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Research Article

DEVLOPMENT & EVALUATION OF COMBINATION FORMULATION FOR THE IMMEDIATE DELIVERY OF VILDAGLIPTIN HCl & THE SUSTAINED DELIVERY OF METFORMINN HCl

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A R T I C L E I N F O

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Vildagliptin hydrochloride, Metformin hydrochloride, bioadhesive sustained release system, Bilayer tablet, immediate release, Anti-diabetic drugs.

A B S T R A C T

Objectives: The present study is concerned with the formulation and evaluation of bilayer tablet with immediate release of Vildagliptin hydrochloride and sustained release of Metformin hydrochloride, used as anti-diabetic drugs in the patients with type-II Diabetes. ***Experimental Work:*** In immediate release layer, Crosspovidone was used as fast disintegrating agent and in sustained release layer, fenugreek mucilage (FNM) for bioadhesion sustained release layer .The attempt has been made to combine FNM with well-studied bioadhesive polymers like HPMC K 100M, HPMC K4M and carbopol 934 P. Tablet was prepared by direct compression method. ***Results:*** FT-IR studies showed no interaction between drugs and polymers used in the study. Optimized formulation gives release of IR layer in 1 hour (99.35%) and SR layer in 8 hours (83.59%). There is no significance change during stability studies. ***Conclusion:*** From the above study we concluded that F_8 batch is the best formulation and it give the satisfactory result of immediate release and sustained release of drug from the dosage form. So this formulation is best for the treatment of patient with the type-II diabetes.

INTRODUCTION

Bilayer tablets were are novel drug delivery systems where combination of two or more drugs in single unit. They are preferred in co-administer two different drug in same dosage form, to minimize physical and chemical incompatibility, for staged drug release, IR and SR in the same tablet. Bilayer tablet can be preliminary option to avoid chemical incompatibility between active pharmaceutical ingredients by physical separation, and to enable the development of different drug release profiles (immediate release with extended release). In the last decade, interest in developing a combination of two or more active pharmaceutical ingredients (API) in a single dosage form (bilayer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. Two drugs in same tablet with different layers. One is immediate release and other is sustained release layer Tablet having sustained release layer and bioadhesive layer. The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and strong substantial benefits for patients. To successfully modulated the gastrointestinal transit time of a drug delivery system through mucoadhesive drug delivery system(MDDS), for maximal gastrointestinal absorption of drugs and site specific delivery, one needs to have a good fundamental understanding of the anatomic and physiological characteristics of the human GIT. Bioadhesive polymers are defined as polymers that can adhere to a biological substrate. The term mucoadhesive is applied when the substrate is mucosal tissue. Diverse classes of polymers have been investigated for their potential use as mucoadhesive. Mucoadhesive polymers are water soluble are water insoluble polymers which are swellable networks joint by cross linking agents.

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MATERIALS AND METHOD

Chemicals

Vildagliptin hydrochloride and Metformin Hydrochloride was obtained from Alembic Pharmaceuticals ltd., Vadodara, and Fenugreek mucilage gum powder from ACS chemicals Pvt. Ltd. And all other Excipients used were of analytical grade.

Instruments

The following instruments were used for the study: UV spectrophotometer (Shimadzu 1800, Kyoto, Japan), FT-IR

(Shimadzu, Japan), Modified balanced method, Digital Weighing balance (Wensar, PGB300), Magnetic stirrer (Remi lab. Instruments), Monsanto tester, Friability tester, VEEGO dissolution apparatus, Disintegration test apparatus, Tablet compression machine, Wensar Weight balance.

Selection of solvent

The solubility of Vildagliptin Hydrochloride and Metformin Hydrochloride was tested in various solvents, and it was determined that the drug was more soluble in water than in any other solvent. The solubility was confirmed by analyzing the sample for quantitative determination by UV spectroscopy, with a scan of 400-200nm. Maximum absorbance was obtained at 266nm and 233nm

Fourier Transform Infrared (FTIR)

The compatibility of drug and the excipients was determined by Fourier Transform Infrared spectroscopy (FTIR). The FTIR spectra of pure drug is compared with that of combination of the drug and all the excipients to check for interaction.

Calibration Curve

Scanning of Vildagliptin hydrochloride by UV spectrometer showed λmax 266nm and standard curve at 266 nm followed beer-lamberts law in the concentration ranging from 5-30µg/ml. and Scanning of metformin by UV spectrometer showed λmax 232nm and the standard curve at 233 nm followed beer-lamberts law in the concentration ranging from 4-14µg/ml.

