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# FORMULATION AND DEVELOPMENT OF FLOATING DRUG DELIVERY SYSTEM OF METFORMIN HYDROCHLORIDE EXTENDED RELEASE AND GLIMEPIRIDE IMMEDIATE RELEASE INTO BILAYERED TABLET DOSAGE FORM: IN VITRO EVALUATION

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**ABSTRACT**

The purpose of the research work was formulation development and evaluation bi-layer floating tablets for metformin hydrochloride and glimepiride to improve the oral therapeutic efficacy Both these drugs exhibit pH dependent solubility and show good permeability from stomach and upper part of the small intestine into systemic circulation. Direct compression method form metformin hydrochloride layer and wet granulation method for glimepiride was used to formulate bi-layer floating tablets. The optimized formula F-5 of metformin layer exhibits float for more than 12 h and extend drug release above 12 h. Different grades of methocel (HPMC) was used as was used as drug release retarding agents in order to get the extended release profile of metformin hydrochloride over a period of 12 h. Glimepiride immediate release layer was formulation using different excipients. HPMC K100M based formulation 5 was showing drug release according to the USP specifications and was optimized and kept of stability studies. The drug release profiles at 1 month in 40◦C and 75%RH suggesting that In various invitro drug release kinetics studies Higuchi model was found to be the best fitted in all dissolution profile having higher correlation coefficient 0.995 followed by Peppas model and first order release, Slope of vergnaurd model obtained is 0.399. Indicates fickian diffusion and the rate of matrix erosion of metformin hydrochloride tablets were found to 0.062 /min from the tablets.

**Keywords**: Extended release, HPMC

## INTRODUCTION

It is a chronic metabolic disorder characterized by a high blood glucose concentration-hyperglycemia (fasting plasma glucose > 7.0 mmol/l or plasma glucose > 11.1 mmol/l 2 hours after a meal) – caused by insulin deficiency. Deficiency of insulin secretion resulting in hyperglycemia an increased blood sugar level. Hyperglycemia occurs because of uncontrolled hepatic glucose output and reduced uptake of glucose by skeletal system with reduces glucogen synthesis. One of the novel approaches in the area of oral sustained release drug delivery is gastroretentive drug delivery system (GRDDS). Drugs those are having a narrow absorption window and having more solubility in gastric region are suitable candidates for GRDDS[1]. Several techniques have been proposed to increases the gastric residence time of dosage forms such as buoyancy or floating system[2], hydro dynamically balanced system[3], expanding or swelling system, bio/mucoadhesive system[4], sedimentation or high density system, geometry or modified shape system may also use to increase gastric residence time. The biphasic system may contain one or two drugs for immediate release and sustained release layer. Literature showed that biphasic release tablets containing two drugs ketoprofen and Praziquantel[5].

The present work relates to the formulation and evaluation of bi-layer floating tablets having

immediate release layer and floating sustained release layer. These tablets showed biphasic drug release means immediate release layer releases drug immediately after contact with dissolution media this as a loading dose. Floating sustained release layer releases drug for prolong time as a maintenance dose. Due to prolong gastric retention of drug, it increases the solubility, bioavailability and reduces drug waste[6].The objective of this proposed research project was to develop a combination drug therapy for ant diabetic agents into bilayered tablet formulation having a synergetic action to complement each other and together effectively lower blood glucose level.

## MATERIALS AND METHODS

***Materials:*** Metformin hydrochloride Hydrochloride-Roquet and wan bury Ltd, Glimepiride - Glen mark, Goa, Micro crystalline cellulose 102-Fmc biopolymer, Micro crystalline cellulose 114 - Chigachi chemical, HPMC K 100 M-Colorcon, Mumbai, Iso propyl alcohol-Dr.Reddy's Lab's, HYD, Polysorbate 80-Reddy's Lab's, HYD, HPC-LF-Dr.Reddy's Lab's, HYD, Poloxamer-188- Basf, Sodium starch Glycolate- Dr.Reddy's Lab's, HYD, Povidone k 25- Isp international, Povidone k 90 D-Isp international, Flow lac 100-Sai mirra inno pharma, Chennai, Lactose-Dr.Reddy's Lab's, HYD, Lake of quinoline yellow ws-Roha dry chemical, Colloidial silicon-di-oxide-Cabot, Magnesium Stearate- Sai mirra inno pharma, Chennai, Meglumine-Merck, Mumbai, sodium bi carbonate, citric acid, Hyderabad, respectively.

***Methods:***

***Manufacturing of bilayered floating tablets:*** Bi-layer floating tablet contains two layers one immediate release layer of glimepiride and second sustained release layer of metformin hydrochloride. Accurately weighted 240 mg of glimepiride immediate release layer blend and 950 mg of metformin hydrochloride floating sustained release layer blend individually. Bilayered tablets were prepared using optimized formula 5 given in Table 1 and optimized formula 12 given in table 2.

