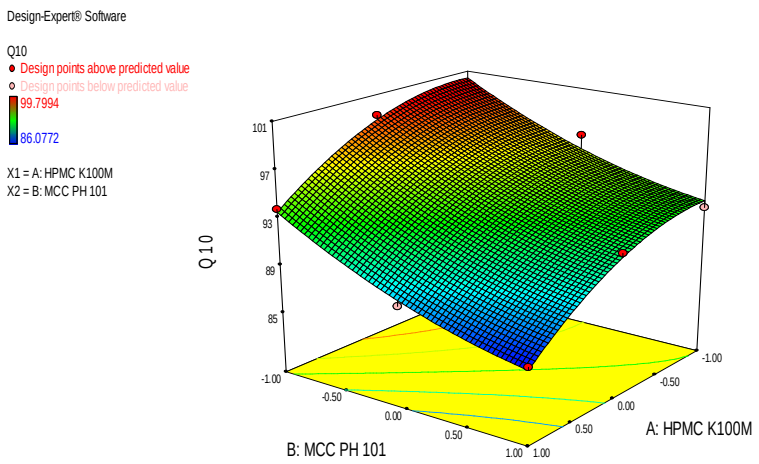


Fig. 6: Response surface plot of Q_{10} (Metformin Hydrochloride)

Table 7: Stability Study

Tests	Limits	Initial	1 Month	2 Months	3 Months
Appearance	No change	No change	No change	No change	No change
Assay	Metformin Hydrochloride	99.60	99.42	99.24	99.13
	Pioglitazone Hydrochloride	101.24	100.93	100.71	100.41
Cumulative Release (%)(M)*	1 h = 25 to 50	41.061	40.878	40.479	40.231
	3 h =45 to 75	71.279	69.787	69.531	69.349
	10 h =NLT 80	96.912	96.437	96.109	95.871
Cumulative Release (%)(P)**	1 h	101.83	100.73	100.21	99.68

* Metformin Hydrochloride, ** Pioglitazone Hydrochloride

Stability Study

The optimized formulation (F4) was selected, packed in aluminium foil and subjected to stability studies as per ICH guidelines, 40 ± 2°C and 75 ± 5% RH (Thermolab). Samples were withdrawn at time intervals of 1, 2 and 3 month.

The samples were evaluated for appearance, assay and in vitro release profile. The results revealed no significant change in the parameters. The studies revealed that F4 formulation is stable (Table 7).

CONCLUSION

The present work lead to development of bilayer tablet for diabetic patients using Metformin Hydrochloride and Pioglitazone Hydrochloride as a model drug candidate. The HPMC K100M and MCC 101 have the ability to maintain the matrix integrity and sustained the release upto the 10 h. The superdisintegrant sodium starch glycolate in combination with microcrystalline cellulose showed the release of drug up to 1 h. The formulation F4 gives release as per IP 2010 specification.

The significant effects of the interaction and polynomial variables on the investigated characteristics (Q_1, Q_3 and Q_{10}) for Metformin Hydrochloride sustained release layer was verified using 3^2 factorial design. The ANOVA shows the predetermined effect of both the dependent and independent variable in both the cases.

The grid analysis was performed for the selection of optimized value for release profile (Q_1, Q_3 and Q_{10}) revealed F4 as the optimized formulation and found to be stable.

Finally it is concluded that an effective, rugged formulation technology is feasible with the advantages of sustained release and immediate release action with a minimum amount of dose for diabetic patients.

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