Preparation of solutions for metformin hydrochloride

Accurately weighed 100mg metformin hydrochloride + 100ml 0.1 N HCl(1000µg/ml) and Take 10ml above solution in 100 ml 0.1N HCl (100µg/ml), Dilute the solution to get the concentration range 4-14µg/ml

Preparation of solutions for Vildagliptin hydrochloride

Accurately weighed 50mg Vildagliptin hydrochloride + 50 ml 0.1N HCl(500µg/ml) and Take 5ml main solution in 50ml 0.1N HCl **,** Dilute the solution to get the concentration range 5-30µg/ml

Simultaneous estimation method: The absorbance of metformin hydrochloride and Vildagliptin hydrochloride were measured at 233 and 266nm, and calibration curves were plotted. The absorptivity values at the particular wavelengths were determined. The absorbance and the absorptivity values at the particular wavelength were calculated and substituted in the following equation, to obtain the concentration.

$$C_{MET} = (A_2 * ay_1) - (A_1 * ay_2) / (ax_2 * ay_1) - (ax_1 * ay_2)$$
$$C_{VILDA} = (A_1 * ax_2) - (A_2 * ax_1) / (ax_2 * ay_1) - (ax_1 * ay_2)$$

Where,
A_1 = absorbance of sample at 233 nm
A_2 = absorbance of sample at 266nm
ax_1 = absorptivity of metformin hydrochloride at 233 nm
ax_2 = absorptivity of metformin hydrochloride at 266 nm
ay_1 = absorptivity of Vildagliptin hydrochloride at 233 nm
ay_2 = absorptivity of Vildagliptin hydrochloride at 266 nm

Formulation of Trial Batches by Direct Compression Method

(A)Weigh accurately Vildagliptin HCl, Crosspovidone, MCC, talc, magnesium stearate and all ingredient pass through sieve# 40 for uniformity and mixed in mortar. Added sunset yellow colour for separate layer.(B) Weigh accurately Metformin HCl, HPMC K100M, HPMC K 4M, Carbopol 934P and sodium alginate with Fenugreek mucilage gum powder and all ingredient are pass through 40# for uniformity. Then the die was initially filled with the weighed amount of sustained release portion (B) and were lightly compressed. Over this compressed layer, the required quantity of the fast release layer powder mixture (A) was placed and compressed using Capsule shaped punch.

Formulation of trial batches of IR layer

Table1 Trial Batches for Ir Layer

Batches	T1	T2	T3
Vildagliptin HCl	50mg	50mg	50mg
Crosspovidone	2%	4%	6%
MCC	q.s.	q.s.	q.s.
Magnesium stearate	1%	1%	1%
Talc	2%	2%	2%
Sunset yellow	q.s.	q.s.	q.s.
Total weight	150	150	150

Formulation of trial batches of SR layer

Table 2 Trial Batches for Sr Layer

Batches	T1	T2	T3	T4	T5	T6	T7	T8	T9
Metformin HCl	500mg	500mg	500mg	500mg	500mg	50mg	500mg	500mg	500mg
FNM	85mg	85mg	85mg	85mg	85mg	85mg	85mg	85mg	85mg
HPMC K 4M	10%	-	-	15%	-	-	10%	12.5%	15%
HPMC K 15M	-	10%	-	-	15%	-	-	-	-
HPMC K 100M	-	-	10%	-	-	15%	10%	10%	10%
Carbopol 934 P	5%	5%	5%	10%	10%	10%	5%	5%	5%
Sodium alginate	10%	10%	10%	15%	15%	15%	10%	10%	10%
Dicalcium phosphate	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%	1%
talc	2%	2%	2%	2%	2%	2%	2%	2%	2%
Total wt.	850mg	850mg	850mg	850mg	850mg	850mg	850mg	850mg	850mg

Where, FNM= Fenugreek mucilage powder

Optimization batch for SR layer by using 3^2 factorial design: A 3^2 Full factorial design was used for the optimization. In this design 2 factors were evaluated at each level and experimental trials were performed using all 9 combinations. In the present investigation, Polymers Carbopol 934 P(X1) and sodium alginate (X2) were selected as independent variables. 3 level selected: High, Medium and low for both factors.

Table 3 Selection of Levels for Independent Variables Factorial design by coded value

Independent Factors	LEVEL		
	-1	0	+1
Percentage of Carbopol 934 P	5%	10%	15%
Percentage of Sodium alginate	5%	10%	15%

Table 4 Factorial Design by actual value

Batches	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)
Metformin HCl	500	500	500	500	500	500	500	500	500
FNM	85	85	85	85	85	85	85	85	85
HPMC K4M	107	107	107	107	107	107	107	107	107
HPMC K100M	85	85	85	85	85	85	85	85	85
Carbopol 934 P	43	43	43	85	85	85	127	127	127
Sodium alginate	43	85	127	43	85	127	43	85	127
DCP	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium stearate	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Talc	12	12	12	12	12	12	12	12	12
Total weight(mg)	850	850	850	850	850	850	850	850	850

Table 5 Final Composition of Ir Layer of Vildagliptin HCl

Ingredients	F_1
Vildagliptin HCl	50mg
Crosspovidone	7.5mg (6%)
MCC	90mg
Magnesium stearate	1%
Talc	2%
Sunset yellow	q.s.
Total	150mg

Drug content for Vildagliptin HCl

10 tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 50mg of Vildagliptin taken in to 100ml volumetric flask. The amount of drug present in a 50mg equivalent amount of powder dissolved in and diluted with 0.1N HCl and UV absorbance was measured at 266nm. Drug concentration was determined from standard graph.