Initially immediate release powder blend fed manually into the dies of 10 stations Rimek minipress-1 tablet machine and then compressed at low compression force to formed uniform layer of powder. Subsequently floating sustained release layer's powder blend was added over precompressed immediate release layer then increased compression force then compressed on 10 stations Rimek minipress-1 tablet machine.

***Evaluation of bi-layer floating tablets:*** Prepared bi-layer floating tablets were evaluated for hardness, friability, weight variation, thickness, floating lag time, and total floating time for floating sustained release layer.

***In vitro buoyancy lag time:*** Buoyancy lag time is the time required for the tablet to rise towards surface and float. The buoyancy of tablets was studied at 37 ± 0.5oC in 900 ml of 1.2 pH buffer (simulated gastric fluid without enzyme). The duration of buoyancy lag time was observed visually and record by using stop watch**.**

***In vitro drug release study:***

In vitro drug release study was performed using USP XXII paddle apparatus (Electrolab TDT- 08L plus, Dissolution tester USP Mumbai, India) at 100 rpm in simulated gastric fluid without enzyme of pH 1.2. Temperature was maintained at 37 ± 0.5oC. Sample 5ml was withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were filtered through membrane filter 0.45μm and analyzed by using UV spectrophotometer (UV Shimadzu 1700 Pharmaspec) at λmax 233 nm and 229 using blank in U.V spectroscopy for metformin hydrochloride and glimepiride. The cumulative percentage drug release was calculated and the release profile of metformin hydrochloride and glimepiride were compared with the specifications of drug release according to USP. This test was performed on 6 tablets and mean ± SD was calculated.

***Kinetics of in vitro drug release:***

To study the release kinetics in vitro drug release data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

***Zero order***

$C=K_O T$ (1)

Where K0 is the zero-order rate constant expressed in units of concentration/time and t is the time in h.

***First order***

LogC LogC Kt2.303 (2)

Where C is the concentration, C0 is the initial concentration of drug, k is the first order constant, and t is the time.

***Higuchi***

$Q_T = K^{1/2} T$ (3)

Where Qt is the amount of the release drug in time t, K is the kinetic constant and t is the

time in h.

***Korsmeyer Peppas***

$M_t / M_\alpha = K t^n$ (4)

Where Mt represents amount of the released drug at time t, M is the overall amount of the drug (whole dose) released after 12 h K is the diffusional characteristic of drug/polymer system constant and n is a diffusional or release exponent that characterizes the mechanism of release of drug.

The value of n indicates the drug release mechanism related to the geometrical shape of the delivery system, if the exponent n = 0.5, then the drug release mechanism is Fickian diffusion. If n < 0.5 the mechanism is quasi-Fickian diffusion, and 0.5 < n < 1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion, n> 1.0 mechanism is non Fickian super case II[7].

***Swelling behaviour and water uptake study:***

Swelling behaviour and water uptake studies was studied in de-ionized water. A 20-mesh screen was placed at the bottom of dissolution flask. A tablet was placed on the mesh to allow the hydration of tablet throughout its surface. A paddle was introduced and operated at 50 rpm. The tablet was removed along with mesh at different time intervals. The weight and swelling of tablet were determined. Percent water uptake and percent axial swelling were determined.

***Matrix Erosion Study:***

Matrix erosion studies of metformin hydrochloride tablets were studied in de-ionized water (glimipride layer was excluded from bilayered tablets). Dissolution apparatus type II was used for this purpose. The dry tablets were weighed, placed in dissolution baskets, and subjected to dissolution in 900 ml of distilled water maintained at 37 $\pm$ 0.5 $^oC$ with the paddle rotating at 75 rpm. At regular intervals, tablets were removed from the dissolution vessels and dried to a constant weight in a hot-air oven at 50 $^oC$. The percentage matrix erosion (E) at time, t, was estimated using the following equation[8];

$$\text{Matrix erosion (\%)} = \frac{(W_i - W_t)}{W} \times 100$$

***Stability Studies****:* Selected formulation was stored at $40^0$ C / 75 % RH and 60$^\circ$C, 80 % RH for one month and in vitro release studies were carried out.

**RESULTS AND DISCUSSION**

***Characterization of granules:***

Glimepiride granules of different formulations were evaluated for LBD, TBD, compressibility index and angle of repose (Table 3). The results of compressibility index (%) ranged from 13.20-13.61for glimepiride granules and shown granules showed good flow property. The results of angle of repose ranged from 21 to 27, less than (<30□ ) indicate good flow properties of granules which was supported the results found from compressibility index. All these results indicate that the granules possessed satisfactory flow properties and compressibility.

