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# FORMULATION AND CHARACTERIZATION OF BILAYER TABLET OF VILDAGLIPTIN

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## ABSTRACT

Based on different concentrations of super disintegrant nine of vildagliptin immediate-release tablets formulations were prepared. For the design of different formulations concentration of super disintegrant were taken as a variable. The dose required for the immediate release formulations were calculated by formula given by Robison and Erikson. Based on the different concentrations of polymers (HPMC K15M and Eudragit RSPO,), different bilayer sustained release matrix formulations were prepared. Concentration and types of polymers were utilized as formulation variables. For all formulations of bilayer tablets, the immediate release layer consisted up optimized formulations of vildagliptin immediate-release tablets. The formulation containing HPMC K15M and Eudragit RSPO showed higher controlled drug release. Formulation F8 showed controlled release up to 12 hrs with max release percentage.

**Keywords:** Super disintegrate, Bilayer tablet, sustained release, multi-layer tablets.

## 1 INTRODUCTION

Bilayer tablet is the new era for the successful development of controlled release formulation. It is also called Dual or Multi component tablet. Bilayer tablet is better than the traditionally used dosage form. It is suitable for sequential release of two drugs in combination. It also capable of separating two types of incompatible substances and also for sustain release tablet in which one layer is immediate release as initial dose and second one is maintenance dose. Bilayer tablet contain immediate and sustained release layers. In which immediate release layer delivers the initial dose which contains super disintegrates (promote drug release rate and attains the onset of action rapidly). It also called as a loading dose. Second layer is sustained release (maintenance dose) layer releases drug in sustained or prolonged time period[1].

Coronary vasodilators, antihypertensive, antihistamines, analgesics, antipyretics and antiallergenic agents are mainly suitable for this type of drug delivery. Some bilayer tablet have both the layers as the sustain release layers for example certain anti diabetic agents. Bi-layer tablets are made by compressing several different granulations fed into a die in succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers. More are possible but the design becomes very special. Ideally, a slight compression of each layer and individual layer ejection permits weight checking for control purposes[2].

### 1.1 Advantages of Bilayer Tablet

- Incompatible substance can be separated by formulating them in separate layer as a two layer tablet or separating the two layers by a third layer of an inert substance as a barrier

between the two.

- Two layer tablet may be designed for sustain release; one layer for immediate release of the drug and second layer for extended release, thus maintaining a prolonged blood serum level.
- The weight of each layer can be accurately controlled, in contrast to putting one drug of a combination product in a sugar coating.
- Monograms and other distinctive markings may be impressed on the surfaces of the multi-layer tablets.
- Analytical work may be simplified by separating of the layers prior to assay.
- They are used as an extension of a conventional technology.
- Bi-layer execution with optional single layer conversion kit.
- Low cost compared to other dosage forms.
- Greatest chemical and microbial stability compared to other oral dosage forms.
- Objectionable odor and taste can be masked by coating technologies.
- Bi-layer tablets can be designed in such a manner as to modify release as either of the layers can be kept as extended and the other as immediate release[3].

### 1.2 Ideal Characteristics of Bilayer Tablet

- It should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.
- It should have graceful product identity, free of defects like chips, cracks, discoloration and contamination.
- Must have a chemical stability shelf life, so as not to follow alteration of the medicinal agents.
- The bilayer tablet must release drug in a expectable and reproducible manner[4].

## 2 VARIOUS APPROACHES OF BILAYER TABLETS

### 2.1 Floating Drug Delivery System

They are designed to have a low density and thus float on the gastric contents after administration until the system either disintegrates or the device absorbs fluid to the point where its density is such that it loses buoyancy and can pass more easily from the stomach with a wave of motility responsible for gastric emptying. The bi-layer tablet is designed in such way that, one layer gives immediate dosing of the drug which gives faster onset of action while other layer is designed as a floating layer which forms a gastro retentive system[5].

### 2.2 Intra Gastric Bilayer Floating Tablets

These are also compressed tablet as contain two layers i.e.

- Immediate release layer
- Sustained release layer

### 2.3 Multiple Unit Type Floating Pills

These systems consist of sustained release pills as ‘seeds’ surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density6.