Drug content for Metformin HCl: 10 tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 100mg of Metformin HCl taken into 100ml volumetric flask. The amount of drug present in a 100mg equivalent amount of powder was determined by dissolving the powder mixture in 0.1N HCl buffer and UV absorbance was measured at 233nm. Drug concentration was determined from standard graph.

Wash-off test

The ex-vivo mucoadhesion time studies were performed (in triplicate) after application of tablets on freshly cut goat stomach mucosa. The mucosa was fixed on a glass slide using adhesive tape and kept in a slanting position in the beaker. A side of each tablet was wetted with one drop and was attached to the mucosa by applying a light force with a fingertip for 30s. The beaker was filled with 250ml of simulated gastric fluid and kept at 37□ºC; a stirring rate of 100 rpm was applied. Tablet behavior and mucoadhesive time were monitored until complete detachment or dissolution occurred

Ex vivo mucoadhesive strength

A modified balance method used for determining the ex vivo mucoadhesive strength. Fresh goat mucosa was obtained and used within 2h of slaughter. The mucosal membrane separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with 0.1 N HCl at 37ºC. The mucosa was cut into the pieces and washed. A piece of mucosa was tied to the Teflon piece, which was kept in beaker filled with HCl pH 1.2 at 37ºC±1ºC. The Teflon piece was tightly fitted into a glass beaker so that it just touched the mucosa surface. The bioadhesive tablet was stuck to the lower side of a pan. The two sides of the balance made equal before the study. A weight of 5 g was kept in the right-hand pan, which lowered the pan along with the talet over the mucosa. The balance was kept in the position for 5min to provide contact time for bioadhesion. The weight was removed. The water (equivalent to weight) was added slowly drop by drop with the infusion set to the left-hand pan until the tablet detached from the mucosal surface. The mucoadhesive strength of the bioadhesive tablet is calculated by formula

Detachment stress (dyne/cm^2) = m.g/A

Where, m= the weight added to the balance in gram,
g= acceleration due to gravity taken as 980cm/sec^2,
A= area of tissue exposed and is equal to πr^2(r-the radius of the circular hole in the aluminum cap)

In- vitro drug release study: The in-vitro drug release study was carried out by USP dissolution test apparatus type-I Basket using 900ml of 0.1 N HCl at basket rotation of 100rpm at 37.5 C0.5C for 8 hours. 10ml samples were withdrawn at an interval of 1 hour, filtered and analysed spectrophotometrically by double beam UV-Visible spectrometer at 266nm and 233nm after suitable dilution of the sample equal volume of the fresh dissolution medium was replaced after each withdrawal. Absorbance value were transformed to concentration with reference to a standard to a standard calibration curve obtained experimentally.

Response surface Analysis for Optimization

Response surface methodology (RSM) is a collection of statistical and mathematical technique useful for developing, improving and optimizing processes and product design. Polynomial equations contourplots and 3-D response surface graphs were generated using the design expert software (version 8.0.7.1, Statease Inc., Minnieapolis, MN). The model was evaluated in terms of statistically significant coefficients, standardized main effects, and ANOVA and R^2 values using the provisions in the same software.

Accelerated stability study

A Present study were subjected to accelerated stability studies in Aluminum/Aluminum pouch pack as aluminum strip is considered the best protecting packaging material but in the present study simulation was made using aluminum foil pouch. As the dosage form is formulated for drug delivery to stomach, no change should occurs in its mucoadhesive strength, retention time and drug dissolution profile. Dose dumping and failure of mucoadhesive strength and retention time are probable effects anticipated during the stability study of such dosage forms. The tablets of best batch were packed in aluminum pouch and charged of accelerated stability at 40□ C and 75% RH for 1.5 months in a humidity jar According to ICH guideline. (*optimized formulations are kept for further stability study)

RESULTS AND DISCUSSION

FTIR studies

The results of the FTIR study show that the major peaks present in the pure drug sample were present in the mixture of the drug and the polymers, which indicates that there is no interaction between the drug and the excipients.