Bi-layer floating tablets were prepared by using optimized immediate release of glimepiride and floating sustained release formula of metformin hydrochloride and considered as batch 01. During the studies, it was observed from in vitro drug release study that immediate release layer disintegrated rapidly in 0.1 N hydrochloric acid buffer pH 1.2 (simulated gastric fluid without enzymes) from bi-layered tablet. Subsequently, floating sustained release layer started floating in 0.1 N hydrochloric acid buffer pH 1.2 and sustained drug release. This showed biphasic drug release i.e. immediate drug release from immediate release layer and then sustained drug release from floating sustained layer.

**Evaluation of bilayered floating tablets**

***In vitro dissolution study:***

Bi-layer floating tablets of metformin hydrochloride were prepared using HPMC K100M. Bi-layer floating tablets were float more than 12 h in 900 ml 0.1 N hydrochloric acid buffer pH 1.2 (simulated gastric fluid without enzyme) at 37 ± 0.5oC. During dissolution, dissolution media goes in to tablet matrix, the interaction of acidic fluid with sodium bicarbonate resulted in to formation of carbon dioxide gas and that entrapped in swollen gel thus causing floatation. The in vitro dissolution study of batch 01 of metformin hydrochloride and glimepiride bi-layer floating tablets were performed using 900 ml 1.2 pH buffer dissolution media (simulated gastric fluid without enzymes). The study was done 37 ± 0.5oC temperature and 100 rpm. Immediate release layer get completely dissolved within 15-20 min. concurrently floating sustained release layer releases the drug up to 12 h.

The release profile of glimepiride and metformin hydrochloride from optimized bilayered tablets batch 01 is given in figure 01 and 02. The in vitro release profile of glimepiride is compared with innovator product amaryal and the release was similar to the innovator product shown in fig. 03. Similarly

metformin hydrochloride release was compared with innovator product glucophage shown in fig.04.

***Effect of hardness of the tablets:***
In order to verify effect of hardness on drug release dissolution studies were conducted on tablets having three different types of hardness (8 kp/cm$^2$, 10 kp/cm$^2$ and 12kp/cm$^2$). Dissolution studies were carried out using USP dissolution apparatus II. The cumulative percentage of metformin hydrochloride released in 12 hours, was 99, 98, and 85% for Tablets with 8, 10, and 12 kp/cm$^2$ hardness, respectively. Of all the three types of tablets, hardness of 10 kp/cm$^2$ were showing desired drug release profiles, this hardness (10 kp/cm$^2$) was considered as ideal hardness.shown in figure 05.

***Swelling behavior and water uptake studies:*** As discussed in methodology these studies are particularly done for hydrogels – which show swelling property as well as water absorbing property. This study was done for metformin hydrochloride layer in bilayered tablets. The results of percentage axial swelling and percentage weight gain were described graphical representation shown in figure 06.

***Matrix erosion study*:** As discussed in methodology chapter these studies were done for metformin hydrochloride tablets. The rate of matrix erosion of metformin hydrochloride tablets was found to **0.062 /min.** the rate of matrix erosion is shown in figure 07.

***In vitro release kinetic***:
The release profiles of metformin hydrochloride from tablets batch 01 were processed into graphs for comparison of different orders of drug release and, to understand the linear relationship, i.e., kinetic principles. The data were processed for regression analysis using MS-Excel statistical functions. The results of dissolution data fitted to various drug release kinetic equations. Higuchi model was found to be the best fitted in all dissolution profile having higher correlation coefficient 0.995 followed by Peppas model and first order release equation.

Slope of Korsemeyer-Peppas model equation indicates type of release phenomena involved. The 'n' value could be used to characterize different release mechanisms. According to Korsemeyer-Peppas model, a value of slope <0.5 indicates a Fickian diffusion. So, it is concluded that release mechanism for metformin hydrochloride tablets follows fickian diffusion.The log percent water uptake with respect to log time for metformin hydrochloride tablet was studied using Vergnaud model shown in figure 12. Slope of vergnaurd model obtained is 0.399. According to Vergnaud model, a value of slope between < 0.45 indicates fickian diffusion. So, it is concluded that release mechanism for metformin hydrochloride tablets follows fickian diffusion. The weight loss and the amount of drug released from metformin hydrochloride tablets are plotted in Figure 13 as a function of time. It is shown that the erosion rate of the matrix is near constant and the release rate is steady up to 95% of drug released.

**STABILITY STUDIES:** Selected formulation was stored at 40$^0$ C / 75 % RH and 60$^\circ$C, 80 % RH for one month and in vitro release studies were carried out shown in figures 14 and15.

The $f_1$ and $f_2$ values in the comparison of release initial with after one-month storage (at 40° C, 75 % RH and 60°, 80 % RH ) are shown in Table 5. The obtained $f_1$ and $f_2$ values are within the specification range $f_1$ value less than 15 and $f_2$ values range between 50 to 100.

