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# FORMULATION AND EVALUATION OF BILAYER MATRIX TABLETS FOR CONTROLLED DELIVERY OF METFORMIN HCL & VILDAGLIPTIN

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**Abstract**

The objective of present work was to formulate and evaluate bilayered tablets of vildagliptin and metformin Hcl for treating diabetes mellitus effectively. Combining vildagliptin with metformin gives additional benefits in comparison with either drug alone and could be considered for patients whose quality of life is impaired by diabetes mellitus.. Vildagliptin is an oral anti-hyperglycemic agent (anti-diabetic drug1) of the new dipeptidyl peptidase-4 (DPP-4) inhibitor class of drugs. Chemically it is (2*S*)-1-[*N*-(3-hydroxy-1-adamantyl) glycyl] pyrrolidine-2-carbonitrile. Metformin is an oral anti-diabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function. The study was performed to design bilayer matrix tablets of sustained release layer of metformin and immediate release layer of vildagliptin. Bilayer matrix tablets comprised of two layers, i.e. immediate release and controlled release layers. The immediate release layer comprised crospovidone super disintegrant (10%) and sustained release layer comprised gaur gum as release retardant polymers (30%). The in vitro release of drug from the formulations was studied in 0.1N Hcl acidic buffer and pH 6.8 phosphate buffer, and it was found that the prepared sustained release layer tablets were able to sustain the release of the drug up to 12hours and In vitro studies of vildagliptin shown more than 80% of drug was released within 30 min. Direct compression method was used for formulation of bilayer tablets. The optimized formulation of both the layer tablets containing different ratios of polymer with drug was found to be compatible from FTIR studies. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. After stability tests, degradation of both drugs were found but the drugs, contents were found to be within the range. Drug release mechanism release exponent (n) were determined for optimized formulations (n > 0.89). The release of vildagliptin was found to follow a first order release model

and the release of metformin was found to follow higuchi model release.

**Key words:** Vildagliptin, Metformin, Guar gum, Cross Povidone, Bilayer tablets.

## Introduction

### Diabetes Mellitus[1,2]:

Diabetes mellitus is a chronic disorder characterized by impaired metabolism of glucose involving distinct pathogenic mechanisms with hyperglycemia as the common denominator. Regardless of the cause, the disease is associated with insulin deficiency, which may be total, partial or relative when viewed in respect of co-existing insulin resistance.

### Causes

Insulin is a hormone produced by the pancreas to control blood sugar. Diabetes can be caused by deficiency of insulin, resistance to insulin or both. People with diabetes have high blood sugar. This is because:

- Their pancreas does not make enough insulin
- Their muscle, fat, and liver cells do not respond to insulin due to insulin resistance.

**Metformin**[3,4] is an oral antihyperglycemic agent that improves glucose tolerance in patients with NIDDM, lowering both basal and postprandial plasma glucose. Metformin is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with NIDDM or healthy subjects and does not cause hyperinsulinemia. Metformin does not affect insulin secretion.Metformin's mechanisms of action differ from other classes of oral antihyperglycemic agents. Metformin decreases blood glucose levels by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization.

**Vildagliptin**[4] belongs to a class of orally active antidiabetic drugs (DPP-IV inhibitors) that appear to have multiple functional benefits beyond simple blood-glucose control. One of these is a potential protective effect on pancreatic beta cells, which deteriorate in diabetes. Vildagliptin appears to be safe, very well tolerated, and efficacious. Following a meal, gut incretin hormones are released. The most important incretin hormones are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). These hormones, secreted in the human small intestine, are responsible for insulin release due to increased glucose levels. In contrast to agents that promote insulin secretion via glucose-independent mechanisms, GLP-1's dependence on glucose concentration is considered beneficial due to

a lower risk of hypoglycemia. GLP-1 also inhibits glucagon secretion and increases beta cell mass by stimulating proliferation and neogenesis. However, the clinical utility of GLP-1 is limited by its short half-life (2 minutes). GLP-1 is rapidly degraded by the proteolytic enzyme DPP-IV. To enhance GLP-1 activity, inhibition of the DPP-IV enzyme is emerging as a novel therapeutic approach in the treatment of diabetes. Administration of vildagliptin enhances GLP-1's ability to produce insulin in response to elevated concentrations of blood glucose, inhibit the release of glucagon following meals, slow the rate of nutrient absorption into the bloodstream, slow the rate of gastric emptying, and reduce food intake.

**Bilayered Tablets Technology[7,9]**

The term bilayered tablets refers to tablet containing subunits that may be either the same (homogeneous) or different (heterogeneous). Bilayer tablets allows for designing and modulating the dissolution and release characteristics. Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances. Bilayer tablets are preferred when the release profiles of the drugs are different from one another.

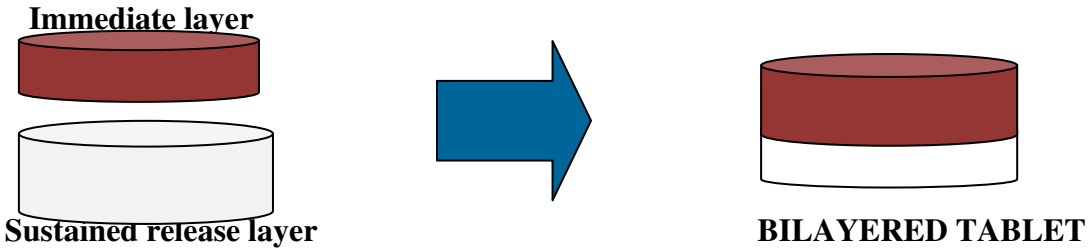


**Fig 1.3.a-Bilayered tablets**

**3. Materials[4]**

Metformin hydrochloride (chandralabs hyderaqbad), vildagliptin ( chandra labsn Hyderabad) HPMC K-100M (MYL CHEM Mumbai), Gaur gum (Myl chem. Mumbai, Eudragit (S.D Fine chem. LTD Mumbai), Croscarmellose (Myl chem Mumbai) Crospovidone(S.D Fine chem. LTD Mumbai), super starch glycolate (Myl chem. Mumbai),. All others reagents and chemicals used were of analytical reagent grade.