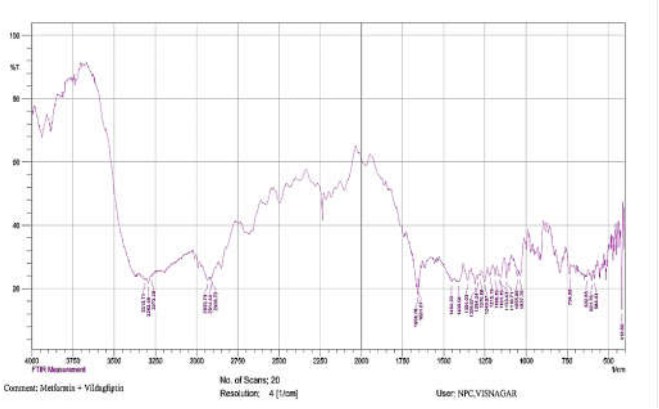


Figure 1 FTIR of Vildagliptin Hydrochloride + Metformin Hydrochloride

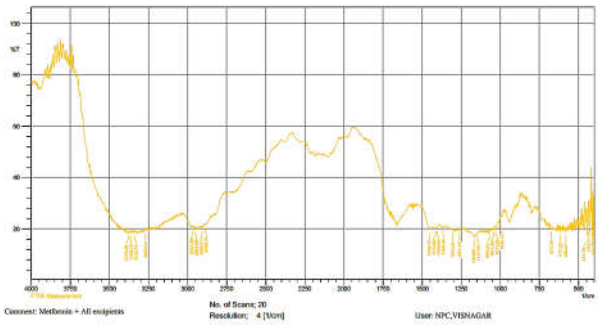


Figure 2 FTIR of Metformin Hydrochloride + Excipients

Table 6 Comparative FT-IR Data of Vildagliptin Hcl

Functional Group	O-H and N-H group (stretching)	C-H Aliphatic group(stretching)	CN Nitrile group (Stretching)	C=O tertiary amide group (stretching)	C-N group (Stretching)
Vildagliptin HCl	3293cm-1	2925-2853cm-1	2238cm-1	1658cm-1	1254cm-1
Vildagliptin HCl + cross povidone	3294cm-1	2915cm-1	2238cm-1	1657cm-1	1254cm-1
Vildagliptin HCl + Metformin HCl	3370.65cm-1	3299.57cm-1	2241cm-1	1630.69cm-1	1244

Table 7 Comparative FT-IR Data of Metformin HCl

Functional Group	N-H group (asym. stretching)	C-H Vibration (CH3sym. stretching)	N-H group (Bending)	C-N group (stretching)	C-N Stretching
Metformin HCl	3367.71cm-1	2974.23cm-1	1546.91cm-1	1199.72cm-1	1039.4cm-1
Metformin HCl + HPMC K 100M + HPMC K4M	3367.71cm-1	2974cm-1	1546.91cm-1	1230.58cm-1	1056.99cm-1
Metformin HCl + all excipients	3367.71cm-1	2974cm-1	1546.91cm-1	1207.44cm-1	1039.63-1

RESULT

The interaction of Vildagliptin HCl and super disintegrating agent like Crosspovidone was studied using FT-IR spectroscopy method and it was found that Vildagliptin HCl had not any interaction with and excipients as revealed from figures and tables. The interaction of Metformin HCl and polymers like HPMC K4M, HPMCK100M, Carbopol 934P.sodium alginate and Fenugreek mucilage gum powder was studied using FT-IR spectroscopy method and it was found that Metformin HCl had not any interaction with excipients

Evaluation of immediate release layer tablet

Disintegration time

Table 8 Result of Vildagliptin HCL Layer Trial Batches

Batch no.	Disintegration time(sec)±SD (n=3)
T1	192±8.88
T2	153±11.59
T3	122±8.02

Table 9 %CDR for Vildagliptin HCL IR Layer

Time	T1	T2	T3
0	0	0	0
5	14.07±0.13	38.24±0.37	41.85±0.38
10	23.56±0.30	52.32±0.26	57.05±0.40
15	31.86±0.17	66.68±0.39	69.91±0.19
30	49.24±0.20	75.89±0.23	80.54±0.46
45	60.63±0.26	83.21±0.24	87.24±0.11
60	81.83±0.22	95.04±0.15	99.68±0.31

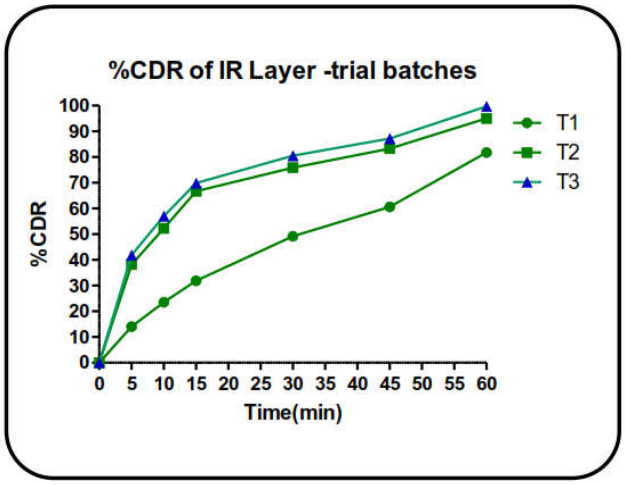


Figure: 3 % CDR of IR Layer-trial batches

Result For Ir Layer Trial Batches

As Crosspovidone increases drug release will faster due to disintegration of F_3 formulation (6%) tablet gives good result from above 3 batches