## CONCLUSION

Results of the present study indicated that the formulations of metformin hydrochloride floating sustained and glimepiride immediate release developed in this investigation was found that drug release was within the specifications and were showing equivalent releases with that of the innovator products. Drug release kinetics from metformin hydrochloride layer follows fickian diffusion. Higuchi model was found to be the best fitted in all dissolution profile having higher correlation coefficient 0.992 followed by Peppas model and first order release equation.

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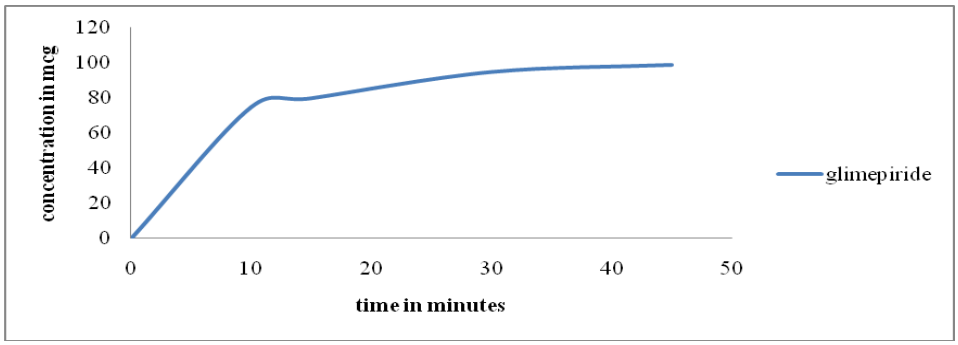


