Research Article

Design and In-Vitro Evaluation of Metformin Hydrochloride (SR) and Glimepiride (IR) As Bilayered Tablets

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ABSTRACT

The present research work was an attempt to design bilayered tablets to improve the oral therapeutic efficacy which contains two anti diabetic drugs. Bilayered tablets have been developed consisting of Metformin hydrochloride as extended release layer, glimepiride as immediate release layer. Total of 12 formulations were developed in which metformin hydrochloride 1-5 formulations and 6-12 for glimepiride formulations. From which formulation 5 containing HPMCK100M of metformin hydrochloride and formulation 12 of glimepiride where optimized and compressed into bilayered tablets. Hydroxypropylmethylcellulose and Hydrogenated castor oil 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. Stability of the drug release profiles at 1 month in 40◦C and 75%RH suggesting that HPMC K100M based sustained release formulation 5 was stable. 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, HCO.

INTRODUCTION

Diabetes mellitus is a chronic endocrine metabolic disorder characterized by a high blood glucose concentration level. 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. In diabetes capillary basement membrane thickening occurs which leads to the various complications like Polyuria, microangiopathy, neuropathy, nephropathy, retinopathy, atherosclerosis etc [1-3].

The objective of this proposed research project was to develop a combination drug therapy for antidiabetic agents into tablet formulation having a synergetic action to complement each other and together effectively lower blood glucose level. Metformin hydrochloride and glimepiride simultaneously targets insulin resistance and insulin deficiency of type 2 diabetes, which may account for the greater effects on glycaemia. Metformin hydrochloride improves hyperglycaemia primarily by suppressing glucose production by the liver (hepatic gluconeogenesis). Glimepiride is a medium-to-longacting sulfonylurea antidiabetic drug. It binds to an ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic beta cells. Metformin hydrochloride de as extended release form and glimepiride as immediate release form were separately developed by wet granulation processt. Metformin hydrochloride extended release form was prepared by matrix system containing hydrophobic polymer HCO and another by using hydrophilic polymer HPMC. The ability of hydrophobic and hydrophilic polymer (hydrogenated castor oil and Hydroxypropylmethylcellulose) to act as a release controlling matrix for highly water soluble metformin hydrochloride were studied in order to design a tablet that would release over a period of 12 hours[4-7].

MATERIALS AND METHODS

Materials

Metformin hydrochloride Hydrochloride-Roquet and wanbury Ltd, Glimepiride - Glenmark, Goa, Micro crystalline cellulose 102-Fmc biopolymer, Micro crystalline cellulose 114 -Chigachi chemical, HPMC K 100 M-Colorcon, Mumbai, Hydrogenated castor oil-Matrix, Hyderabad, Iso propyl alcohol-Dr.Reddy's Lab's, HYD, Opadry pink-Colorcon, Mumbai, 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. Methanol, Aceto nitrile, Triethilamine-Merck, Mumbai, respectively.

Methods

Preparation of Metformin hydrochloride and glimepiride granules

Granules of metfromin hydrochloride and glimepiride were prepared separately by using wet granulation technique. The compositions of active pharmaceutical ingredients along with other excipients are summarized in Table 1 and 2. Granules were dried at 60°C for 2 hours in a tray dryer and moisture of the granules was kept between 2.5 to 3.0%. The dried granules were collected and screened through a #20 mesh sieve. Granules were blended with magnesium state separately prior to compression.

Determination of loss on drying (LOD)

LOD is determined using electronic LOD determination apparatus as shown in the. Approximately one gram of sample is taken on lid, tarred for accurate weight and closed the lid. Temperature is adjusted to 105 °C and operated the equipment. LOD value was displayed automatically after getting a constant value.

Bulk Density

LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by pacing 2 g of powder from each formula (previously lightly shaken to break any agglomerates formed) into a 10-ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The reading of tapping was continued until no further change in volume was noted and calculated using the following equation.

LBD and TBD were calculated:
LBD = Weight of the powder / volume of the packing.
TBD = Weight of the powder / Tapping volume of the packing.

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = {(TBD – LBD) X 100}/TBD

Angle of Repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

Angle of Repose θ = tan-1 h/r

Where, *h* = Height of the powder cone.