Evaluation of Trial Batches of Sustained Release Layer

Table 10 In vitro wash off test of trial batches of SR layer

Batches	TIME(min)
F1	160
F2	159
F3	162
F4	324
F5	310
F6	440
F7	586
F8	530
F9	604

Table 11 % CDR of SR layer – Trial batches

TIME (HOUR)	T1	T2	T3	T4	T5
0	0	0	0	0	0
1	48.27±0.13	40.02±0.37	24.18±1.24	18.23±1.22	15.19±1.04
2	67.28±0.30	52.18±0.26	50.23±1.14	45.18±1.05	39.71±0.83
3	78.91±0.17	65.23±0.39	71.89±1.14	68.71±0.96	60.68±1.33
4	87.22±0.20	71.18±1.15	87.18±1.10	79.23±1.22	75.27±1.09
5	98.97±0.22	83.27±1.19	98.72±1.21	85.17±1.10	83.13±1.38
6		97.13±1.08		99.20±1.70	93.71±1.07
7		98.85±1.25			98.13±1.28

TIME (HOUR)	T6	T7	T8	T9
0	0	0	0	0
1	36.14±1.02	29.83±1.05	11.17±1.38	13.15±1.19
2	45.52±1.12	36.90±0.67	35.40±1.03	32.28±1.07
3	54.20±1.12	45.81±1.10	47.66±0.833	51.25±1.52
4	69.14±1.50	57.72±1.43	60.68±1.06	65.67±1.00
5	78.11±1.14	68.12±1.44	75.27±1.16	72.89±1.14
6	86.93±1.04	79.18±1.52	83.13±1.05	79.45±1.51
7	95.67±1.34	87.23±1.14	93.71±1.24	85.21±0.66
8		98.11±1.10	96.13±	91.78±1.31

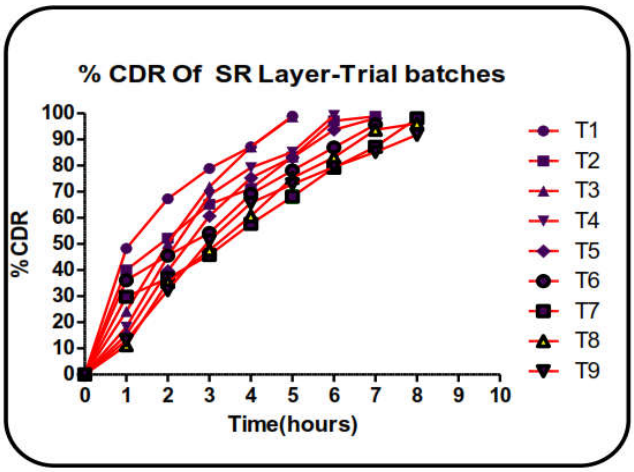


Figure: 4 %CDR for Metformin HCL Trial Batches

RESULT

From the above trial batches low concentration of HPMC K4 M and HPMC K 100M did not sustained drug release for desired period of time So, that F9 batch combination of HPMC K4M and HPMC K 100M in higher concentration with lower concentration of carbopol and sodium alginate was selected for the bioadhesive sustained release.

Optimization of Bilayer Tablet By 3^2 Factorial Design

Table 12 Preliminary Evaluation of Immediate Release Layer

No. of batches	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's Ratio	Angle of repose
F_1	0.33±0.015	0.34±0.011	12.62±0.015	1.20±0.04	32.80±1.27
F_2	0.29±0.059	0.30±0.015	18.60±0.025	1.41±0.02	26.98±1.98
F_3	0.31±0.030	0.31±0.06	24.94±0.022	1.18±0.04	28.30±1.23
F_4	0.32±0.034	0.42±0.025	19.01±0.015	1.24±0.04	32.09±1.45
F_5	0.29±0.024	0.38±0.06	14.50±0.029	1.14±0.03	30.02±1.34
F_6	0.33±0.016	0.39±0.030	15.82±0.015	1.25±0.06	29.65±2.07
F_7	0.31±0.022	0.42±0.017	16.27±0.014	1.14±0.02	30.11±1.32
F_8	0.33±0.014	0.44±0.024	20.15±0.056	1.25±0.04	32.05±0.96
F_9	0.29±0.050	0.39±0.023	16.28±0.034	1.19±0.09	28.63±2.01

Table 13 Preliminary Evaluation of Bioadhesive Sustained Release Layer

No. of batches	Bulk density(gm/cm^3)	Tapped density(gm/cm^3)	Carr's index (%)	Hausner's Ratio	Angle of repose
F_1	0.35±0.020	0.40±0.011	11.94±0.052	1.15±0.03	24.05±1.27
F_2	0.31±0.013	0.37±0.022	19.87±0.015	1.33±0.06	27.01±2.08
F_3	0.30±0.016	0.42±0.041	23.09±0.030	1.24±0.04	29.30±1.98
F_4	0.33±0.012	0.43±0.025	22.65±0.029	1.43±0.02	31.61±1.23
F_5	0.32±0.025	0.39±0.017	20.33±0.012	1.05±0.02	32.45±1.45
F_6	0.34±0.012	0.41±0.030	16.10±0.019	1.23±0.05	28.02±1.31
F_7	0.33±0.031	0.38±0.016	15.88±0.018	1.41±0.02	31.56±2.08
F_8	0.35±0.017	0.40±0.021	24.21±0.034	1.22±0.04	33.89±1.58
F_9	0.31±0.014	0.44±0.030	21.45±0.025	1.31±0.02	26.81±1.62

RESULT

Preliminary formulations were evaluated for the immediate release layer and bioadhesive sustain release layer powder blend property like bulk density, Tapped density, Carr's index, Hausner's ratio and angle of repose(table:4.9). The bulk density of all formulations was in the range of 0.29 to 0.35. The Carr's index was found to be in range of 12 to 23 which was considered as good to fair flow property. Angle of repose was considered as good to excellent flow property of the powder blend. Hausner's ratio of all formulations was below 1.5 indicating good compression characteristics. All the parameters were interrelated to the tablet properties like hardness, friability etc. these results indicating that, the powder blend possess satisfactory flow and compressibility properties.