**Methods**

**Evaluation of Pre compression Blend:** Prior to compression granules were evaluated for the flow properties, such as bulk density, tapped density, carr's index.

**Preformulation Studies**

**Drug-Excepients Compatibility Studies by I.R.**

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

**Formulation of Vildagliptin Immediate Release Layer**

Immediate release layer of vildagliptin [f1-f8] were prepared by direct compression[4] method as per composition in table 1. Accurately weighed amounts of vildagliptin, Super disintegrants in different concentrations, and diluent were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes.The powder blend was then lubricated with magnesium stearate for 2 minutes. Then the vildagliptin layer was compressed using 8mm round punch

**Composition of Immediate Release Layer.**

| **Ingredients (mg)** | **$F_1$** | **$F_2$** | **$F_3$** | **$F_4$** | **$F_5$** | **$F_6$** | **$F_7$** | **$F_8$** |
|---|---|---|---|---|---|---|---|---|
| **Vildagliptin** | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| **Crospovidone** | 9.0 | _ | _ | 15 | 18.75 | 22.05 | _ | - |
| **Croscarmellose sodium** | _ | 9.0 | _ | _ | _ | _ | 15 | _ |
| **Sodium starch glycolate** | _ | _ | 9.0 | _ | _ | _ | _ | 15 |
| **Magnesium stearate** | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| **Microcrystalline Cellulose** | 89 | 89 | 89 | 89 | 89 | 89 | 89 | 89 |
| **Total weight** | 150 | 150 | 150 | 150 | 150 | 150 | 150 | 150 |

**Table No-1: Formulation table for immediate release layer.**

**Formulation of Metformin HCl SR Layer**

Granules of Sustained release layer was formulated by wet granulation method by uniformly mixing required amount of Metformin HCl with measured quantities of polymer and diluent as specified in the formulation table 2 using 1:1 ratio of ethanol and water as diluting fluid. Now the wet damp mass was passed through sieve no #20 and the granules were dried in hot air oven at 50 $^{\circ}$C. Talc and magnesium stearate were added and mixed thoroughly before compression of granules. The final weight of the SR layer was fixed to 950 mg

**Composition of Sustained Release Layer.**

**Table No-2: Formulation table for sustained release layer.**

| Ingredients(mg.) | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ | $F_8$ |
|---|---|---|---|---|---|---|---|---|
| **Metformin** | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| **HPMCE15** | 28.5 | 28.5 | 28.5 | 28.5 | 28.5 | 28.5 | 28.5 | 28.5 |
| **Mg.stearate** | 9.5 | 9.5 | 9.5 | 9.5 | 9.5 | 9.5 | 9.5 | 9.5 |
| **Aerosil** | 4.75 | 4.75 | 4.75 | 4.75 | 4.75 | 4.75 | 4.75 | 4.75 |
| **HPMCK 100M** | 142.5 | 237.5 | 285 | _ | _ | _ | _ | _ |
| **Gaur gum** | _ | _ | _ | 142.5 | 237.5 | 285 | _ | _ |
| **Eudragit** | _ | _ | _ | _ | _ | _ | 142.5 | 285 |
| **Dicalcium phosphate** | 264.75 | 169.75 | 122.25 | 264.75 | 169.75 | 122.25 | 264.75 | 122.25 |
| **Total wt.** | 950 | 950 | 950 | 950 | 950 | 950 | 950 | 950 |

**Bilayered Tablet Punch**

After the batch was optimized in both immediate release layer (F4) and sustained release layer (F6).The optimized batch in both was compressed by using same ingredients.

**Table No-3: Composition of Bilayer tablet (mg/tablet).**

| Ingredients | IR Formulation (IF4) | SR Formulation (SF3) | Bilayer Tablet (BF) |
|---|---|---|---|
| Metformin HCl | - | 500 | 500 |
| HPMCE15 | | 28.5 | 28.5 |
| Mg.stearet | | 9.5 | 9.5 |
| Guar gum | | 285 | 285 |
| Dicalcium phosphate | - | 122.25 | 122.25 |
| Aerosil | - | 4.75 | 4.75 |
| Vildagliptin | 50 | - | 50 |
| Magnesium stearate | 2.0 | - | 2.0 |
| Crospovidone | 15 | - | 15 |
| Microcrystalline cellulose | 83 | - | 83 |
| Iron oxide red | QS | - | QS |
| Total weight | 150 | 950 | 1100 |

**Evaluation of Tablets**

**Weight variation test:**

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

**Method:**

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

**Friability**:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

**Method**:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

$$\% \text{ friability} = (W_1 - W_2) / W_1 \text{ X } 100$$

$W_1$ = Weight of tablets before test

$W_2$ = Weight of tablets after test

**Thickness:** The thickness of the tablets was measured by vernier calipers. It is expressed in **mm**.

**Hardness:** Tablets require a certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packing and shipping. The hardness of tablet was measured by Monsanto hardness tester. The tablets from each batch were used for hardness studies and results are expressed in **$Kg/cm^2$**.

