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# In vivo evaluation of glyburide extended release trilayer matrix tablets by geomatrix

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## ABSTRACT

The aim of the present investigation is to design and evaluate the controlled release Glyburide trilayer matrix tablets, to achieve zero-order drug release for sustained plasma concentration.

Matrix tablets were prepared by direct compression whereas three-layer tablets were prepared by compressing polymer barrier layers on both sides of the core containing the drug. Formulations were prepared by using different grades of hydroxy propyl methyl cellulose and Ethyl cellulose. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF16 was found to be optimized formulation. In vivo bioavailability studies were carried out on the optimized formulation (HF16), mean time to attain peak drug concentration ($T_{max}$) was 6.01±0.04 and 4.00±0.01h for the optimized and marketed product respectively, while mean maximum drug concentration ($C_{max}$) was 7.21±0.03 ng/ml and 5.00±0.01 ng/ml respectively. $AUC_{0-\alpha}$ and $AUC_{0-t}$ for optimized formulation was significantly higher ($p<0.05$) as compared to marketed product. A fair correlation between the dissolution profile and bioavailability for the optimized formulation was observed. The results indicate that the approach used could lead to a successful development of a controlled release formulation of the drug. The HF16 was shown significant plasma concentration with controlled release and maintained for 24 hrs with patient compliance by reducing the dosage frequency, when compared with marketed product in the efficient management of Diabetes mellitus.

**Keywords:** Glyburide, Trilayer matrix tablets, Type II Diabetes, HPMC, Bioavailability studies.

## INTRODUCTION

Conventional oral dosage forms such as tablets and capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability [1]. Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration and flexibility in the design of the dosage form. There are many ways to design modified release dosage forms for oral administration and one of them is multi layered matrix tablet [2]. A multi-layer system consists, usually, of a hydrophilic matrix

core containing the active ingredient and one or two impermeable or semipermeable polymeric coatings (barrier-layer) applied on one or both faces of the core during tableting [3, 4].

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Hydrophilic polymers have been given considerable attention in the formulation of controlled release drug delivery systems for various drugs. HPC, HPMC and sodium CMC & Carbopol are a few representative examples of the hydrophilic polymers that have been extensively used in the formulation of controlled release systems [5].

### Geomatrix technology

There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix. The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release [6].

Glyburide is a second-generation sulfonyl urea that is an orally bioavailable hypoglycaemic agent used in the management of type 2 diabetes. Different research has reported that glyburide has a low bioavailability, which is attributed to its poor dissolution properties. It has short half-life of 4-6 hours. Glyburide in oral conventional dosage form has the dosage regime of three times a day due to having short elimination half-life of 5 hour. Controlled release concept and technology has received increasing attention in the face of growing awareness to toxicity and ineffectiveness of drugs. When drugs are administered as conventional dosage forms such as tablets, capsules etc. usually produce wide ranging fluctuations in drug concentration in the blood stream and tissues and consequently undesirable toxicity and efficiency [7]. Thus, this study was undertaken to develop controlled release trilayer matrix tablets of Glyburide using release retardant and HPMC polymers upto 24h.

## MATERIALS AND METHODS

### Materials

Glyburide pure drug was generous gift from Aurobindo Pharma Ltd., Hyderabad. Sodium carboxyl methyl cellulose, Ethyl cellulose, HPMC K 4 M, HPMC K 15 M & HPMC K 100 M was obtained from Rubicon labs, Mumbai. Carbopol-934P was obtained from Hetero health care, India. Karaya Gum was obtained from Nutriroma, Hyderabad. Magnesium stearate, Talc, Dibasic calcium phosphate was obtained from S D Fine - Chem Ltd, Mumbai. All other chemicals used were of analytical grade.

## METHODS

### Micromeretic Studies of Glyburide

Angle of Repose [8], Carr's compressibility Index [9], Bulk Dentistry [10], Tapped Density [11], Hausner Ratio.

### Formulation of controlled release Glyburide Trilayer matrix tablets

The Trilayer matrix tablets of Glyburide were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90% drug release during 12hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) to continue the drug release for 24 h.

### Preparation of middle active layer

Sixteen formulations (F1-F16) for active layer were prepared by direct compression method using polymers like different HPMC grades, Sodium CMC and Ethyl Cellulose. All the formulations were varied in concentration of polymers, talc (1.5mg) & magnesium stearate (1.5mg) constituted in all the formulations. These materials were screened through ≠60 and mixed together in motor by using pestle. Final mixtures were compressed by using 11mm diameter flat punches on a sixteen-station rotary tablet press. Formulation of active layer was depicted in Table 1, 2. The prepared tablets were subjected to dissolution studies.

### Preparation of upper and lower layers

The barrier layers were formulated employing hydrophobic swellable polymer natural wax i.e. Carbopol-934P the swelling erosion modelling fillers which include water soluble DCP, EC and Gum Karaya. The procedure tried to make the compacts was via direct compressions. For the first procedure the wax, Gum Karaya and the filler was mixed in mortar and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted in Table 1, 2.