### 2.4 Polymeric Bio Adhesive System

These are designed to imbibe fluid flowing administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened. These are prepared as a one layer with immediate dosing and other layer with bio adhesive property[7].

### 2.5 Swelling System

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g. less than approximately 23 mm long and less than 11 mm wide for an oval or capsule-shaped tablet whereas 10-12 mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles enables it to leave stomach. The simple bi-layer tablet may contain an immediate release layer with the other layer as extended release or conventional release or both as controlled release layer[8].

## 3 METHODOLOGY

### 3.1 Characterization of Drugs

*3.1.1 Melting point*

The drug was inserted in a capillary tube and placed in a melting point equipment to visually see the melting Temprature melting temperature range across which it melts which is 154ºC

*3.1.2 Dose calculation*

For sustained drug release up to 12 hours, the immediate dose of drug was calculated from total dose of vildagliptin extended release tablet, which is 50 mg. According pharmacokinetic data[9].

Dt = Dose (1 + 0.693 × t/t $_{1/2}$) Where, Dt = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, $t_{1/2}$ = Half-life of drug. Half-life of vildagliptin is 2 hr.

Like, Vildagliptin: 100 = Dose [1+ (0.693 ×12)/2)], Dose = 19.38 mg vildagliptin. According to dose calculation, IR dose of drug can be taken 19.38 mg vildagliptin for the preparation of bilayer tablets; thus 19.38 mg g of vildagliptin was taken in IR layer and 80.62 mg of vildagliptin was taken in SR layers.

### 3.2 Formulation of Vildagliptin Bilayer Sustained Release Matrix Tablet

Bilayer matrix tablets of vildagliptin contained two types of granules *i.e.* first layer consists of the optimized immediate release tablet granules and second layer, the sustained release layer. Based on the different concentration of superdisintegrants (Polyplasdone XL, pregelatinized starch and Sodium starch glycolate), different immediate release formulations were prepared. The sustained release layers were prepared by using different proportion of hydrophilic polymer (HPMC K15M) and hydrophobic polymer (Eudragit RSPO ). Wet granulation methods were adopted for the preparation of both immediate release and sustained release layer granules. Accurate quantities of all ingredients except magnesium stearate and talc were weighed and passed through sieve no #80 previously their use in formulations. A lump wet mass was produced by adding appropriate quantity of PVP as granulating agent. The lumps developed were initially dried for 5 to 10 minutes to cut down moisture level that is required to avoid sticking with sieves. The lumps were then passed through sieve # 20 to get wet granules. The granules were dried in a hot air oven maintaining temperature at 40$^{o}$C for 20 minutes to reduce moisture content upto 2-5%. The dry granules were blended with magnesium stearate and talc for 2 to 3 minutes. After lubrication with magnesium stearate and talc; the granules of both the layer were subjected to evaluation of precompression parameters *i.e*. angle of repose, bulk and tapped density, Carr's index and Hausner's ratio; preceding compression[10].

The evaluated immediate release and sustained release layer granule were compressed into bilayer tablets on a 10-station rotary bilayer tablet punching machine using 16 mm concave punches. For preparation of immediate release tablets single punch machine with 12 mm concave punches was used. All the tablets were stored in airtight packages for further study. The processed bilayer tablet was evaluated for various post compression characterizations such as average thickness, weight variation, hardness, friability, drug content study and *in vitro* dissolution studies.

Table –1: Formulation of immediate release layer

| CONTENTS | IR1 | IR2 | IR 3 | IR 4 | IR 5 | IR 6 | IR 7 | IR 8 | IR 9 |
|---|---|---|---|---|---|---|---|---|---|
| Vildagliptin | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| SSG | 4 | 8 | 12 | - | - | - | - | - | - |
| Polyplasdone XL | - | - | - | 4 | 8 | 12 | - | - | - |
| Pregelatinized starch | - | - | - | - | - | - | 4 | 8 | 12 |
| PVP-K 30 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Microcrystalline cellulose | 27 | 23 | 19 | 27 | 23 | 19 | 27 | 23 | 19 |
| Mg stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