Post Compression Parameters

Table 14 Post Compression Parameter

Sr no.	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Weight variation
1	5.6	0.35	4.50	PASS
2	5.7	0.30	4.28	PASS
3	5.9	0.29	4.56	PASS
4	5.8	0.37	4.59	PASS
5	5.8	0.66	4.44	PASS
6	5.6	0.58	4.53	PASS
7	5.8	0.25	4.57	PASS
8	5.9	0.24	4.51	PASS
9	5.9	0.59	4.60	PASS

Table 15 Drug content analysis of Bilayer tablets

Formulation code	% Drug Content For Ir Layer	% Dryg Content For Sr Layer
F_1	97.11±0.96	96.12±0.78
F_2	98.48±0.85	97.60±0.80
F_3	95.74±0.71	94.98±0.83
F_4	98.64±0.91	95.58±0.73
F_5	98.11±0.89	97.18±0.85
F_6	95.21±1.21	98.20±0.96
F_7	98.12±0.98	96.40±0.74
F_8	98.85±0.75	98.40±0.95
F_9	94.97	99.01±0.93

Table 16 Mucoadhesive Strength of Full Factorial

Formulation No.	Mucoadhesive Strength (dyne/cm^2)
F_1	17.33
F_2	21.67
F_3	30.34
F_4	26.00
F_5	43.34
F_6	65.02
F_7	60.68
F_8	67.62
F_9	56.35

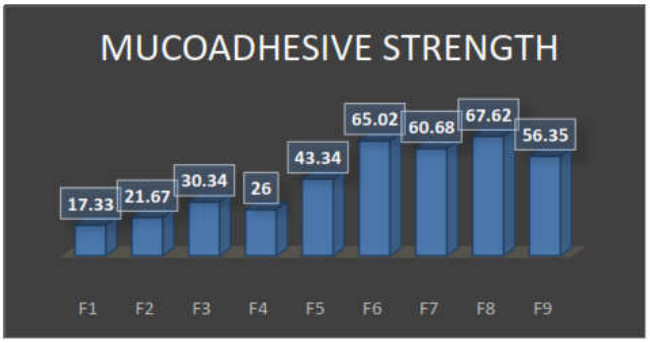


Figure: 5 Mucoadhesive strength of factorial Batches

Ex Vivo Wash-Off Test

All the formulations showed good mucoadhesive retention time which is more than 12 hours except F_1 and F_2 batches. They retained the tablet for 8 hours because of their lower concentration of bioadhesive polymer (Carbopol 934 P, Sodium alginate).

Table 17 In Vitro Dissoultion Study For Ir Layer (% CDR)

TIME	F_1	F_2	F_3	F_4	F_5
0	0	0	0	0	0
5	20.21±0.96	15.14±1.06	13.28±1.12	20.64±0.94	21.20±1.05
10	31.86±1.06	21.81±0.86	19.21±1.02	29.18±0.78	36.85±0.98

15	49.24±1.52	36.95±0.95	28.64±0.09	53.08±0.86	47.24±0.99
30	60.63±1.09	59.33±1.09	48.77±1.10	69.74±1.30	59.41±0.63
45	81.83±1.06	75.58±1.23	71.96±0.96	85.52±1.11	86.52±0.47
60	98.86±1.25	89.74±1.20	88.89±0.85	93.95±1.22	98.32±0.98

TIME	**F_6**	**F_7**	**F_8**	**F_9**
0	0	0	0	0
5	10.34±0.87	39.81±0.96	41.85±0.98	38.24±0.96
10	16.20±0.82	64.75±1.03	69.91±0.99	59.68±0.85
15	34.19±1.08	81.92±1.31	79.24±0.97	71.21±0.98
30	56.84±1.25	88.50±1.10	86.29±1.40	83.87±1.07
45	78.04±0.89	91.22±1.89	93.44±1.32	94.66±1.46
60	82.74±0.98	99.11±0.81	99.35±0.93	98.21±1.21