**Drug Content Analysis**

**Drug content for metformin HCl:** 10 tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 50 mg of metformin HCl taken into 100 ml volumetric flask. The amount of drug present in a 50 mg equivalent amount of powder was determined by, dissolving the powder mixture in 0.1 N HCl buffer and suitably diluted. Further 1ml of the above solution was diluted to 10ml with 0.1N HCl buffer and UV absorbance was measured at 238 nm. Drug concentration was determined from standard graph.

**Drug content for vildagliptin:** 10 tablets of each formulation were weighed and powdered. A quantity of powder equivalent to 50 mg of vildagliptin taken into 100 ml volumetric flask. The amount of drug present in a 50 mg equivalent amount of powder dissolved in and diluted with 0.1N HCl buffer. Further 1ml of the above solution was diluted to 10 ml with 0.1N HCl and UVabsorbance was measured at 246 nm. Drug concentration was determined from standard graph.

**Drug content for metformin HCl in pH 6.8 Phosphate buffer:**

10 tablets of each formulation of sustained release layers were weighed and powdered. A quantity of powder equivalent to 50mg of metformin HCl taken into 100 ml volumetric flask. The amount of drug present in a 50mg equivalent amount of powder was determined by dissolving the powder mixture in Phosphate buffer pH 6.8 and suitably diluted with Phosphate buffer pH 6.8. Further 1ml of the above solution was diluted to 10ml with Phosphate buffer pH 6.8. UV absorbance was measured at 238 nm. Drug concentration was determined from standard calibration curve.

***In Vitro* Drug Release Studies**

**Invitro Dissolution Study for Immediate Release Layer**

900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 $\pm$ 0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 60 minutes at 50 rpm. At definite time intervals, 5 ml of the fluid wa withdrawn; filtered

and again 5ml of the fresh buffer was replaced. Suitable dilutions.Were done with the dissolution fluid and the sample were analysed spectrophotometrically at 246 nm

**In-Vitro Dissolution Study for Sustained Release Layer**

In-vitro release studies were carried out USP II paddle type dissolution test apparatus. 900 ml of 0.1 N HCl (PH 1.2) was filled in dissolution vessel and the temperature of the medium were set at 37° C ± 0.1°C.The speed was set at 50 rpm. 5 ml of sample was withdrawn at predetermined time intervals for 12 hrs and same volume of fresh medium was replaced. The samples were analyzed for Drug content against 0.1N HCL as a blank at λmax 238 nm using spectrophotometer

**Dissolution Profile of Optimized Bilayer Tablets**

% drug release can be calculated by simultaneous equation method for a bilayer tablet.

**Simultaneous Estimation**: The estimation of both vildagliptin and Metformin was done by simultaneous estimation method. Firstly, the absorptivity values of both the drugs were determined at $\lambda_{max}$ of vildagliptin (246 nm, $\lambda_1$) and Metformin (238 nm, $\lambda_2$). The absorptivity value of the drugs is the ratio of absorbance at selected wavelengths with the concentration of drugs in µg/ml. Using the absorptivity values a set of two simultaneous equations were framed (Eqs. 1 and 2).The stock solution of the samples was further diluted with 0.1N Hcl to get standard solution of concentration 10 µ g/ml. The absorbance of the solution was measured at the selected wavelengths and absorptivity was determined as a mean of three independent determinations. Concentration of the drug in the samples was obtained using the following equation

$$Cx = \frac{A1\ ay2 - A2\ ay1}{ax1\ ay2 - ax2\ ay1} \quad \text{..... eq. 1}$$

$$Cy = \frac{A1\ ax2 - A2\ ax1}{ay1\ ax2 - ay2\ ax1} \quad \text{..... .eq. 2}$$

Cx and Cy are concentrations of vildagliptin and Metformin $A_1$ is absorbance value at wavelength $\lambda_1$

$A_2$ is absorbance value at wavelength $\lambda_2$

$ax_1$ is absorptive value of vildagliptin at $\lambda_1$

$ax_2$ is absorptive value of vildagliptin at $\lambda_2$

$ay_1$ is absorptive value of Metformin at $\lambda_1$

$ay_2$ is absorptive value of Metformin at $\lambda_2$

By substituting in these equations, the % drug release can be calculated by simultaneous equation method for a bilayer tablet.

**3.7 Kinetic Analysis of Dissolution Data:**

To analyze the in vitro release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou et al., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

**3.8 Stability Studies:**

The accelerated stability studies were carried out according to ICH guidelines. Optimized formulation F4f6 was packed in strips of aluminum foil laminated with PVC by strip packing and this packed formulation was stored in ICH certifie stability chambers (Thermo labs, Mumbai) maintained at $40^{O}C$ and 75% RH (zone II conditions as per ICH $Q_1$ guidelines) for 3 months. The tablets were evaluated before and after one month of stabilization for the drug content, Friability, hardness, disintegration and *in vitro* release.