Manufacturing of bilayered tablets

Bilayered compression machine make rimeck was used. Metfromin hydrochloride layer was compressed first followed by glimepiride layer using 19 mm-diameter die of an infrared hydraulic press to obtain hardness in the range of 25-35 KP.

Table 1: Composition of Metformin Hydrochloride granules

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
HCO	311.00	321.00	-	-	-
HPMC K 100M	-	-	210.00	280.00	270.00
PVP K 90D	25.00	25.00	85.00	85.00	85.00
MCC	-	-	150.00	80.00	90.00
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
Lactose	62.00	66.00	64.00	62.00	62.00	-	-
MCC 114	43.00	54.00	53.00	100.00	97.00	97.00	97.00
Crosspovidone	6.00	6.00	6.00	-	-	-	-
Povidone K 25 BP	3.00	3.00	3.00	3.00	3.00	3.00	-
Polysorbate 80	1.00	1.00	1.00	1.00	1.00	1.00	-
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s
MCC 102	28.73	33.70	26.73	62.23	63.00	63.00	53.00
Flow lac	35.00	35.00	35.00	-	-	-	-
Crosspovidone	7.50	7.50	7.50	-	-	-	-
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

In vitro drug release

In vitro drug release of tablets was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml purified water, was placed into the dissolution flask maintaining the temperature of 37 ± 0.5 ^{o}C and rpm of 70 for metformin hydrochloride and rpm of 100 for glimepiride. The apparatus was allowed to run for 12 hours and samples measuring 10 ml were withdrawn after every 2, 4, 8 and 12 hours using auto sampler for metformin hydrochloride and Samples measuring 10 ml were withdrawn after every 10,15,30 and 45 minutes using auto sampler for Glimepiride. During sampling samples were filtered through 10 µm filter which was in, in line with auto sampler. The fresh dissolution medium (37 ^{o}C) was replaced every time with the same quantity of the sample. Collected samples were suitably diluted with Phosphate buffer P^{H} 6.8 and analysed at 233 nm using Phosphate buffer P^{H} 6.8 as blank in U.V spectroscopy and for glimepiride the collected samples were suitably diluted with Phosphate buffer P^{H} 7.8 and analysed in High Performance liquid Chromatography (HPLC) for 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[8-12].

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 using the following equations.

$$\text{Percent water uptake (weight gain)} = \frac{\text{(Wet weight - dry weight)}}{\text{Dry weight}} \times 100$$

$$\text{Percent axial swelling} = \frac{\text{(Swollen thickness-original thickness)}}{\text{Original thickness}} \times 100$$

Matrix Erosion Study[13]

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 ± 0.5 ^{o}C 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 ^{o}C. The percentage matrix erosion (E) at time, t, was estimated using the following equation;

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

RESULTS AND DISCUSSION

Characterization of granules

Metformin hydrochloride and glimepiride granules of different formulations were evaluated for LBD, TBD, compressibility index, angle of repose, drug content, uniformity of weight and loss on drying and their results are given Table 3 and table 4. The results of compressibility index (%) ranged from 12.5-13.26 for metformin hydrochloride granules and 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.

Table 3: Physical properties of the blend of Metformin Hydrochloride of Formulations 1 to 5

Parameter	F-1	F-2	F-3	F-4	F-5
LBD, mg/cc	0.4540	0.4497	0.4326	0.4849	0.4727
TBD, mg/cc	0.5679	0.5579	0.5301	0.5874	0.5621
Angle of repose	19.20	18.32	21.01	20.42	22.11
Compressibility, %*	20.05	19.40	18.39	17.44	15.86
Drug content, %**	97	98	99	99	99
Uniformity of weight, mg*	840 ±10	850 ±10	950±5	950±5	950±5
LOD**	1.62	1.71	1.84	1.69	1.72

Table 4: 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

In vitro release study

Release of metformin hydrochloride from formulations (F-1, F-2) containing HCO and formulation F-3, F-4 and F-5 containing HPMC K 100 M are represented graphically in figure-01 and figure-02.