**Fig. 01 Release profile of glimepiride from bilayered tablets**

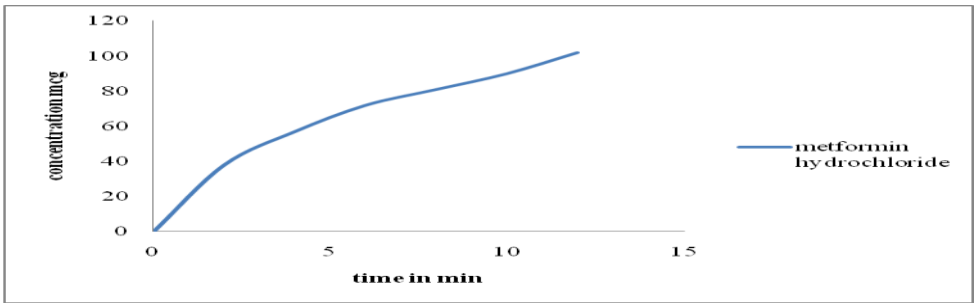


**Fig.02 Release profile of metformin hydrochloride from bilayered tablets**

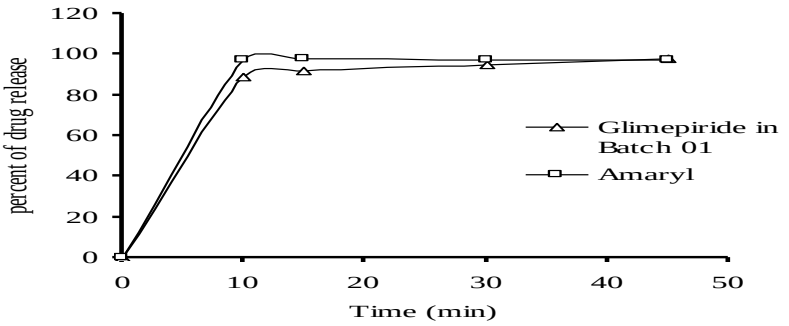


**Fig. 03** Comparative dissolution profile of glimepiride test and innovator product**.**

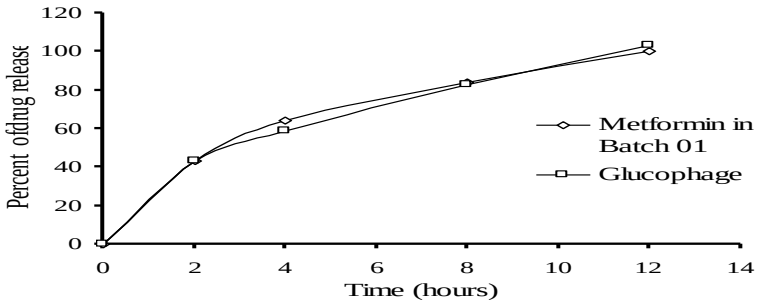

**Fig.04** Comparative drug release of Metformin Hydrochloride test and innovator product (glucophage)

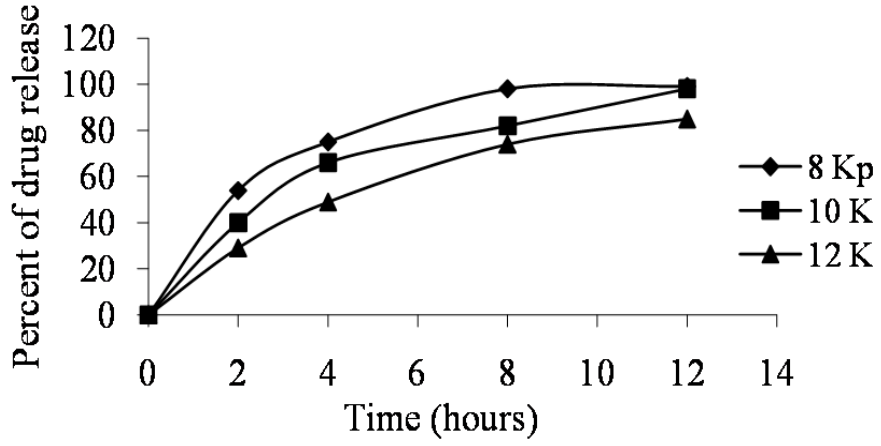


**Fig. 05** Cumulative percent of metformin hydrochloride release from tablets of different hardness.

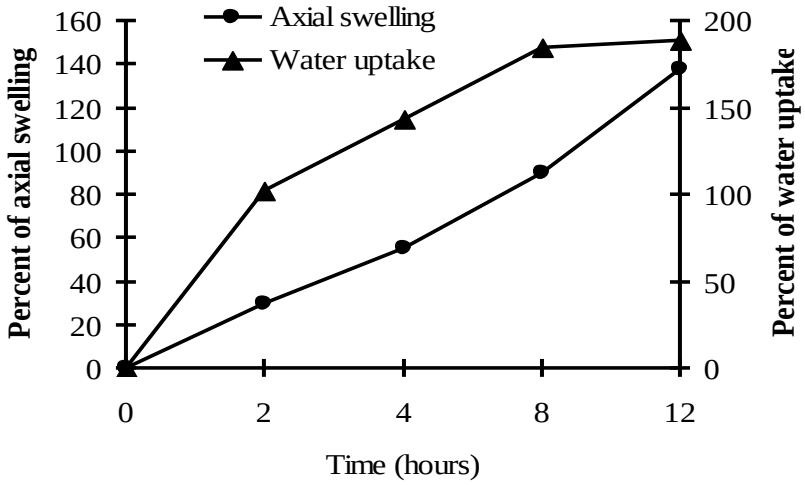


**Fig.06** The percent swelling and water uptake of Metformin hydrochloride layer in bilayered tablet.

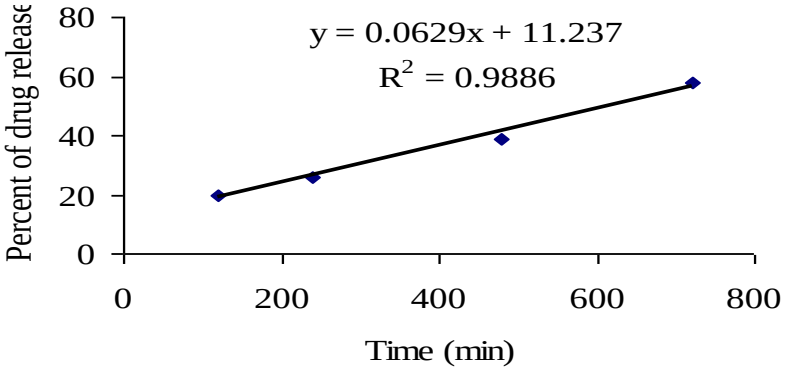


Fig.07 The percent matrix erosion of metformin hydrochloride layer in bilayered tablet