**Results and Discussion**

**Drug excipient compatibility studies of optimized bilayer tablets.**

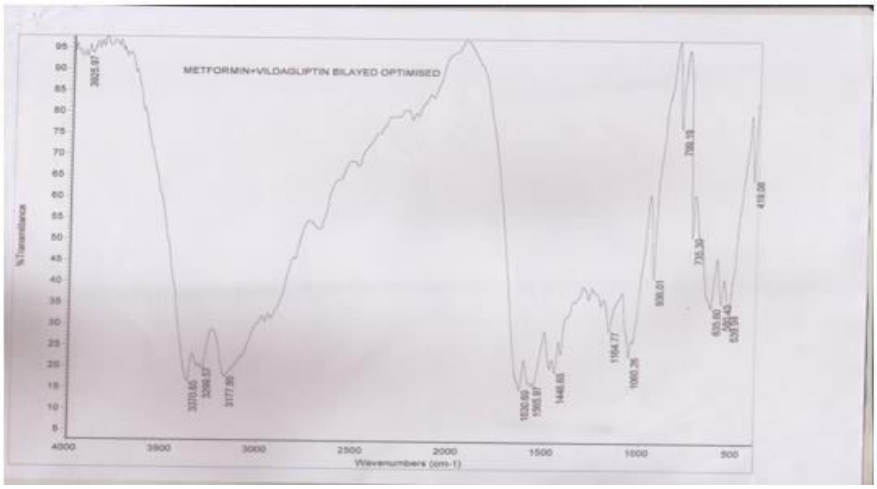


**Fig no-1: IR Spectra of Metformin HCL with vildagliptin.**

| Wave numbers (cm-1) | Functional group |
|---|---|
| Vildagliptin + Metformin Hcl | |
| 3370.65 | N-H stretching |
| 3299.57 | O-H bending |
| 3177.85 | C-H stretching |
| 1630.69 | C=O stretching |

There is no significant change in the shift of major peaks of drug in the above graph ,hence there is no drug and excipient interactions was found.

**Evaluation of Precompressed Blends**

**Table No-4: Evaluation of Precompression parameters of immediate release layer.**

| Formulations | Angle of Repose (θ) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | %Compressibility | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 26.39 | 0.37 | 0.42 | 11.90 | 1.14 |
| **F2** | 28.10 | 0.35 | 0.41 | 14.63 | 1.17 |
| **F3** | 27.12 | 0.34 | 0.39 | 12.82 | 1.15 |
| **F4** | 26.14 | 0.36 | 0.42 | 14.29 | 1.17 |
| **F5** | 27.37 | 0.30 | 0.35 | 14.29 | 1.17 |
| **F6** | 26.35 | 0.33 | 0.38 | 13.16 | 1.15 |
| **F7** | 25.38 | 0.38 | 0.44 | 13.64 | 1.16 |
| **F8** | 26.25 | 0.31 | 0.36 | 13.89 | 1.16 |

**Table No-5: Precompression parameters of sustain release layer.**

| Formulations | Angle of Repose (θ) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | %Compressibility | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 27.45 | 0.36 | 0.41 | 12.20 | 1.14 |
| **F2** | 26.38 | 0.32 | 0.37 | 13.51 | 1.16 |
| **F3** | 27.36 | 0.35 | 0.40 | 12.50 | 1.14 |
| **F4** | 25.13 | 0.37 | 0.43 | 13.95 | 1.16 |
| **F5** | 28.49 | 0.33 | 0.38 | 13.16 | 1.15 |
| **F6** | 24.09 | 0.38 | 0.44 | 13.64 | 1.16 |
| **F7** | 27.31 | 0.32 | 0.37 | 13.51 | 1.16 |
| **F8** | 26.71 | 0.36 | 0.41 | 12.20 | 1.14 |

**Discussion:**

From the above pre-compression parameters it was clear evidence that powdered blend has Good in both (IR ) and (in SR) flow properties and is suitable for direct compression.

**4.3.1 Drug content analysis:**

The content uniformity test was performed for all formulations and results were shown in below Tables. Three replicates from each test were recorded. The mean and standard deviation of all the formulations are calculated. The drug content of vildagliptin of tablets in 0.1N Hcl buffer was to be between 95.22±0.88 to 98.86±0.76. The

drug content of metformin of tablets in 0.1N Hcl buffer was found between 94.85±0.75 to 98.13±0.98 The drug content of metformin layer of tablets in phosphate buffer pH 6.8 was to be between 94.93±0.73 to 98.29±0.68. The cumulative percentage drug released by each formulation *in vitro* release studies was calculated on mean content of the drug present in the respective tablet in the respective dissolution medium.

**Table No-6: Drug content analysis of immediate release tablets.**

| Formulation Code | %DRUG CONTENT 0.1NHCL |
|---|---|
| **F1** | 97.13±0.98 |
| **F2** | 96.48±0.86 |
| **F3** | 95.22±0.88 |
| **F4** | 97.65±0.64 |
| **F5** | 98.11±1.42 |
| **F6** | 98.86±0.76 |
| **F7** | 94.85±0.75 |

**Table No-7: Drug content analysis of sustain release tablets.**

| Formulation Code | %DRUG CONTENT | |
|---|---|---|
| | **0.1NHCL** | **6.8P$^{H}$ PHOSPHATE** |
| **F1** | 97.13±0.98 | 96.10±0.79 |
| **F2** | 96.48±0.86 | 96.60±0.84 |
| **F3** | 95.22±0.88 | 94.93±0.73 |
| **F4** | 97.65±0.64 | 95.54±0.81 |
| **F5** | 98.11±1.42 | 97.18±0.53 |
| **F6** | 98.86±0.76 | 98.29±0.68 |
| **F7** | 94.85±0.75 | 94.40±0.81 |
| **F8** | 98.13±0.98 | 98.10±0.79 |