### Formulation of Glyburide Trilayer tablets

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortar and pestle for about 20 minutes. Initially, the volume of die cavity; (12mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (600mg). Then the pre-weighed amount of powder equivalent to bottom layer (125mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted and 100mg of the drug containing middle active layer optimized formulation (F16) was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre-weighed (125mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test.

### Evaluation of Trilayer matrix tablets of Glyburide

Hardness [12], Friability [13], Weight variation [14], Drug content / Assay [15].

### *In-vitro* drug release profile

In vitro drug release studies for developed Trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900ml Phosphate buffer pH 6.8 at 37± $0.5^0$C temperature. The amount of drug release was determined by UV visible spectrophotometer (Shimadzu UV 1800) at 242nm.

## DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared Spectroscopy (FTIR) and Differential Scanning Calorimetry (DSC) [17]

### Stability studies

The stability study of the formulated Trilayer tablets were carried out under different conditions according to ICH guidelines using stability chamber (REMI make). Accelerated Stability studies were carried out at 40 $^0$C / 75 % RH for the best formulations for 6 months. The tablets were characterized for the hardness, friability, drug content and cumulative % drug released during the stability study period.

### Pharmacokinetic studies of Glyburide

### Animal Preparation

Male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature $25^0$C, Relative Humidity 45% and 12 h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee (**IAEC NO: P44/VCP/IAEC/2015/10/DBP/AE12/Rabbits).**

### *In vivo* study design

The rabbits were randomly divided into two groups each group contains three animals. The group A was received prepared Glyburide matrix tablets (5 mg), marketed product (5 mg) was administered group B with equivalent dose of animal body weight. Blood samples (approximately 0.5ml) were obtained with syringes by marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24hrs post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000 rpm in cooling centrifuge for 5min to 10 minutes and stored frozen at −20°C until analysis.

## HPLC study

For HPLC C18 column with 5 µm particle size and the mobile phase consisting of a combination of acetonitrile and 25mM monobasic potassium dihydrogen orthophosphate (pH 3.5 adjusted with phosphoric acid) at 60:40 v/v the flow rate was 0.5 ml/min and the detection wavelength was 253nm nm. Internal standard glibenclamide was used. The retention time was Glyburide and glibenclamide were 4.7 and 8.23h respectively [18].

## Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature.

## Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration ($C_{max}$), time to attain $C_{max}$ i.e., $T_{max}$ and $t_{½}$ values, area under plasma concentration–time curve from zero to the last sampling time ($AUC_{0-t}$), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). $AUC_{0-t}$ was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$$\mathbf{AUC_{0-\infty} = AUC_{0-t} + C_t / K_E}$$

# RESULTS AND DISCUSSION

## Pre-compression parameters

All the powder mixture belonging to different formulations was tested for micrometrics studies in order to determine the flow properties. All the formulations AF16 to HF16 showed good flow properties, the results are summarized in Table 5.

## Preparation of middle active layer

The matrix tablets of Glyburide were prepared without the barrier layers. All the formulation trails were subjected to *in vitro* dissolution to determine the release profiles.