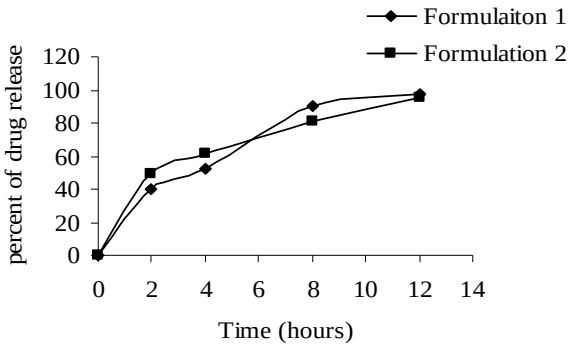

Fig. 1: Comparative dissolution profile of metformin hydrochloride in Formulations 1 & 2

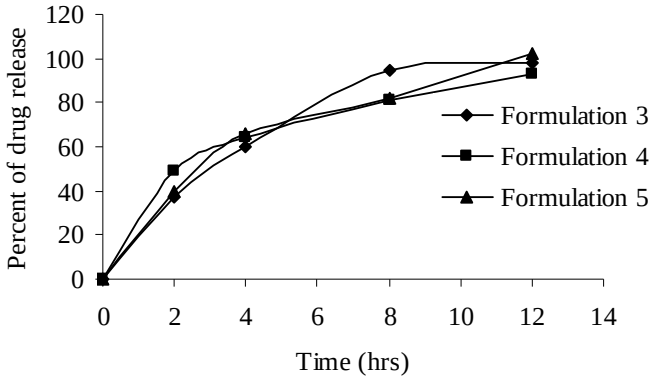

Fig. 2 Comparative dissolution profiles of metformin hydrochloride of Formulations 3, 4 & 5

Blend of Formulation 1 were subjected to compression as described in methodology section. The obtained tablets were subjected to dissolution studies as per USP specification protocol. The release obtained in dissolution studies shows fluctuations in release pattern which are out of USP specification therefore Formulation 1 was discarded. In order to control the release rate of metformin from the tablet Formulation 1 was modified by increasing HCO 311 to 321 mg to get Formulation 2. In addition to this the process variables were adjusted, such as impeller and chopper operation time was increased while granulating blend of Formulation 2 and compressed into tablets.

Metformin tablets of Formulation 2 were subjected to the dissolution studies and the release was observed consistent and matching within the USP specification limits. The drug release pattern of both formulations one and two are shown in Figure 01 and seems to be suitable for metformin layer only.

Further formulation of glimepiride trials were done and are compressed individually into bilayered tablets along with metformin hydrochloride blend. Granules of glimepiride were formulated as mentioned in table 2.

Bilayered tablets of metformin hydrochloride (HCO as release retarding agent) and glimepiride were produced by selecting the granules of Formulation 2 and Formulation 6. The obtained tablets were subjected for the dissolution studies for glimepiride. Drug release from formulation 6 was not uniform and out of USP specifications.

The physical observation of bilayered tablets indicated deformation of the metformin layer this might be due to the melting of HCO due to high compression forces during compression. Because of this reason Formulation 2 not selected.

In Formulation 3 (shown in Table 1) the changes made were HPMC K 100M and MCC were added and HCO was deleted. In this HPMC K 100M acts as release retardant whereas MCC used as release modulator.

The release profiles of metformin layer of Formulation 3 to formulation 5 are shown in Figure 02. The release studies of formulation 3 indicated that after four hours sufficient sustained release was not observed. To modulate sustained release of metformin another two trials were made in Formulation 4 and 5. in Formulation 4 the HPMC K 100M quantity was increased by 70 mg. simultaneously the quantity of MCC reduced by 70 mg compared to Formulation 3 .The release rate of metformin of formulation 4 is shown after 12 hours only 93 percent of metformin hydrochloride is released. To achieve maximum and complete amount of metformin release in Formulation 5 HPMC K 100M was reduced by 10 mg and MCC was increased by 10 mg compared to Formulation 4 in order to get complete release. Compression parameters of Formulation 5 were found satisfactory. The compressed metformin tablets were subjected for dissolution studies and the release was according to the USP specifications and formulation 5 was optimized for metformin layer.