**4.4 Evaluation of post compression parameters.**

**Table No-8: Post compression parameters of the immediate release tablets containing 150 mg vildagliptin.**

| Formulation Code | Weight Variation(mg) | Hardness ($kg/cm^2$) | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| **F1** | 149± 1.34 | 4.5± 0.020 | 1.58 ± 0.035 | 0.18 |
| **F2** | 148± 1.33 | 4.8± 0.015 | 1.62 ± 0.032 | 0.16 |
| **F3** | 150± 1.31 | 5.0± 0.026 | 1.52 ± 0.025 | 0.14 |
| **F4** | 150± 1.64 | 5.3 ±0.012 | 1.53 ± 0.017 | 0.12 |
| **F5** | 152± 2.13 | 4.4 ±0.024 | 1.62 ± 0.028 | 0.18 |
| **F6** | 150± 1.32 | 4.8 ±0.029 | 1.58 ±0.018 | 0.15 |
| **F7** | 148± 1.31 | 4.2± 0.026 | 1.65 ±0.025 | 0.20 |
| **F8** | 148± 2.13 | 4.6± 0.026 | 1.60 ±0.035 | 0.16 |

**Discussion:** The results of the uniformity of weight, hardness, thickness and friability of the tablets are given in Table 4.4.a. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 148±1.31 mg to 152±2.13 mg. The hardness of the tablets ranged from 4.2±0.026 to 5.3±0.012kg/$cm^2$, the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 1.52±0.025 to 1.65±0.025 mm. Thus all the physical attributes of the prepared tablets were found be practically within control.

**Post compression evaluation of sustain release tablets.**

| Formulation Code | Weight Variation (mg) | Hardness ($kg/cm^2$) | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| **F1** | 948± 1.34 | 6.10 ± 0.020 | 4.68 ± 0.035 | 0.38 |
| **F2** | 948± 1.33 | 7.25 ± 0.015 | 4.28 ± 0.032 | 0.24 |
| **F3** | 948± 1.31 | 6.28± 0.026 | 4.44 ± 0.025 | 0.32 |
| **F4** | 947± 1.64 | 6.83 ± 0.012 | 4.53 ± 0.017 | 0.36 |
| **F5** | 949± 2.13 | 6.65± 0.024 | 4.40 ± 0.028 | 0.21 |
| **F6** | 950 ± 1.31 | 6.10 ± 0.029 | 4.69 ± 0.018 | 0.26 |
| **F7** | 951± 2.13 | 7.14 ± 0.015 | 4.18± 0.017 | 0.28 |
| **F8** | 950± 1.68 | 6.25 ± 0.015 | 4.62± 0.028 | 0.30 |

**Table No-9: Post compression parameters of the matrix tablets containing 500 mg metformin HCl as a SR formulation.**

**Discussion:** The results of the uniformity of weight, hardness, thickness and friability of the tablets are given in Table 4.4.b. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 947±1.64 mg to 951±2.13mg.

The hardness of the tablets ranged from 6.10±0.020 to 7.65±0.024 kg/cm$^2$, the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.10±0.017 to 4.68±0.035 mm. Thus all the physical attributes of the prepared tablets were found be practically within control.

**Post Compression Evaluation parameters for optimized Bilayer tablets**

**Table No-10: Post Compression Evaluation Parameters for optimized Bilayer tablets.**

| Formulation Code | Weight Variation (mg) | Hardness (kg/cm$^2$) | Thickness (mm) | Friability (%) |
|---|---|---|---|---|
| $f_4F_6$ | 1110±2.32 | 8.9±0.08 | 5.28±0.18 | 0.19 |

**Table no-11: Comparative invitro dissolution studies of vildagliptin IR tablets.**

| Time (min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 00 | 0 | 0 | 0 | 0 |
| **5** | 20.21 | 8.68 | 6.86 | 39.81 | 38.24 | 41.85 | 9.22 | 7.18 |
| **10** | 31.86 | 15.24 | 13.28 | 64.75 | 66.68 | 69.91 | 17.86 | 15.84 |
| **15** | 49.24 | 21.81 | 19.21 | 81.92 | 83.21 | 87.24 | 20.64 | 21.21 |
| **30** | 60.63 | 28.64 | 25.68 | 99.89 | 99.24 | 99.68 | 29.18 | 27.62 |
| **45** | 81.83 | 33.21 | 36.11 | | | | 32.48 | 34.86 |
| **60** | 99.86 | 49.24 | 45.68 | | | | 48.98 | 47.24 |

**Discussion:** Results of dissolution profiles of various IR formulation showed that formulation IF4 showed 99.89% drug release at the end of 30 minutes which is much more than the other formulation. Thus due to fast release of drug within stipulated time IF4 was chosen as best formulation