Table – 2: Formulation of bilayered floating tablets

| CONTENTS | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| IR3 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 | 70 |
| Vildagliptin | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 | 80 |
| HPC | 60 | 70 | 80 | - | - | - | 50 | - | 50 |
| HPMC K 15M | - | - | - | 60 | 70 | 80 | - | 50 | 50 |
| Eudragit RSPO | - | - | - | - | - | - | 50 | 50 | - |
| NaHCO3 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| PVP K 30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Mg stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Dicalcium phosphate | 45 | 35 | 25 | 45 | 35 | 25 | 5 | 5 | 5 |
| Total(mg) | 350 | 350 | 350 | 350 | 350 | 350 | 350 | 350 | 350 |

### 3.3 Evaluation of Precompression Parameters

Table – 3: Precompression parameters of powder blend

| Batch Code | Bulk density (gm/cc) | | Tap density (gm/cc) | | Hausner's Ratio | | Compressibiliy Index | | Angle of Repose | |
|---|---|---|---|---|---|---|---|---|---|---|
| | IR | Sustain | IR | Sustain | IR | Sustain | IR | Sustain | IR | Sustain |
| **F1** | 0.5 | 0.5 | 0.6 | 0.6 | 1.1 | 1.1 | 13.2 | 13.3 | 28.3 | 22.2 |
| **F2** | 0.5 | 0.4 | 0.6 | 0.5 | 1.1 | 1.2 | 15.3 | 19.2 | 30.4 | 24.2 |
| **F3** | 0.6 | 0.4 | 0.7 | 0.5 | 1.2 | 1.0 | 18.7 | 18.7 | 29.0 | 27.0 |
| **F4** | 0.5 | 0.5 | 0.6 | 0.5 | 1.1 | 1.0 | 16.0 | 8.7 | 32.8 | 24.2 |
| **F5** | 0.5 | 0.4 | 0.6 | 0.5 | 1.7 | 1.1 | 14.8 | 14.8 | 31.2 | 28.3 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **F6** | 0.5 | 0.4 | 0.6 | 0.5 | 1.1 | 1.2 | 12.6 | 18.0 | 29.7 | 27.0 |
| **F7** | 0.5 | 0.5 | 0.6 | 0.6 | 1.2 | 1.1 | 17.3 | 9.5 | 32.0 | 31.3 |
| **F8** | 0.5 | 0.4 | 0.6 | 0.6 | 1.1 | 1.5 | 15.7 | 30.1 | 29.0 | 25.6 |
| **F9** | 0.5 | 0.5 | 0.6 | 0.5 | 1.1 | 1.0 | 13.7 | 8.7 | 33.6 | 24.2 |

## 3.4 Post Compression Evaluation of Formulations

3.4.1 *In vitro disintegration test for immediate release tablets*

According to USP, the disintegration apparatus for oral immediate release tablets is used without the covering plastic disks. A time period of 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements whereas < 2 min for immediate release dosage form. The test was performed using tablet disintegration apparatus. In vitro disintegration tests were performed using an altered disintegration method (n = 6) with disintegration test apparatus maintained at $37^0$C ± $0.5^0$C in HCl buffer pH 1.2. The tablets were positioned in the basket and the time taken for the tablet to disintegrate completely into smaller particles was noted. Wetting time and water absorption ratio for immediate release formulations[11]

*3.4.2 Wetting time and water absorption ratio for immediate release formulations*

Wetting time of the immediate release tablet formulations reflects the disintegration process. Lesser the wetting time of the tablet, more is the disintegration rate. For the determination of wetting time, tissue paper was twice folded and placed in a petri dish with an internal diameter of 6.5 cm containing 10 ml of HCl buffer pH 1.2 with 0.1% w/v methylene blue. A tablet from each formulation of immediate release tablets was carefully placed on the surface of the tissue paper in the petri dish. The time required for the dye under study to reach the upper surface of the tablet was recorded as wetting time of the immediate release tablets. Measurements were carried out in triplicate and mean with standard deviations were also determined[12,13].

Water absorption ratio (R) is also another property of immediate release tablets that directly affects disintegration time. It can be estimated by simple procedure that includes weighing ($W_b$) of the tablet prior to the placing it on the petri dish that contained dissolution fluid under study. Then after recording the wetting time, the wetted tablet was taken out, blotted in a tissue paper and reweighed ($W_a$).