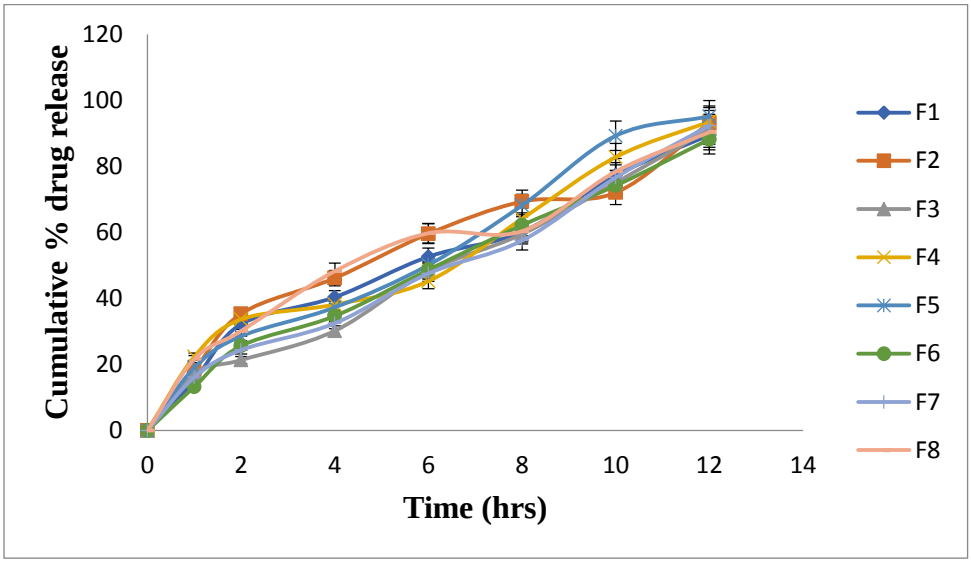


**Figure 1: *In vitro* Dissolution profile of F1-F8 Glyburide active layer formulations**

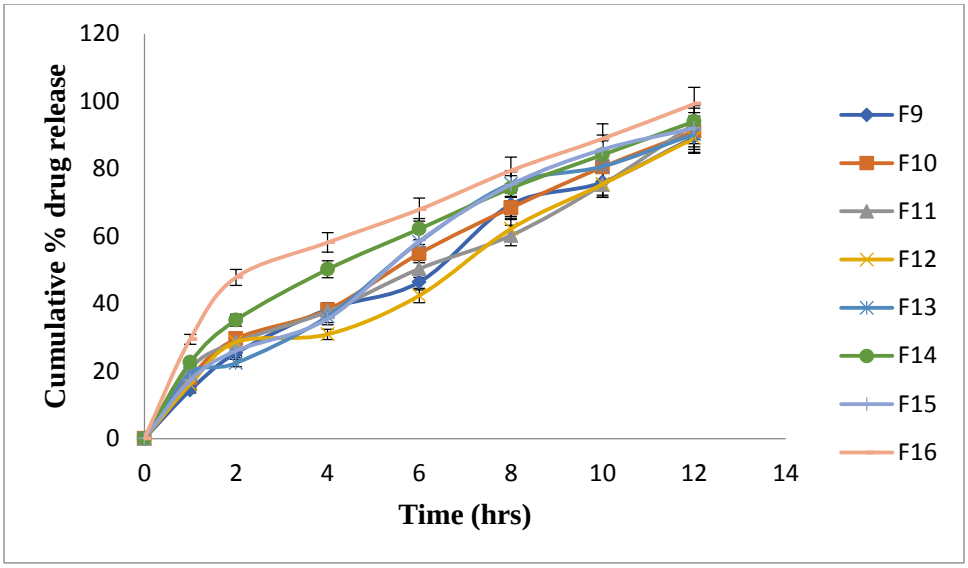


**Figure 2: *In vitro* Dissolution profile of F9-F16 Glyburideactive layer formulations**

From the above results, among all the formulations the formulation F16 was decided as optimized formulation for active layer based on the highest drug release i.e. 99.24±5.25 within 12hrs when compared with other preparations (Tables 3,4; Figures 1,2). Formulation F16 was chosen as active layer for further studies.

## Evaluation of Trilayer matrix tablets of Glyburide

**Figure 3: Glyburide Trilayer matrix tablets**

The Glyburide Trilayer matrix tablets are shown in Figure 3. Sustained release tablets generally have hardness in the range of 7-10 kg/cm$^2$. In case of Trilayer tablets the hardness of the tablets was found to be 7.2 to 8.4 kg/cm$^2$. The friability of the formulations was found to be less than 1% and hence the tablets with lower friability may not break during handling on machines and or shipping. All the batches of the tablets complied with the weight variation limits as per the IP. The drug content in different formulation was highly uniform and the results are depicted in Table 9. In phosphate buffer pH 6.8, HPMC showed good swelling property. In Trilayer tablets of Glyburide, HF16 showed highest degree of swelling index

209.11%, where as in AH16 showed leased swelling with a swelling index of 126.99%.

### *In vitro* dissolution studies of Glyburide Trilayer tablets

The release of Glyburide from different formulations was carried out in phosphate buffer pH 6.8 and the results are depicted in Table 7. The Trilayer tablets extended the drug release up to 24 hrs. The highest drug release was found in the formulation HF16 i.e. 99.26 % within 24 h. HF16 was found to be optimized formulation based on the dissolution and other evaluation parameters. The results are shown in Table 6. The comparison of marketed product and optimized formulation HF16 was shown in figure 4. The drug release from marketed product was 94.21% within 24hrs.