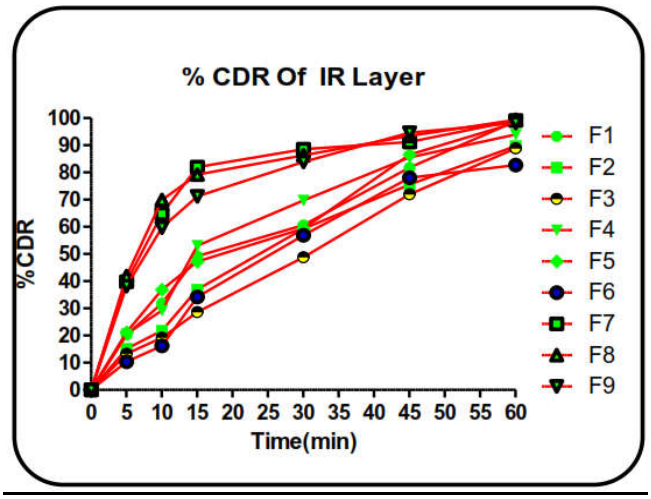


Figure: 6 % CDR OF IR LAYER

Table18 In Vitro Dissolution Study For Sr Layer (%CDR)

TIME	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**
0	0	0	0	0	0
1	29.47±1.34	25.41±0.99	28.25±1.20	23.62±0.97	31.10±0.98
2	39.59±1.31	31.84±0.92	40.16±0.96	39.82±0.96	43.92±1.39
3	48.64±1.64	49.26±0.83	58.39±0.63	45.37±0.74	52.71±1.52
4	56.15±0.96	60.42±1.32	78.74±0.87	50.61±1.32	69.62±1.30
5	69.86±0.85	79.25±1.08	83.16±0.89	66.62±1.47	81.75±0.85
6	89.21±1.02	85.16±1.41	99.25±1.02	83.74±0.57	97.64±0.94
7	99.64±1.26	91.53±1.22	-	98.79±0.96	99.06±0.99
8	-	98.79±1.06	-	99.21±1.25	99.39±1.08

TIME	**F_6**	**F_7**	**F_8**	**F_9**
0	0	0	0	0
1	11.71±0.87	24.16±0.99	20.92±2.01	20.21±
2	47.25±0.99	33.21±1.30	35.84±1.22	29.86±0.85
3	59.60±0.65	46.24±1.22	48.48±1.07	37.86±2.04
4	65.40±1.78	68.79±1.56	59.21±1.45	60.84±0.98
5	79.45±1.26	75.42±1.36	64.68±0.89	71.86±1.05
6	86.70±0.78	88.64±1.24	70.81±0.99	85.41±1.10
7	89.01±0.99	94.85±0.96	81.92±0.75	89.67±0.84
8	90.31±1.02	99.85±0.82	83.59±1.05	93.29±0.48

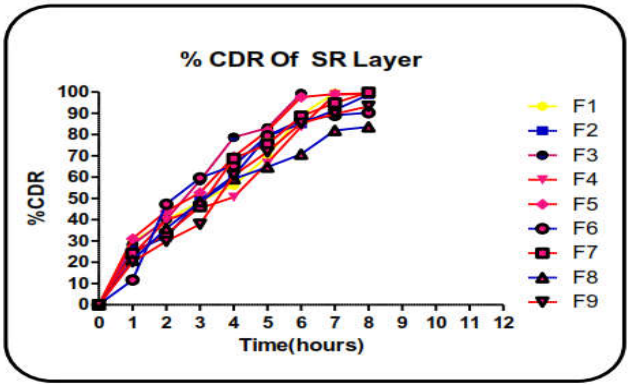


Figure: 7 % CDR OF SR Layer

DISCUSSION

All above batches were prepared using Fenugreek Mucilage powder and combination of HPMC K4M and HPMC K100M with different concentration of Carbopol 934 P and Sodium Alginate.

It shows that increase in concentration of bioadhesive polymers increase the mucoadhesive strength.

Full and Reduced Models for Mucoadhesive Strength

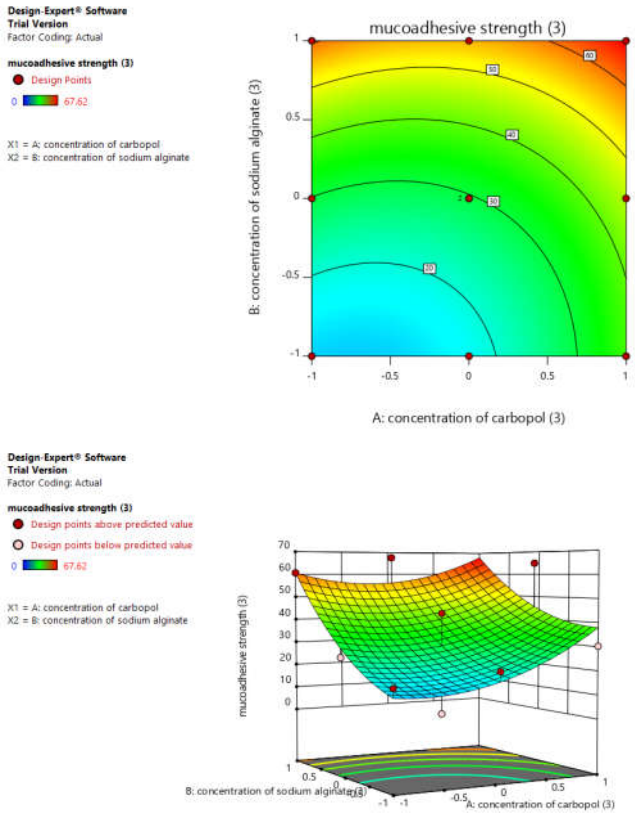
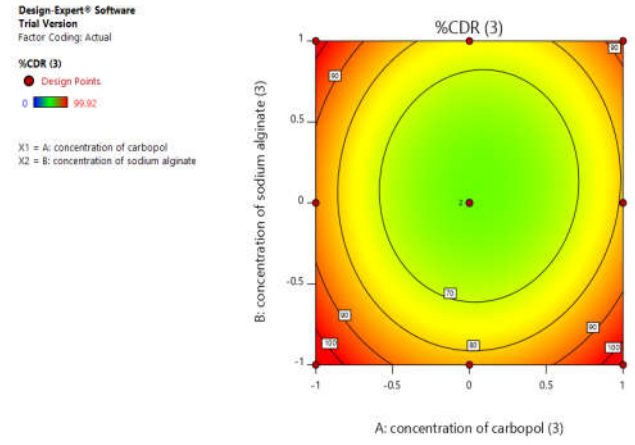