During compression of granules of metformin and glimepiride the problems observed was, the glimepiride layer was not intact; this might due to the less weight of components of glimepiride layer. Therefore, in the next Formulation (F-7) the total weight of glimepiride blend was increased from 190 to 210 mg in which weights of ingredients such as lactose and MCC 102 were increased.

Formulation 7 was subjected for content uniformity studies and the values obtained are as follows 105,102,109,115 and 100 and drug release was of higher side which are not satisfactory.

In Formulation 8 the total weight was reduced from 210 to 200 mg by reducing the quantity of MCC 114 and MCC 102. The tablets obtained from this formulation were subjected to dissolution studies. The release profile of glimepiride is compared innovator product and was not compiling with USP specification (95 percent in 45 minutes).

To achieve dissolution profile with that of the innovator product following changes were made in the Formulation 8 to get Formulation 9. (i) Flowlac is completely removed in addition MCC 102 and was increased from 26 to 62.23 mg. (ii) Crosspovidone was completely removed by replacing it with sodium starch glycolate of 8 mg. So MCC 102 was increased and MCC 114 was decreased by 3 mg.

The granules of glimepiride of Formulation 9 and granules of metformin hydrochloride of Formulation 5 were compressed into bilayered tablets and are subjected to dissolution studies. During the dissolution impurities are generated. So in next Formulation 10, meglumine was added to increase the stability of glimepiride.

The blend of glimepiride of F-10 and blend of metformin hydrochloride of F-5 were compressed into bilayered tablets. The compressed tablets were subjected for dissolution studies. During dissolution there was a formation of moron color in the dissolution medium. This may be due to the condensation reaction between lactose and amine group present in the meglumine. In the Formulation 10 lactose was replaced with mannitol with same quantity to get formulation 11.

The glimepiride blend of the Formulation 11 and metformin blend of the Formulation 5 were compressed into bilayered tablets. The compressed tablets were subjected to the dissolution studies. During dissolution color (lake of sunset yellow) was disappeared, so therefore, PVP K 90D was replaced with HPC-LF, similarly polysorbate was replaced with poloxomer to get Formulation 12

Final blend glimepiride of Formulation 12 and blend of metformin hydrochloride of Formulation 5 were compressed into bilayered tablets and the compressed tablets were subjected to the dissolution studies. The drug release of glimepiride was matching within the USP specification and also with the innovator product (Amaryl) shown Figure-03. Therefore Formulation 12 was optimized.

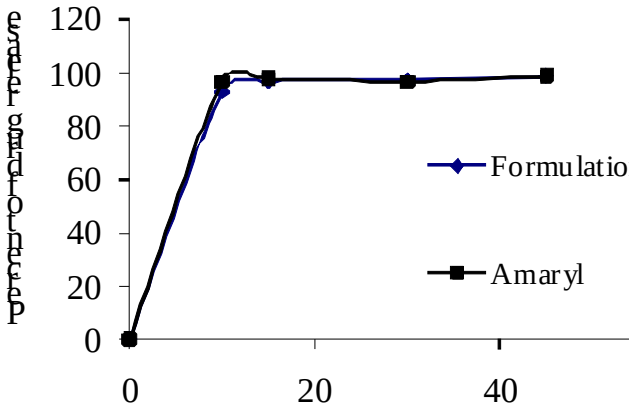

Fig. 3: Comparative dissolution profile of glimepiride in Formulation 12 with Amaryl

Further, optimized formula 5 of metformin hydrochloride and formula 12 of glimepiride were compressed into bilayered tablets and considered as batch 01 for further studies.

Drug release profiles of glimepiride and metformin hydrochloride was compared with innovator products amaryl and glucophage represented in figure-04 and figure-05.