### *In vitro* dissolution studies of Glyburide Trilayer tablets formulated in different trails

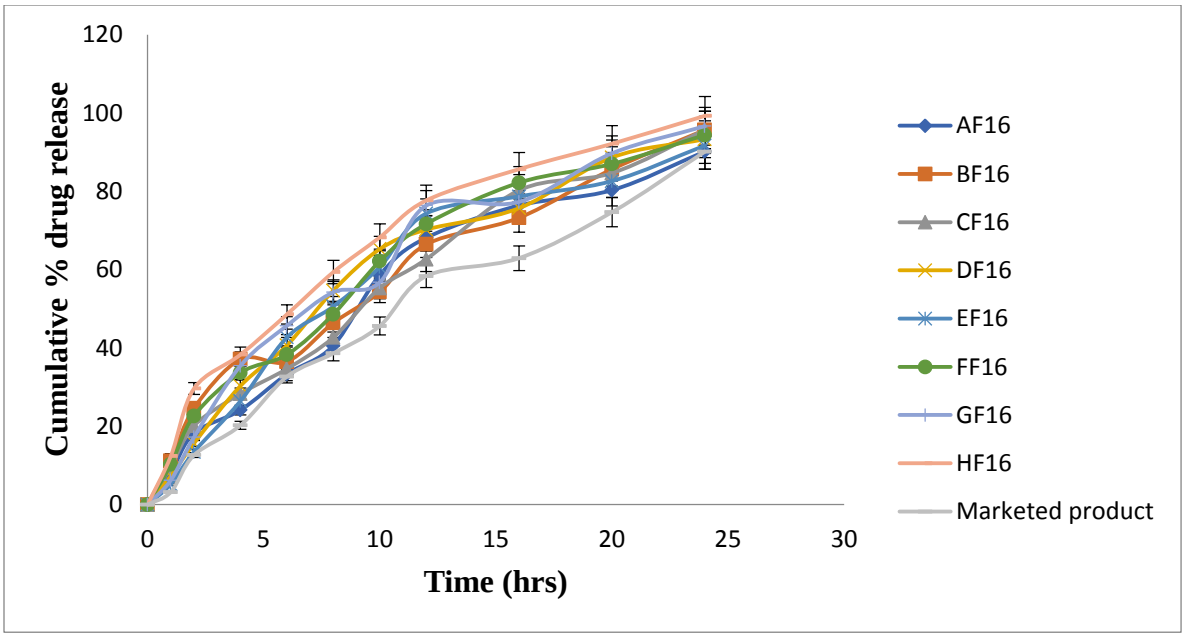


**Figure 4: *In vitro* dissolution studies of AF16-HF17**

## CHARECTERIZATION

### FT-IR studies

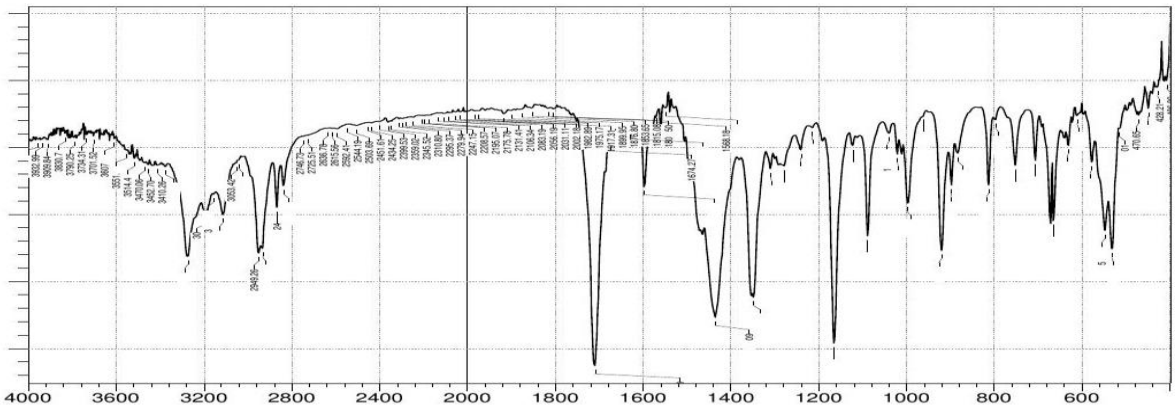


**Figure 7: FT-IR spectrum of pure drug Glyburide**

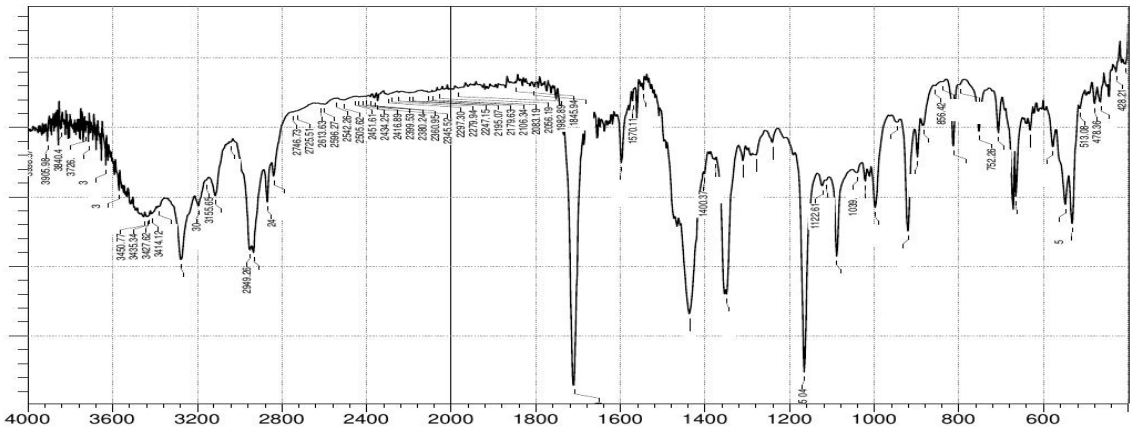


**Figure 8: FT-IR spectrum of Glyburide and other polymers**

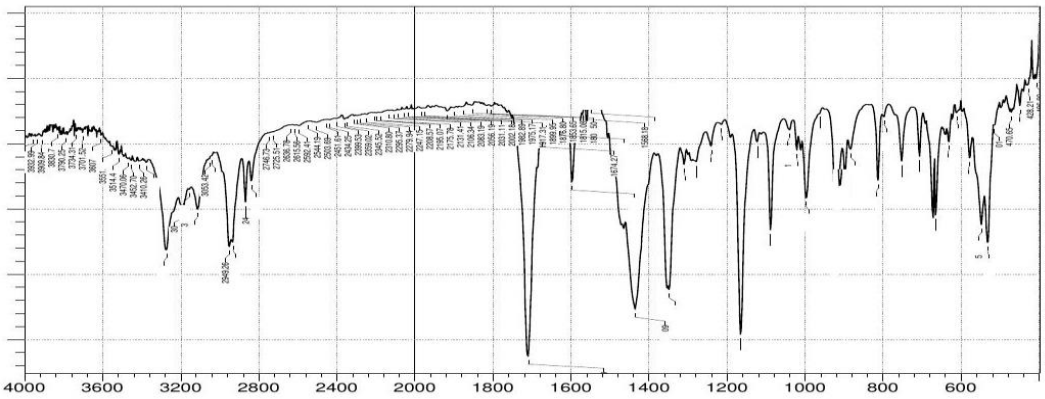


**Figure 9: FT-IR spectrum of** Glyburide **optimized formulation HF16**

There was no alteration in peaks of Glyburide pure drug (**Figure 7**) and optimized formulation (**Figure 9**), suggesting that there was no interaction between drug & excipients. FT-IR spectrum of pure drug and other polymers are shown in **(Figure 8)**. There are additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug, indicating absence of any interaction.

## DSC studies

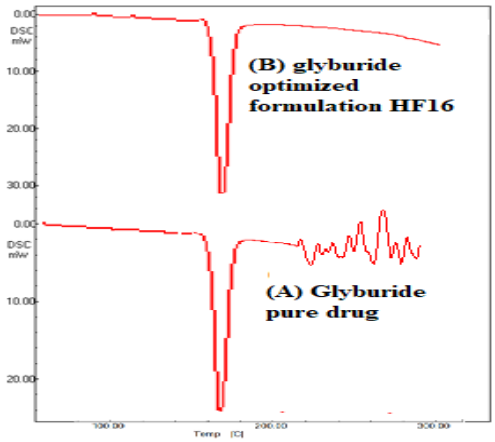


**Figure 10: DSC thermogram of Glyburide pure drug (A) and optimized formulatin HF16 (B)**

DSC was used to detect interaction between Glyburide and excipients. The thermogram of Glyburide exhibited a sharp endotherm melting point at 169 $^0$C. The thermogram of optimized formulation of Glyburide exhibited a sharp endotherm melting point at 172 $^0$C. The DSC thermogram retained properties of Glyburide, as well as polymer properties. There is no considerable change observed in melting endotherm of drug in optimized formulation (**Figure 10**). It indicates that there is no interaction between drug & excipients used in the formulation.

## STABILITY STUDIES

The optimized trilayer matrix tablets (HF16) formulation was subjected to stability studies for 6 months to evaluate its stability and the integrity of the dosage form. There was no significant change observed in the friability, hardness, cumulative % drug content and in vitro drug release of HF16 at 40 $^0$C / 75 % RH for 6 months. The tablets were characterized for the hardness, friability, drug content and cumulative % drug released during the stability study period. From these results it was concluded that, optimized formulation was stable and retained their original properties with minor differences.