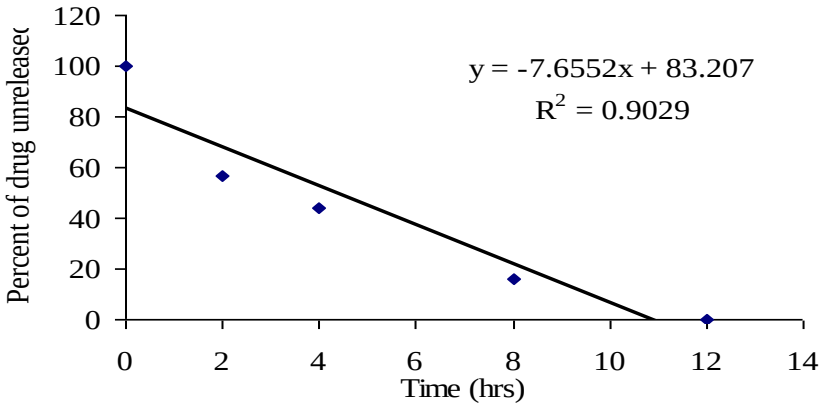


**Fig.8** In vitro release profile of metformin hydrochloride tablet treated in Zero order release

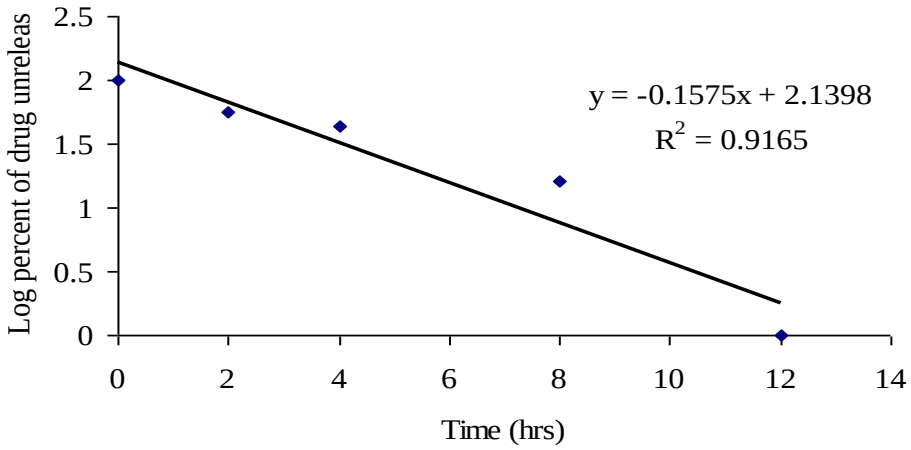


**Fig.09**. In vitro release profile of metformin hydrochloride tablet treated in First order release

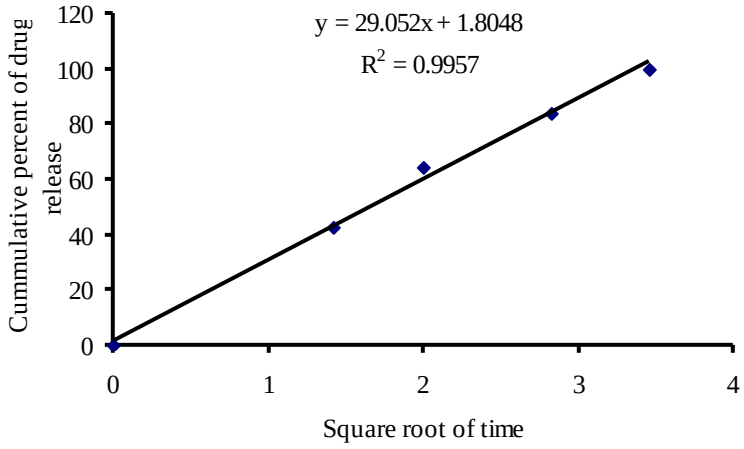


**Fig.10.** In vitro release profile of metformin hydrochloride tablet treated in Higuchi's mode

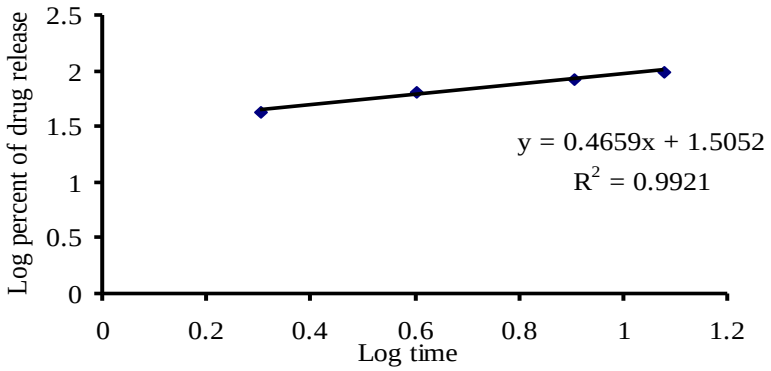


**Fig.11.** Vitro release profile of metformin hydrochloride tablet treated in Peppas model

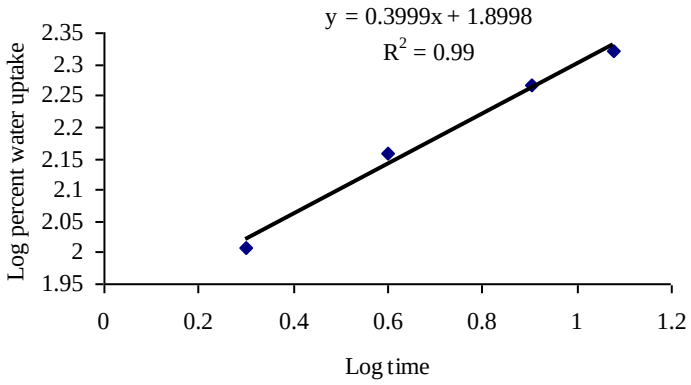


**Fig.12** In vitro water uptake of metformin hydrochloride tablet (**Vergnaud model)**

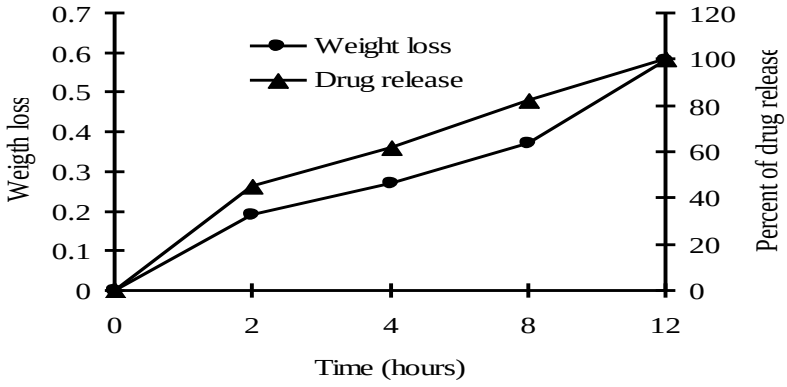


**Fig.13**. Weight loss and release studies of tablets containing 500 mg of metformin hydrochloride

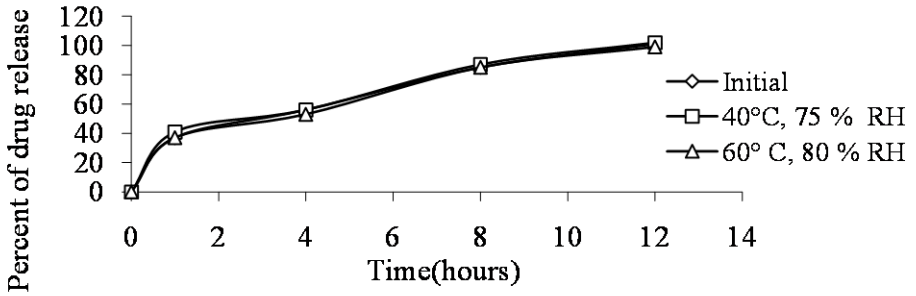


**Fig 14.** Comparative release of metformin hydrochloride of initial and accelerated stability condition after one month storage

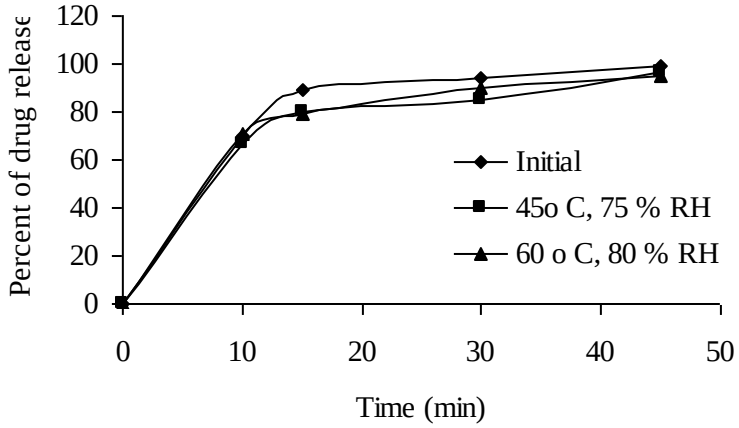


**Fig.15** Comparative release of glimepiride of initial and accelerated stability condition after one month storage

Table 1: Composition of metformin hydrochloride blend

| Ingredients | Quantity per tablet (mg) | | | | |
|---|---|---|---|---|---|
| | F-1 | F-2 | F-3 | F-4 | F-5 |