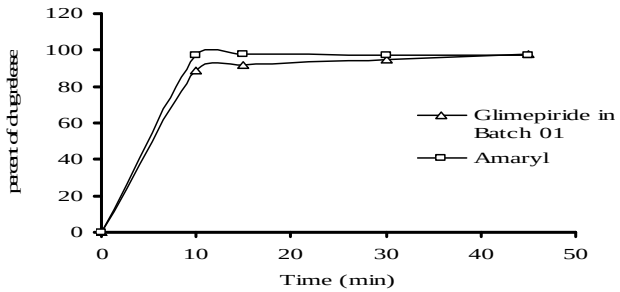

Fig. 4: Comparative dissolution profile of glimepiride test and innovator product

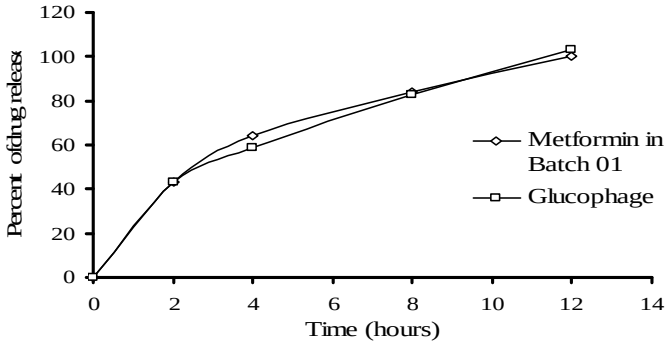

Fig. 5: Comparative drug release of Metformin Hydrochloride test and innovator product (glucophage)

Effect of hardness of the Tablets

In order to verify effect of hardness on metformin 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 percent of metformin release with respect to different hardness shown in figure-06. And 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.

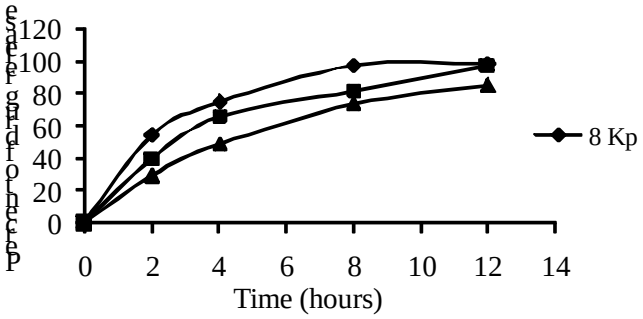

Fig. 6: Cumulative percent of metformin hydrochloride release from tablets of different hardness

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-07.

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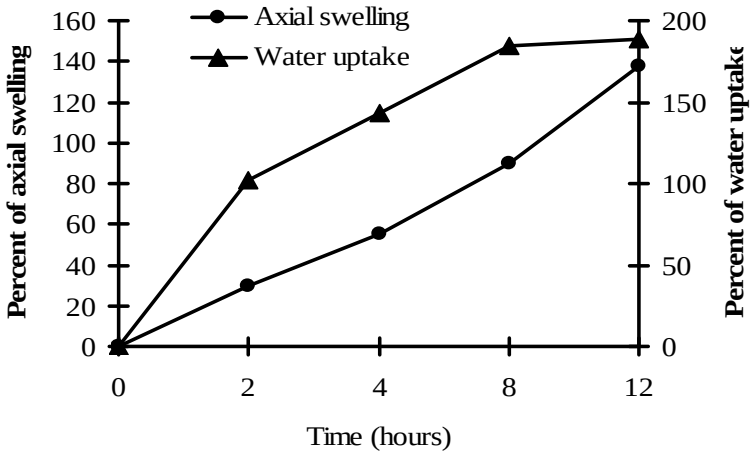

Fig. 7: The percent swelling and water uptake of Metformin hydrochloride layer in bilayered tablet

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 with respect to time is shown in figure-08.

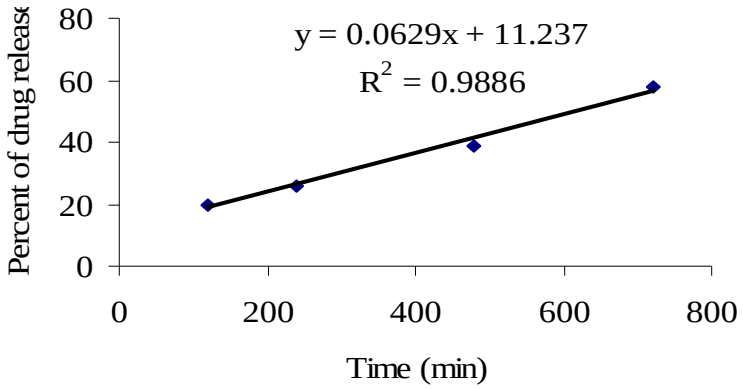

Fig. 8: The percent matrix erosion of metformin hydrochloride layer in bilayered tablet

In vitro **release kinetic**

The release profiles of metformin hydrochloride from batch 01 tablets were processed into graphs for comparison of different orders of drug release and, to understand the linear relationship, i.e., kinetic principles. The obtained data given in table 5 data and were processed for regression analysis using MS-Excel statistical functions.