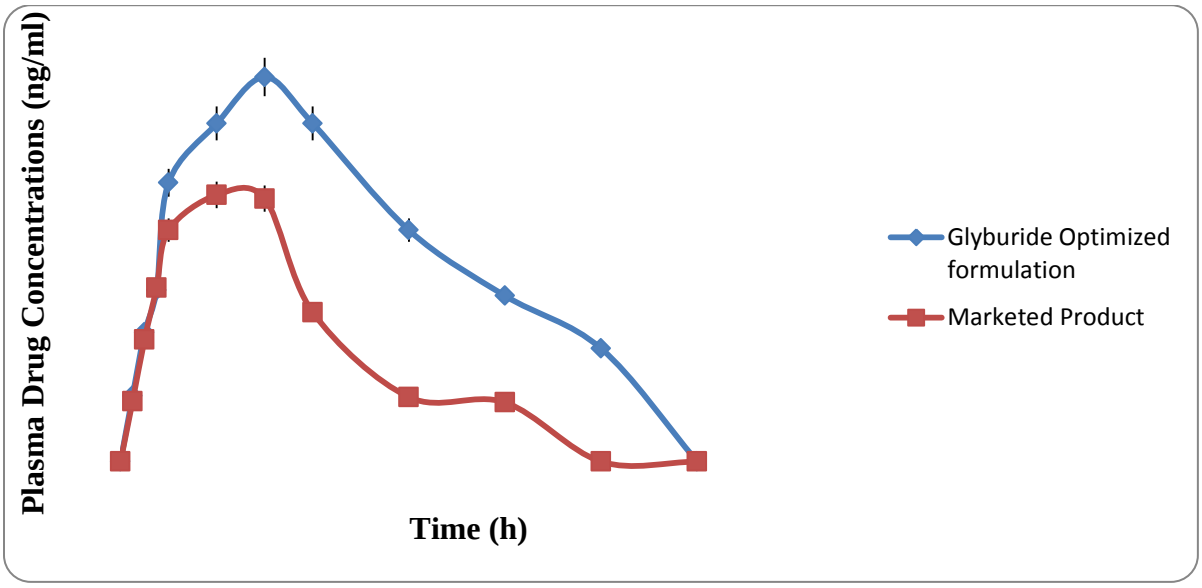


**Figure 11: Plasma Concentrations of Glyburide optimized formulation and Marketed Product at different time intervals**

### Bioavailability Parameters

Mean plasma concentration profiles of prepared Glyburide optimized formulation and Marketed product are presented in **Figure 11**. Glyburide optimized formulation exhibited as sustained release *in vivo* when compared with Marketed product. All the pharmacokinetics parameters displayed in **Table 10**. The release pattern of both marketed and test formulation showing sustained release pattern. The $T_{max}$ of the optimized formulation was (6.01±0.04h) and Marketed Product $T_{max}$ was (4.00±0.01h). This delayed absorption of test and marketed preparations most likely due to the sustained release of the drugs. On the other hand, the $C_{max}$ of reference formulation (5.00±0.01ng/ml) was significantly different from the test preparation (7.21±0.03ng/ml). However, the $AUC_{0-\infty}$ values for the two formulations were significantly different test formulation (55.12±0.02 ng h/ml) and marketed (45.18±0.02 ng h/ml). This suggests that the Glyburide contained in the test product was completely absorbed showing more bioavailability when compared with marketed Product.

**Table 1: Formulation trails for Glyburide middle active layer**

| INGREDIENTS (mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Glyburide | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| HPMC K 4M | 25 | 30 | 35 | --- | --- | ---- | ---- | ---- | ---- | 15 | 15 | 15 | ---- | ---- | ---- | ---- |
| HPMC K 15M | --- | ---- | ---- | 25 | 30 | 35 | ---- | ---- | ---- | 10 | 15 | 20 | ---- | ---- | ---- | ---- |
| HPMC K 100M | --- | --- | --- | ---- | --- | ---- | 25 | 30 | 35 | ----- | ---- | ---- | 25 | 30 | 35 | 40 |
| Gum Karaya | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| MCC | 30 | 25 | 20 | 30 | 25 | 20 | 30 | 25 | 20 | 30 | 25 | 20 | 30 | 25 | 20 | 15 |
| Dibasic calcium phosphate | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

**Table 2: Composition of Glyburide trilayer matrix tablet**

| INGREDIENTS | AF16 | BF16 | CF16 | DF16 | EF16 | FF16 | GF16 | HF16 |
|---|---|---|---|---|---|---|---|---|
| **MIDDILE ACTIVE LAYAER (F16) (mg)** | | | | | | | | |
| **Glyburide** | **5** | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| **HPMC K 100M** | **40** | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| **Gum Karaya** | **20** | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **MCC** | **15** | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| **Dibasic calcium phosphate** | **20** | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| **UPPER AND LOWER LAYER (mg)** | | | | | | | | |
| **Carbopol-934P** | 20 | 25 | 30 | 35 | 40 | 42.5 | 45 | 50 |
| **Ethyl cellulose** | 52 | 50 | 52 | 47 | 50 | 42.5 | 42 | 42 |
| **Dibasic calcium phosphate** | 50 | 47 | 40 | 40 | 32 | 35 | 35 | 30 |
| **Magnesium stearate** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| **Talc** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |

**Table 3: Dissolution profile of different formulations Glyburide active layer (F1-F8):**

| TIME (hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| 0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 |
| 1 | 15.08±0.95 | 22.04±1.32 | 14.09±0.93 | 17.28±0.95 | 19.34±0.99 | 20.24±1.30 | 18.93±0.99 | 21.32±0.94 |
| 2 | 24.17±1.35 | 31.15±2.09 | 27.25±1.35 | 24.16±1.35 | 30.28±2.09 | 32.28±2.02 | 29.05±2.08 | 28.05±1.89 |
| 4 | 35.36±2.05 | 46.20±2.50 | 40.32±2.46 | 42.05±2.46 | 46.17±2.51 | 44.16±2.50 | 43.36±2.46 | 46.45±2.49 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6 | 47.20±2.50 | 55.56±2.89 | 52.40±2.81 | 50.34±2.83 | 58.36±2.96 | 56.38±2.89 | 58.27±2.96 | 58.36±2.99 |
| 8 | 59.19±2.90 | 69.39±3.19 | 62.28±3.10 | 64.28±3.15 | 70.45±3.82 | 68.20±3.18 | 62.54±3.09 | 68.28±3.58 |
| 10 | 78.24±3.93 | 79.26±3.93 | 82.36±4.90 | 85.08±4.89 | 82.19±4.28 | 75.19±3.80 | 80.38±4.25 | 81.37±4.05 |
| 12 | 88.39±4.97 | 90.74±5.01 | 89.74±4.44 | 93.36±5.06 | 92.36±5.04 | 91.02±5.02 | 94.37±5.12 | 90.12±5.01 |