| Metformin hydrochloride | 500.00 | 500.00 | 500.00 | 500.00 | 500.00 |
| HPMC K 100M | 180 | 200 | 210.00 | 280.00 | 270.00 |
| PVP K 90D | 100 | 100 | 85.00 | 85.00 | 85.00 |
| MCC | 100 | 120 | 150.00 | 80.00 | 90.00 |
| Citric acid | 5 | 5 | 8 | 10 | 15 |
| Sodium bicarbonate | 15 | 20 | 50 | 60 | 65 |
| Magnesium stearate | 4.00 | 4.00 | 5.00 | 5.00 | 5.00 |
| Total weight | 840.00 | 850.00 | 950.00 | 950.00 | 950.00 |

Table 2: Composition of glimepiride granules

| Ingredients | Quantity per tablet (mg) | | | | | | |
|---|---|---|---|---|---|---|---|
| | F-6 | F-7 | F-8 | F-9 | F-10 | F-11 | F-12 |
| Glimepiride | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 | 2.00 |
| MCC 114 | 43.00 | 54.00 | 53.00 | 100.00 | 97.00 | 97.00 | 97.00 |
| Povidone K 25 BP | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | 3.00 | - |
| MCC 102 | 28.73 | 33.70 | 26.73 | 62.23 | 63.00 | 63.00 | 53.00 |
| S.S.G | - | - | - | 8.00 | 8.00 | 8.00 | 16.00 |
| Mannitol | - | - | - | - | - | 62.00 | 62.00 |
| Poloxomer-188 | - | - | - | - | - | - | 6.00 |
| Meglumine | | - | - | - | 2.00 | 2.00 | 2.00 |
| Lake of Sunset yellow ws | 0.27 | 0.27 | 0.27 | 0.27 | 0.50 | 0.50 | 0.50 |
| Magnesium Sterate | 1.50 | 1.50 | 1.50 | 1.50 | 1.50 | 1.50 | 1.50 |
| Total weight | 190.00 | 210.00 | 200.00 | 240.00 | 240.00 | 240.00 | 240.00 |