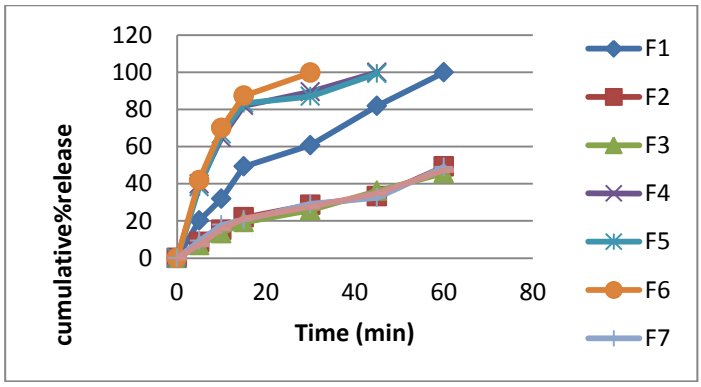


**Fig.No-2: Comparative *In vitro* drug release of immediate release layers.**

**Table No: 12 Comparative Invitro Dissolution Studies of Metformin Hcl Sr Tablets.**

| Time [hr] | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| **0** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **1** | 48.64 | 31.84 | 24.16 | 28.25 | 20.21 | 20.92 | 50.61 | 48.71 |
| **2** | 69.86 | 49.26 | 33.21 | 40.16 | 29.86 | 35.84 | 66.62 | 69.62 |
| **3** | 89.21 | 60.42 | 46.24 | 58.39 | 37.86 | 48.48 | 83.74 | 81.75 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **4** | 99.64 | 79.25 | 68.79 | 78.74 | 60.84 | 59.21 | 98.96 | 99.39 |
| **5** | _ | 87.16 | 75.42 | 83.16 | 71.86 | 64.68 | _ | _ |
| **6** | _ | 98.79 | 88.64 | 99.25 | 85.41 | 70.81 | _ | _ |
| **8** | _ | _ | 99.92 | _ | 99.29 | 81.92 | _ | _ |
| **10** | _ | _ | _ | _ | _ | 91.86 | _ | _ |
| **12** | - | _ | _ | _ | _ | 98.91 | _ | _ |

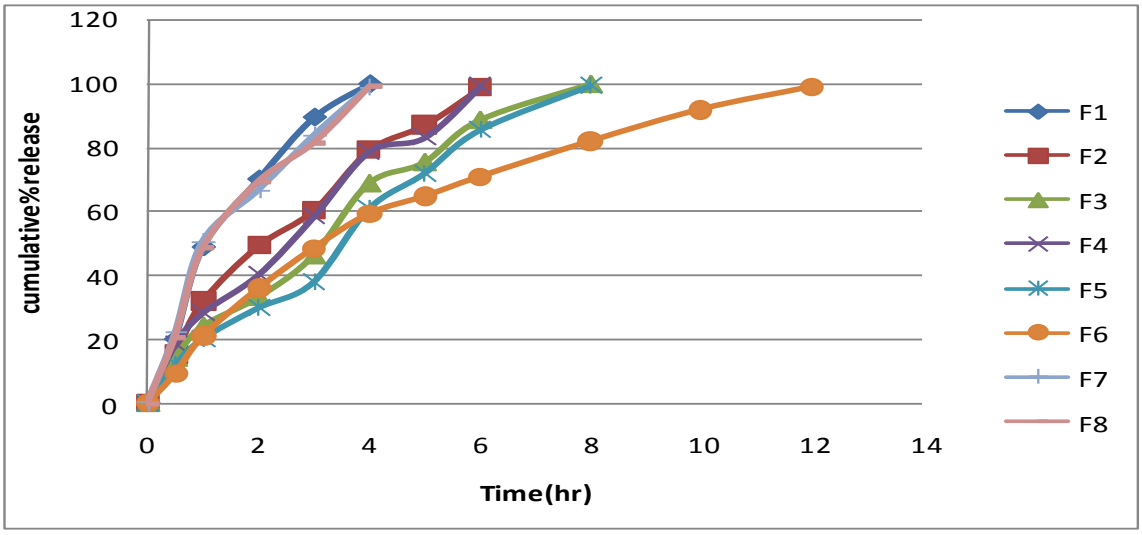


**Fig N o: 3 Comparative *In vitro* drug release of sustain release layers of metformin.**

**Discussion:** The optimized controlled release bilayer matrix tablets were evaluated for hardness, thickness, friability and it was found to be 8.9±0.08kg/cm$^2$, 5.28±0.18mm, 0.19% respectively.

**Table No-13: % Swelling Index of SR Tablet.**

| **Time (hrs)** | **Formulation code** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** |
| **1** | 11.71 | 16.65 | 10.21 | 12.93 | 8.71 | 14.32 | 9.61 | 6.51 |
| **2** | 16.4 | 27.89 | 19.25 | 17.29 | 12.41 | 23.94 | 15.66 | 13.87 |
| **4** | 59.6 | 52.05 | 51.9 | 63.1 | 41.61 | 49.61 | 40.7 | 42.2 |
| **8** | 76.45 | 79.57 | 80.69 | 80.21 | 57.24 | 80.07 | 50.06 | 47.45 |
| **12** | 90.31 | 98.48 | 101.5 | 88.31 | 100.9 | 103.8 | 69.05 | 77.64 |

**Table No-14: % Drug release profile of optimized bilayer tablets of vildagliptin & metformin HCL.**

| Time | % Drug release | |
|---|---|---|
| | vildagliptin | Metformin HCl |
| 0 | 0 | 0 |
| 5 min | 38.86 | - |
| 10 min | 65.74 | - |
| 15 min | 85.21 | - |
| 30 min | 99.86 | - |
| 1 hr | - | 21.81 |
| 2 hr | - | 34.48 |
| 3 hr | - | 46.68 |
| 4 hr | - | 58.21 |
| 5 hr | - | 66.81 |
| 6 hr | - | 71.86 |
| 8 hr | - | 83.21 |
| 10 hr | - | 93.86 |
| 12 hr | - | 99.25 |

**Discussion:** The cumulative amount of drug release from optimized Bilayer formulation was found to be 99.86% in 30 mins followed by the SR release i.e, 99.25% in 12 hrs.