*3.4.3 Disintegration time determination*

Table-4: Disintegration time of immediate release formulations

| **Batch code** | **IR1** | **IR2** | **IR3** | **IR4** | **IR5** | **IR6** | **IR7** | **IR8** | **IR9** |
|---|---|---|---|---|---|---|---|---|---|
| **Disintegration time (min)** | 3.25 | 2.75 | 1.30 | 3.55 | 2.54 | 2.10 | 4.45 | 3.56 | 2.26 |

3.4.4 *Determination of wetting time and water absorption ratio*

Table-5: Evaluation of Wetting time and Water absorption ratio

| **F. code** | **Wetting time (sec)** | **Water absorption ratio** |
|---|---|---|
| **IR1** | 60±0.25 | 25.52±0.34 |
| **IR 2** | 42±0.36 | 32.46±0.30 |
| **IR 3** | 28±0.42 | 35.18±0.54 |
| **IR 4** | 89±0.32 | 18.38±0.42 |
| **IR 5** | 76±0.37 | 22.35±0.35 |
| **IR 6** | 44±0.36 | 29.39±0.27 |
| **IR 7** | 60±0.62 | 17.45±0.38 |
| **IR 8** | 50±0.41 | 25.29±0.51 |
| **IR 9** | 38±0.45 | 30.43±0.39 |

*3.4.5 Post compression parameters*

In the evaluation of prepared tablet hardness was found to be in the range of 6 to 7kgs/$cm^2$. Where as friability was with in limits for all the formulation (0.4%-0.5%) and other parameters like thickness, weight variation, drug content were found to be in limits[14].

Table-6: Post-compression parameters of bilayer tablets

| **Batch Code** | **Thickness (mm)** | **Hardness (kg/cm3)** | **Friability (%)** | **Weight variation (mg)** | **Drug content (%)** |
|---|---|---|---|---|---|
| **F1** | 6.12± 0.12 | 6.57± 0.12 | 0.44 | 351.47± 0.81 | 99.21 |
| **F2** | 6.05± 0.11 | 6.42± 0.32 | 0.46 | 351.07± 0.51 | 99.38 |
| **F3** | 6.11± 0.15 | 6.35± 0.42 | 0.45 | 349.87± 0.75 | 99.21 |
| **F4** | 6.10± 0.14 | 6.75± 0.22 | 0.41 | 351.48± 0.56 | 99.56 |
| **F5** | 6.11± 0.12 | 6.77± 0.15 | 0.43 | 354.47± 0.56 | 101.11 |
| **F6** | 6.06± 0.13 | 6.80± 0.85 | 0.45 | 353.77± 0.45 | 98.51 |
| **F7** | 6.08± 0.14 | 6.56± 0.52 | 0.42 | 352.07± 0.55 | 99.11 |
| **F8** | 6.07± 0.16 | 6.87± 0.42 | 0.42 | 350.57± 0.71 | 100.53 |
| **F9** | 6.11± 0.17 | 6.88± 0.52 | 0.41 | 355.47± 0.81 | 97.11 |

### 3.5 *In Vitro* Buoyancy Studies for Vildagliptin Bilayer Floating Matrix Tablets

In vitro buoyancy studies were determined to verify the residence time of the formulations in the gastric fluid by the mechanism of floating. In these formulations, the mechanism of floating is due to effervescence of $CO_2$ gas by reaction between sodium bicarbonate that is present in the formulations and secreted hydrochloric acid in the stomach. The prepared bilayer floating tablets were placed in a 250 ml beaker maintaining temperature at 37±0.5 $^0$C containing 200ml of HCl buffer pH1.2. The time needed for the tablet to ascent to the surface for floating was determined as the floating lag time whereas the total time period of floating of all tablets was determined as floating duration. These two properties were noticed by visual observation[15,17].

*3.5.1 In vitro buoyancy studies*

Table-7: Evaluation of floating lag time and total floating time

| Batch Code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Floating lag time(Sec) | 48 | 45 | 42 | 55 | 51 | 52 | 40 | 39 | 41 |
| Total Floating time (hrs) | >12 | >12 | >12 | >12 | >12 | >12 | >12 | >12 | >12 |

*3.5.2 In vitro drug release study*

Dissolution studies are prerequisite process for the determination of *in vitro* release profile for tablet formulations. The *in vitro* release studies were carried out for all the tablet formulations by using an eight station dissolution test apparatus USP type-II maintained temperature at 37 ± 0.5ºC. Different types of dissolution media were used for different formulations under study.