**Table 4: Dissolution profile of different formulations Glyburide active layer (F9-F16)**

| TIME (hrs.) | F9 | F10 | F11 | F12 | F13 | F14 | F15 | F16 |
|---|---|---|---|---|---|---|---|---|
| 0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | **0**±0 | 0±0 | 0±0 |
| 1 | 17.12±0.94 | 25.24±1.37 | 19.56±0.99 | 16.17±0.96 | 22.67±1.20 | 20.12±1.20 | 24.45±1.36 | 28.16±1.97 |
| 2 | 25.36±1.37 | 29.39±1.97 | 28.24±1.97 | 24.34±1.36 | 30.42±2.08 | 38.18±2.18 | 27.20±1.96 | 36.24±1.36 |
| 4 | 38.29±2.42 | 38.15±2.40 | 37.30±2.40 | 32.54±2.10 | 42.19±2.61 | 45.67±2.65 | 30.14±2.08 | 53.15±2.40 |
| 6 | 46.68±2.67 | 54.29±2.70 | 50.15±2.60 | 47.67±2.66 | 54.36±2.70 | 52.20±2.75 | 52.35±2.62 | 65.47±2.63 |
| 8 | 69.07±3.26 | 68.38±3.25 | 60.39±3.10 | 57.38±2.99 | 65.17±3.22 | 65.89±3.52 | 67.47±3.25 | 79.34±3.10 |
| 10 | 75.36±3.83 | 80.17±4.32 | 75.28±3.83 | 76.94±3.83 | 78.48±3.83 | 89.36±4.98 | 72.36±3.80 | 88.67±3.94 |
| 12 | 89.17±4.99 | 91.60±5.02 | 93.56±5.10 | 92.56±5.08 | 90.56±5.01 | 96.46±5.42 | 94.19±5.12 | 99.24±5.25 |

**Table 5: Powder flow properties of Glyburide, powder blends of active layer and barrier layer polymers**

| Powder properties | AF16 | BF16 | CF16 | DF16 | EF16 | FF16 | GF16 | HF16 |
|---|---|---|---|---|---|---|---|---|
| **Bulk density (g/cc)** | 0.7151±0.04 | 0.7121±0.46 | 0.512±0.02 | 0.7050±0.14 | 0.714±0.56 | 0.684±0.78 | 0.695±0.02 | 0.704±0.56 |
| **Tapped density(g/cc)** | 0.787±0.10 | 0.790±0.93 | 0.629±0.17 | 0.767±0.2 | 0.795±0.93 | 0.746±0.82 | 0.781±0.048 | 0.796±0.93 |
| **Angle of repose (o)** | 33.69±0.63 | 34.93±0.66 | 33.12±0.63 | 31.89±0.43 | 24.39±0.66 | 33.09±0.27 | 28.15±0.02 | 26.39±0.66 |
| **Carr's index** | 8.09±0.91 | 8.02±0.93 | 9.49±0.51 | 8.29±0.91 | 8.35±0.94 | 7.62±0.58 | 7.28±0.33 | 8.15±0.94 |

**Table 6: Physical evaluation of Trilayer tablets**

| Formulation code | Thickness (mm) | Hardness ($kg/cm^2$) | Friability (%) | Weight variation (mg) | % Drug content |
|---|---|---|---|---|---|
| **AF16** | 5.58 | 7.2±0.24 | 0.15 | 596±20 | 97.51 |
| **BF16** | 5.60 | 6.3±0.38 | 0.28 | 599±20 | 96.82 |
| **CF16** | 5.45 | 6.5±0.45 | 0.26 | 595±20 | 96.25 |
| **DF16** | 5.73 | 7.3±0.24 | 0.30 | 594±20 | 97.08 |
| **EF16** | 5.71 | 6.5±0.45 | 0.35 | 597±20 | 95.74 |
| **FF16** | 5.62 | 7.6±0.42 | 0.18 | 595±20 | 97.47 |
| **GF16** | 5.54 | 6.1±0.23 | 0.23 | 596±20 | 96.25 |
| **HF16** | 5.70 | 7.8±0.50 | 0.24 | 600±20 | 98.91 |