**Table 3: Physical properties of the blend of glimepiride of Formulations 6 to 12**

| Parameter | F-6 | F-7 | F-8 | F-9 | F-10 | F-11 | F-12 |
|---|---|---|---|---|---|---|---|
| LBD, mg/cc | 0.6529 | 0.5418 | 0.5698 | 0.5246 | 0.5426 | 0.5569 | 0.5278 |
| TBD, mg/cc | 0.7926 | 0.6946 | 0.7084 | 0.6785 | 0.6487 | 0.6947 | 0.6814 |
| Angle of repose | 20.59 | 21.65 | 19.66 | 19.32 | 20.14 | 18.65 | 22.55 |
| Compressibility, % | 17.62 | 21.99 | 19.56 | 22.41 | 16.32 | 19.81 | 22.54 |
| Drug content, %** | 97 | 98 | 97 | 98 | 99 | 100 | 99 |
| Uniformity of weight, mg* | 190 | 200 | 200 | 240 | 240 | 240 | 240 |
| LOD** | 2.75 | 2.13 | 2.62 | 2.96 | 3.10 | 3.21 | 3.24 |

***Table 4: Physical evaluation of bilayered tablets were conducted and given in following table***

| **Formulation No.** | **Weight variation(mg)** | **Friability** | **Hardness ($Kg/cm^2$)** | **Thickness( mm)*** |
|---|---|---|---|---|
| **Formulation 1** | 1145-1168 | 0.0054 | 18.5-21.4 | 7.45-7.75 |
| **Formulation 2** | 1139-1158 | 0.004 | 17-20.4 | 7.36-7.68 |
| **Formulation 3** | 1139-1165 | 0.0024 | 19-25.6 | 7.24-7.55 |
| **Formulation 4** | 1137-1161 | 0.0012 | 16.6-22.4 | 7.45-7.79 |
| **Formulation 5** | 1141-1158 | 0.0014 | 17.5-25.4 | 7.49-7.89 |
| **Formulation 6** | 1175-1199 | 0.0036 | 22.6-28.2 | 7.48-7.78 |
| **Formulation 7** | 1188-1195 | 0.0014 | 27.5-30.5 | 6.91-7.32 |
| **Formulation 8** | 1185-1198 | 0.0025 | 25.4-29.2 | 7.12-7.32 |
| **Formulation 9** | 1181-1192 | 0.0012 | 24.8-29.4 | 7.51-7.62 |
| **Formulation 10** | 1175-1193 | 0.0016 | 23.6-29.4 | 7.62-7.72 |
| **Formulation 11** | 1220-1270 | 0.0025 | 28.4-32.8 | 6.91-7.22 |
| **Formulation 12** | 1230-1262 | 0.0017 | 27-34.8 | 6.8-7.14 |

**Table 5: In Vitro release of metformin hydrochloride from bilayered tablet**

| Time (hrs) | Square root of time | Log of time | Cumulative % of drug released | % drug remain Unreleased | Log % of drug remain Unreleased | Log %of drug released |
|---|---|---|---|---|---|---|
| 0 | 0.00 | 0.00 | 0.00 | 100 | 2.00 | 0.00 |
| 2 | 1.414 | 0.301 | 43.00 | 57.00 | 1.7558 | 1.6334 |
| 4 | 2.00 | 0.602 | 64.00 | 44.00 | 1.6434 | 1.8061 |
| 8 | 2.828 | 0.903 | 84.00 | 16.00 | 1.2041 | 1.9242 |
| 12 | 3.464 | 1.072 | 100.00 | 0.00 | 0.00 | 2.00 |

**Table 6: $f_1$ and $f_2$ values in the comparison of release initial with after one-month storage (at accelerated conditions, 40° C, 75 % RH and 60°, 80 % RH )**

| **Metformin hydrochloride** | | **Glimepiride** | |
|---|---|---|---|
| 40° C, 75 % RH | 60° C, 80 % RH | 40° C, 75 % RH | 60° C, 80 % RH |
| $f_1 = 2.50$<br>$f_2 = 80.10$ | $f_1 = 1.79$<br>$f_2 = 84.29$ | $f_1 = 2.84$<br>$f_2 = 78.12$ | $f_1 = 3.69$<br>$f_2 = 68.77$ |

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