Figure 8 Generation of contour plot and response surface plot for response Y_1 (mucoadhesive strength)

Full and Reduced Models for % CDR



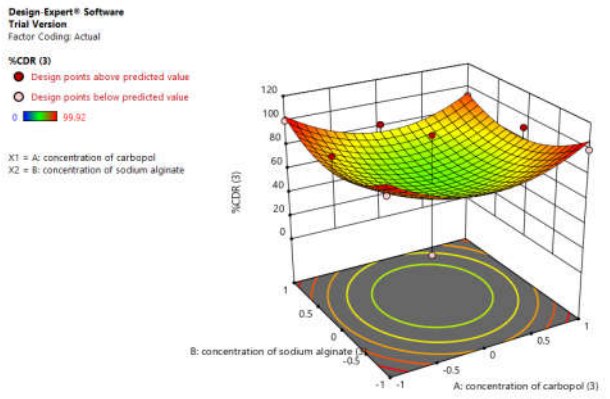


Figure 9 Generation of contour plot and response surface plot for response Y_2 (%CDR)

Table 22 Evaluation of Formulation (F_8) Kept For Stability Study at 40℃ / 75% RH

Parameters	Initial	After 1.5 months
Weight variation	PASS	PASS
% Drug content	98.40	97.8
Hardness(kg/cm^2)	5.9	5.9
Friability (%)	0.24	0.20
Mucoadhesive strength	67	65
Ex vivo wash off test	≥12hours	≥12hours

Table 23 In-Vitro Drug Release Study of Formulation Kept For Stability Study at 40℃/75%RH

TIME (HRS)	% CDR	
	Initial	After 1.5 months
0	0	0
1	20.92	18.98
2	35.84	29.85
3	48.48	40.51
4	59.21	52.28
5	64.68	59.84
6	70.81	68.87
7	81.92	73.11
8	83.59	81.24

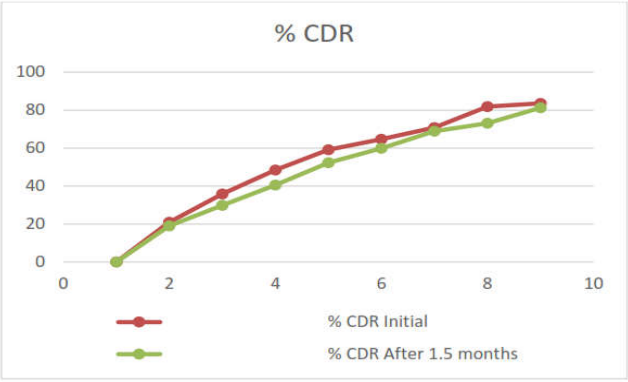


Figure: 10 Dissolution profile after 1.5 months

CONCLUSION

Bilayer tablet was prepared by direct compression method for Vildagliptin HCl immediate release layer of F_8 which contain (6%) CP showed good evaluation parameters like disintegration time and drug content. It showed good immediate release which match to the target dissolution profile. Metformin HCl sustained release layer of formulation F_8 containing Carbopol 934 P (127mg) and sodium alginate (85mg) with combination of HPMC K4M +HPMC K 100M with natural polymer like fenugreek mucilage powder as a bioadhesive polymers showed that 75% Metformin HCl is released in 8 hrs for 12 hours target dissolution profile. Bilayer tablet of formulation F_8 also showed good hardness, weight variation test and friability test. The kinetic studies of the formulation F_8 revealed that Metformin HCl release was best explained y higuchi's equation and from Korsmeyer-Peppas equation; n value of F_8 indicated that mechanism of drug release was non- fickian diffusion drug release. So from all the formulations F_8 found to be most promising formulations. Stability studies conducted for the optimized formulation F_8 as per ICH guidelines for a period of 45 days revealed the stability of the formulation

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