**4.5 Analysis of Dissolution Data**

**Table No-15: Analysis of release mechanism of all sustained release formulations.**

| Formulation | Zero order $\mathbf{R^2}$ | First order $\mathbf{R^2}$ | Higuchi $\mathbf{R^2}$ | Peppas (**n**) |
|---|---|---|---|---|
| F1 | 0.921920719 | 0.837340108 | 0.998569857 | 2.082160117 |
| F2 | 0.961122007 | 0.821764442 | 0.985538734 | 1.640538959 |
| F3 | 0.963489671 | 0.723920074 | 0.956653694 | 1.510528982 |
| F4 | 0.975739995 | 0.748695741 | 0.956653694 | 1.679914928 |
| F5 | 0.849422713 | 0.709864 | 0.962496545 | 1.340677025 |
| F6 | 0.913290325 | 0.88969808 | 0.992722257 | 1.207526056 |
| F7 | 0.918283761 | 0.842718122 | 0.998029932 | 2.042891742 |
| F8 | 0.919492055 | 0.800243588 | 0.998079248 | 2.054831659 |

**Kinetics data for optimised sustained release formulation:**

**Table No-16: Release kinetics for F6 formulation for sustained release layer.**

| | ZERO | FIRST | HIGUCHI | PEPPAS |
|---|---|---|---|---|
| | % CDR Vs T | Log % Remain Vs T | %CDR Vs √T | Log C Vs Log T |
| **Slope** | 7.657357811 | -0.13982192 | 29.98649388 | 1.207526056 |
| **Intercept** | 18.21047516 | 2.137728262 | -3.569486116 | 0.881403488 |
| **Correlation** | 0.955662244 | -0.943238082 | 0.996354484 | 0.786697338 |
| **R 2** | 0.913290325 | 0.88969808 | 0.998722257 | 0.618892701 |