**Table 7: In-vitro dissolution studies of Glyburide Trilayer tablets:**

| TIME (hrs) | AF16 | BF16 | CF16 | DF16 | EF16 | FF16 | GF16 | HF16 | Marketed product |
|---|---|---|---|---|---|---|---|---|---|
| **0** | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 | 0±0 |
| **1** | 8.24±0.45 | 11.21±0.85 | 9.67±0.48 | 7.28±0.43 | 5.21±0.35 | 10.24±0.80 | 6.21±0.40 | 12.36±0.90 | 3.20±0.30 |
| **2** | 18.24±0.98 | 24.61±1.36 | 20.13±1.20 | 15.64±0.95 | 13.48±0.89 | 22.65±1.20 | 17.21±0.97 | 29.63±1.97 | 12.63±0.90 |
| **4** | 24.13±1.36 | 37.12±2.17 | 28.31±1.97 | 30.31±2.08 | 26.45±1.95 | 33.67±2.12 | 35.45±1.30 | 38.29±2.18 | 20.24±1.20 |
| **6** | 33.29±2.12 | 36.51±2.15 | 34.67±1.29 | 40.67±2.60 | 42.67±2.61 | 38.29±2.18 | 45.67±2.67 | 48.56±2.70 | 32.67±2.10 |
| **8** | 40.61±2.25 | 46.39±2.68 | 42.68±2.61 | 54.66±2.70 | 50.61±2.60 | 48.61±2.70 | 54.23±2.70 | 59.36±2.99 | 38.63±2.18 |
| **10** | 58.63±2.99 | 54.32±2.41 | 55.31±2.71 | 65.23±3.52 | 60.67±3.10 | 62.14±3.20 | 56.74±2.72 | 68.24±3.26 | 45.60±2.67 |
| **12** | 68.12±3.26 | 66.45±2.64 | 62.67±3.12 | 70.21±3.79 | 74.32±3.82 | 71.67±3.80 | 76.34±3.83 | 77.66±3.84 | 58.34±2.99 |
| **16** | 76.36±3.83 | 73.24±3.80 | 80.24±4.32 | 75.69±3.82 | 78.69±3.83 | 82.19±4.34 | 80.29±3.84 | 85.64±3.96 | 62.93±3.12 |
| **20** | 80.29±4.32 | 85.63±3.90 | 84.66±3.89 | 88.63±4.88 | 82.61±4.34 | 86.98±3.96 | 89.68±4.98 | 92.13±5.01 | 74.67±3.81 |
| **24** | 90.16±5.01 | 95.64±5.15 | 92.67±5.02 | 93.29±5.05 | 91.67±5.02 | 94.38±5.10 | 96.62±5.18 | 99.26±5.45 | 94.21±5.01 |

**Table 8: Release kinetics of innovator product with correlation coefficient**

| Formulation Code | Zero Order | | First Order | | Higuchi | | Korsmeyer-Peppas | |
|---|---|---|---|---|---|---|---|---|
| | $R^2$ | K | $R^2$ | K | $R^2$ | K | $R^2$ | N |
| HF16 | 0.9825 | 4.118 | 0.9302 | 0.0706 | 0.979 | 21.453 | 0.962 | 0.616 |
| Marketed product | 0.9612 | 3.1699 | 0.835 | 0.0652 | 0.948 | 15.753 | 0.833 | 0.638 |

**Table 9: Physico-chemical characteristics of optimized formulation HF16**

| Retest Time for optimized formulation (HF16) | Friability (%) | Hardness ($kg/cm^2$) | Drug content uniformity (%) ± SD | *In-vitro* drug release profile (%) |
|---|---|---|---|---|
| **0 days** | 0.24 | 7.8 | 98.91 | 99.26 |
| **30 days** | 0.23 | 7.2 | 97.56 | 98.85 |
| **60 days** | 0.21 | 6.9 | 97.05 | 98.02 |
| **120 days** | 0.20 | 6.1 | 96.24 | 97.56 |
| **180 days** | 0.19 | 5.7 | 95.01 | 97.05 |

**Table 10: Pharmacokinetic Parameters of Glyburide optimized formulation and marketed product**

| Parameters | Glyburide optimized formulation | Marketed product |
|---|---|---|
| **$C_{max}$ (ng/ml)** | 7.21±0.03 | 5.00±0.01 |
| **AUC $_{0-t}$ (ng h/ml)** | 36.12±0.01 | 30.19±0.01 |
| **$AUC_{0-\infty}$ (ng h/ml)** | 55.12±0.02 | 45.18±0.02 |
| **$T_{max}$ (h)** | 6.01±0.04 | 4.00±0.01 |
| **t $_{1/2}$ (h)** | 7.25±0.004 | 5.12±0.05 |

## CONCLUSION

It was concluded that Trilayer matrix tablets of Glyburide can be successfully prepared by direct compression technique using different polymers combination. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF16 was found to be optimized formulation. The drug release from HF16 was found to fit Zero order of concentration independent and best fitted to Higuchi's model confirming to be diffusion assisted mechanism. In vivo bioavailability studies were carried out on the optimized formulation (HF16), mean time to attain peak drug concentration ($T_{max}$) was 6.01±0.04 and 4.00±0.01h for the optimized and marketed product respectively, while mean maximum drug concentration ($C_{max}$) was 7.21±0.03 ng/ml and 5.00±0.01 ng/ml respectively. $AUC_{0-\alpha}$ and $AUC_{0-t}$ for optimized formulation was significantly higher ($p<0.05$) as compared to marketed product. A fair correlation between the dissolution profile and bioavailability for the optimized formulation was observed. The results indicate that the approach used could lead to a successful development of a controlled release formulation of the drug. The HF16 was shown significant plasma concentration with controlled release and maintained for 24 hrs with patient compliance by reducing the dosage frequency, when compared with marketed product in the efficient management of Diabetes mellitus.

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