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

The results of regression analysis were represented in graphs for zero order shown in figure-09, first order shown in figure-10, higuchi's and peppas models shown in following figures-11 and12.

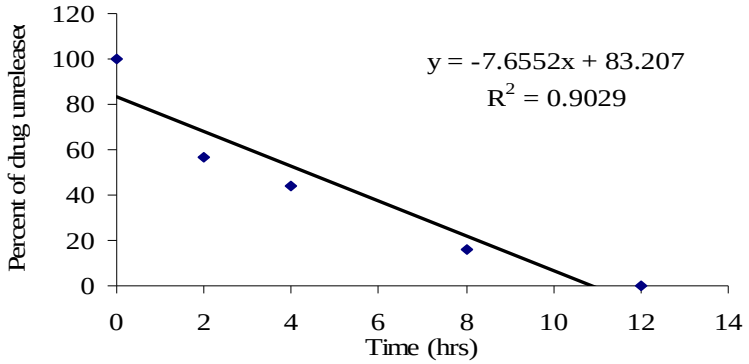

Fig. 9: *In vitro* release profile of metformin hydrochloride tablet treated in Zero order release

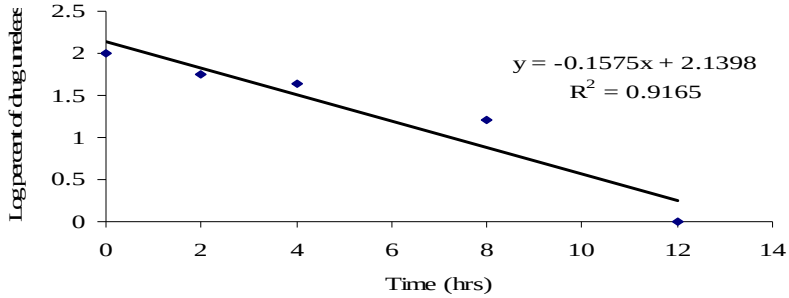

Fig. 10: *In vitro* release profile of metformin hydrochloride tablet treated in First order release

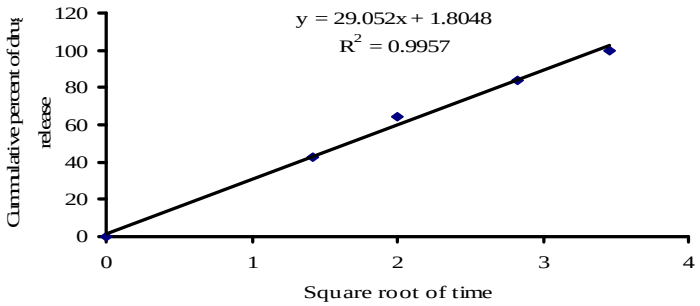

Fig. 11: *In vitro* release profile of metformin hydrochloride tablet treated in Higuchi's mode

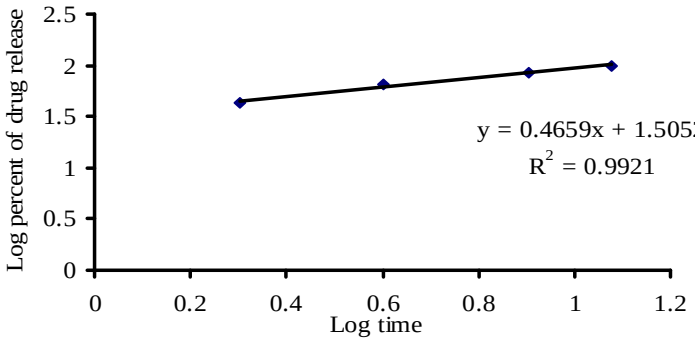

Fig. 12: *Vitro* release profile of metformin hydrochloride tablet reated in Peppas model

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 and shown in figure-13 using Vergnaud model.