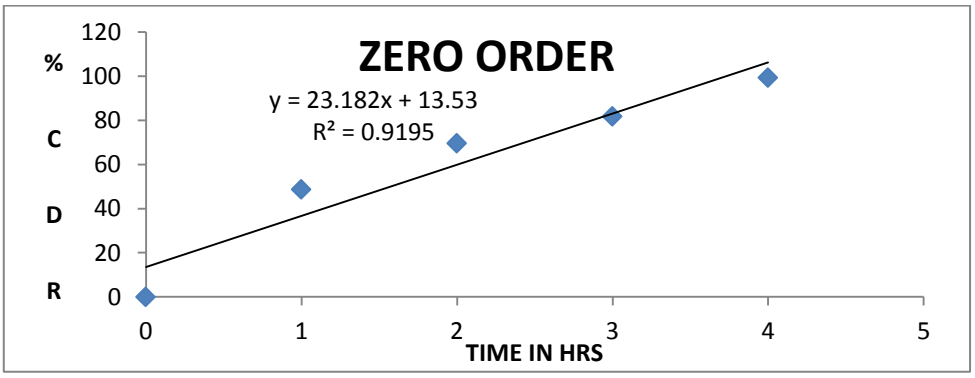


**Fig. no-4: Zero order release graph for Optimized Bilayer formulation**

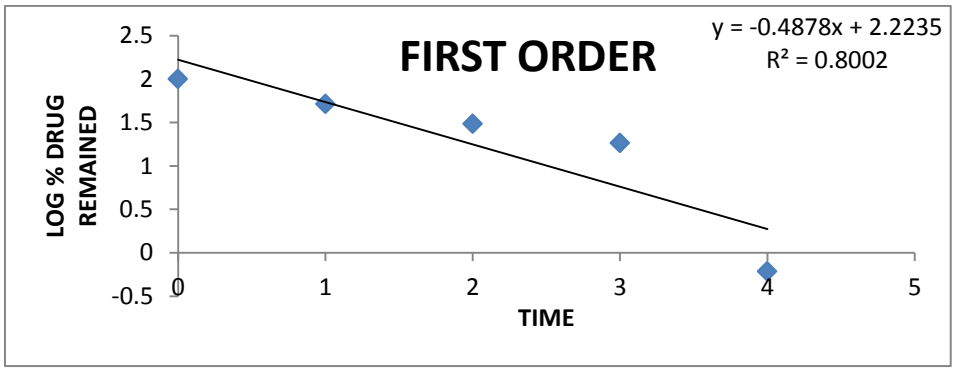


**Fig no-5: First order release graph for Optimized Bilayer formulation**

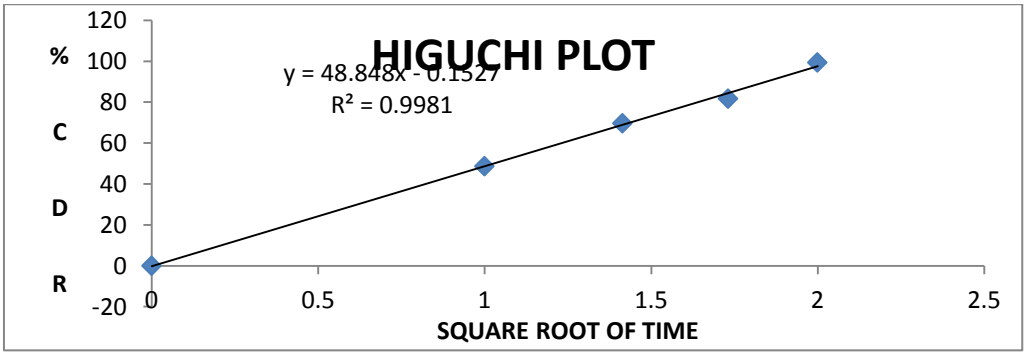


**Fig no-6: Higuchi model graph for Optimized Bilayer formulation**

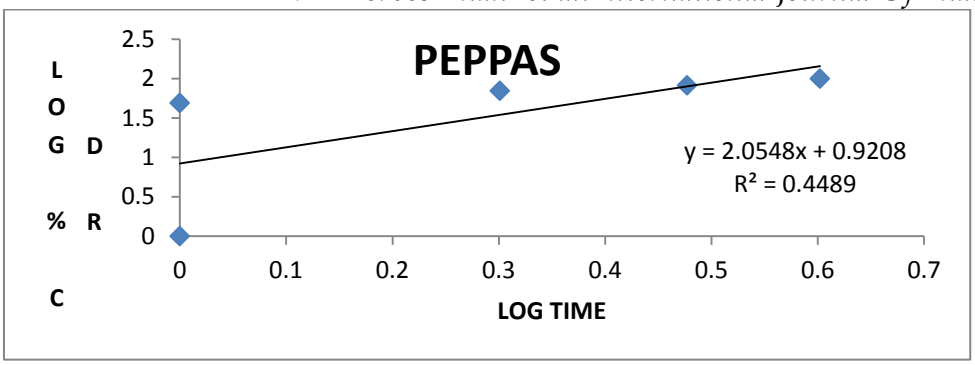


**Fig no-7: Peppa's model graph for Optimized Bilayer formulation.**

**Stability studies of bilayer optimized tablet.**

**Table No-17: Stability Studies As Per ICH Guidelines.**

| Time | Colour | Assay. | | Cumulative % drug release at 30minutes | | Cumulative % drug release at 12 hrs | |
|---|---|---|---|---|---|---|---|
| | | $25\pm2^0$c and 65±5%RH | $40\pm2^0$c and 75±5%RH | $25\pm2^0$c and 65±5%RH | $40\pm2^0$c and 75±5%RH | $25\pm2^0$c and 65±5%RH | $40\pm2^0$c and 75±5%RH |
| First day | White | 99.87 | 99.38 | 99.89 | 98.34 | 99.25 | 98.92 |
| 30 days | White | 99.86 | 99.27 | 99.87 | 97.94 | 98.67 | 98.96 |
| 60 days | White | 99.76 | 99.18 | 99.82 | 97.86 | 98.38 | 98.98 |
| 90 days | White | 99.73 | 98.99 | 99.78 | 97.82 | 98.11 | 99.87 |

**Discussion:** Short term stability studies were carried out at accelerated conditions of $25\pm2^0$c and 65±5%RH and $40\pm2^0$c and 75±5%RH in accordance with ICH Guidelines Q1. There was no change in physical appearance in the optimized batch over a period of three months .There was no significant change in % release of drug after 3 months indicating that the formulation is stable.

**4. Conclusion**

From the present study it was concluded that controlled release Bilayer matrix tablets of vildagliptin formulated with 10% crospovidone for immediate release layer and 30% guar gum for metformin HCL sustained release layer showed promising results of drug release characteristics and and it was found that the prepared sustained release layer tablets were able to sustain the release of the drug up to 12hours and In vitro studies of vildagliptin shown more than 80% of drug was released within 30 min. Short term stability studies (3 months) showed that the Formulation is stable Therefore, necessitating to continue further research on *Invivo* small animal experimentation and also intermediate and long term stability studies.

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**References**

1. Catherine C. C. Diabetes-Vital Statistics.USA: American Diabetes Association; 1996. p. 65-8.
2. Harris MI, Diabetes in America, National Institute of Health, National Institute of Diabetes, and Digestive and Kidney Disease. 2nd ed. NIH Publication, 1995; 95: 1468.
3. DRUG BANK http://www.drugbank.ca/drugs/DB00661.
4. Indian Pharmacopoeia, Govt of India, Ministry of Health and Family welfare, Vol. 2, Delhi: Publication by Controller of Publication, 1996.
5. Sharma HL, Sharma KK. Principles of Pharmacology 1st ed. New Delhi. Paras Medical Publishers: 344-346.
6. Kibbe HA. Hand book of Pharmaceutical Exicipents.3rd ed.London:American Pharmaceutical Association, Pharmaceutical Press; 2000.
7. Joseph RR. Sustained and Controlled Release Drug Delivery System. NewYork: Marcel Dekker; 1978.
8. R.F. Shangraw. Compressed tablets by direct compression in Pharmaceutical dosage forms: Tablets. 2nd ed. New York: Marcel Dekker; 1989. p. 195.
9. Vishnu M. Patel, Bhupendra G. Prajapati, and Madhabhai M. Patel Formulation, Evaluation and Comparison of Bilayered and Multilayered Mucoadhesive Buccal Devices of Propranolol Gwen MJ, Joseph RR. Modern Pharmaceutics.1996.580-893. (Vol 72).
10. Patel M, Sockan GN, Kavitha, Tamizh M. Challenges In The Formulation of Bilayered Tablets: A Review International Journal of Pharma Research and Development. 2010; 2(10):30-42.
11. Libermann HA, Lachman L. (editors). Pre formulation testing: Pharmaceutical dosage forms- Tablets. New York: Marcel Dekker Inc; 1980. p. 1-8.

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