For the *in vitro* release studies of vildagliptin bilayer tablets, a proper simulation of gastrointestinal (GIT) condition was maintained by altering the pH of dissolution medium at different time intervals succeeding two step dissolution conditions. To simulate the physiological conditions of GIT, the dissolution was conducted in 900 ml of HCl buffer (0.1N HCl, pH 1.2) At each hourly interval, the aliquots were withdrawn and analyzed for drug using the UV-Visible After each sampling, an equal volume of fresh dissolution fluid was replaced to the dissolution medium. Furthermore for the studies of dissolution profiles of drug immediate release tablets, HCl buffer (0.1N HCl, pH 1.2) was used as dissolution medium. The study was performed in triplicate and the results were expressed as mean with standard deviation. The *in vitro* release studies of drug immediate release and bilayer sustained release floating matrix tablets were performed using 900 ml of HCl buffer pH1.2 as dissolution medium with rotation speed of 50 rpm. At regular interval of time, 5 ml of the samples were withdrawn and replaced with an equal volume of fresh buffer. The drug released at each hourly interval was measured using an UV- visible spectrophotometer at 224 nm after suitable dilution. The study was performed in triplicate and the results were expressed as mean with standard deviation[18-20].

Table-8: *In vitro* % Cumulative drug release (F1-F9)

| Time in hrs | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0.25 | 18.21 | 19.45 | 18.26 | 17.98 | 18.65 | 16.97 | 18.72 | 19.44 | 18.26 |
| 0.50 | 25.64 | 27.35 | 24.64 | 26.24 | 25.65 | 27.34 | 25.31 | 26.87 | 25.35 |
| 1 | 33.54 | 50.65 | 39.16 | 38.47 | 35.54 | 31.94 | 38.47 | 34.21 | 51.48 |
| 2 | 38.48 | 60.48 | 53.75 | 47.69 | 45.44 | 39.19 | 47.69 | 46.66 | 60.12 |
| 3 | 42.16 | 67.18 | 62.64 | 58.13 | 52.68 | 47.72 | 58.23 | 58.13 | 67.29 |
| 4 | 48.59 | 75.21 | 70.33 | 66.51 | 64.60 | 53.14 | 66.12 | 69.24 | 72.64 |
| 5 | 58.64 | 79.57 | 77.33 | 72.30 | 71.08 | 66.54 | 72.30 | 77.56 | 75.68 |
| 6 | 67.54 | 83.79 | 79.32 | 81.04 | 76.87 | 70.25 | 81.14 | 81.22 | 81.99 |
| 7 | 76.48 | 87.61 | 83.47 | 85.80 | 79.38 | 75.96 | 85.80 | 88.24 | 84.64 |
| 8 | 85.67 | 89.59 | 84.25 | 89.01 | 81.20 | 78.72 | 89.01 | 90.56 | 86.88 |
| 9 | 88.64 | 90.44 | 87.39 | 91.54 | 83.89 | 84.12 | 91.54 | 92.45 | 87.65 |
| 10 | 94.34 | 91.75 | 88.70 | 93.71 | 85.87 | 86.33 | 93.74 | 94.53 | 89.79 |
| 11 | 95.45 | 93.88 | 90.10 | 94.59 | 88.54 | 87.24 | 94.65 | 96.47 | 91.67 |
| 12 | 96.23 | 94.44 | 91.10 | 96.56 | 89.45 | 88.79 | 95.45 | 99.57 | 91.88 |

## 4 CONCLUSIONS

In the present investigations, bilayer floating matrix tablets of vildagliptin were successfully developed. The main objective of using hydrophobic polymer Eudragit with HPMC was to prevent initial burst release of the hydrophilic drug under study with hydrophilic polymer like HPMC which was successfully developed. The Sodium bicarbonate was added as a gas generating agent to promote the floating capacity of tablet which reduces the floating lag time and increase the floating time more than 12 hours. Thus the results of the current study clearly indicated that the vildagliptin bilayer floating tablet under present investigation has a promising potential as dosage form and can be used as an alternative to the available marketed conventional dosage form as it released an initial loading dose followed by maintenance dose in a prolonged release manner for better therapeutic benefits.

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