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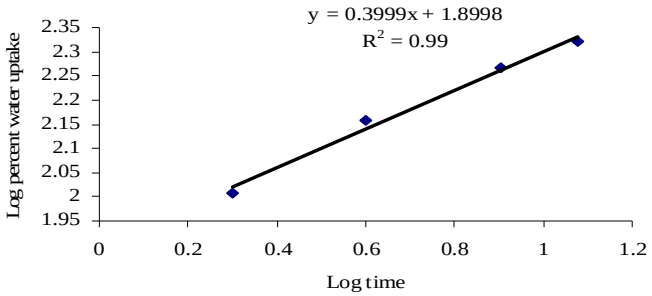

Fig. 13: *In vitro* water uptake of metformin hydrochloride tablet (Vergnaud model)

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 14 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.

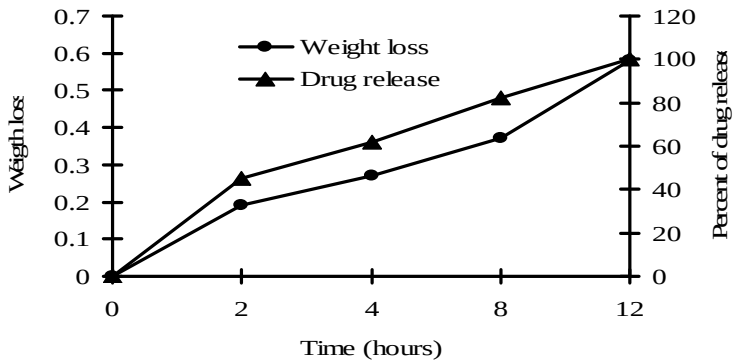

Fig. 14: Weight loss and release studies of tablets containing 500 mg of metformin hydrochloride

Comparative dissolution profile of in house and marketed products

Release of glimepiride and Metformin hydrochloride from in house developed bilayered tablets were compared with different marketed products like lupin,torrent and glenmark represented graphically in figure-15 and figure-16.

.

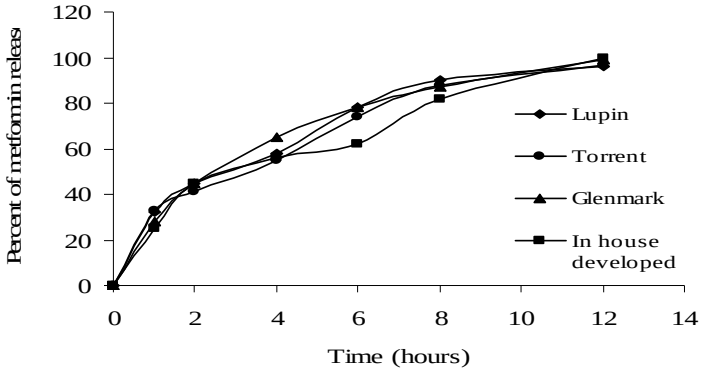

Fig. 15: Cumulative percent of metformin hydrochloride release from three different marketed and in house developed products

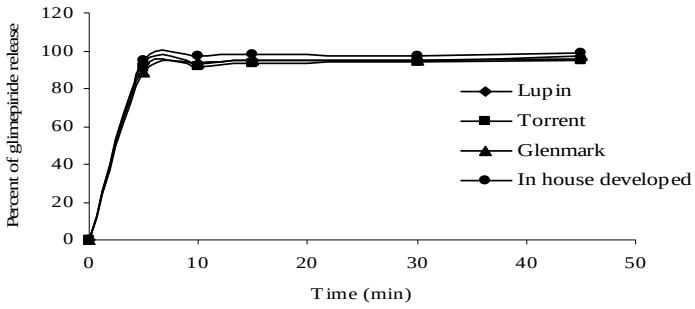

Fig. 16: Cumulative percent of glimepiride release from three different marketed and test product

Stability Studies

Selected formulation was stored at 40^0 C / 75 % RH and 60°C, 80 % RH for one month and *in vitro* release studies were carried out. The release profiles at three different conditions were studied and represented graphically in figure-17 and figure-18.

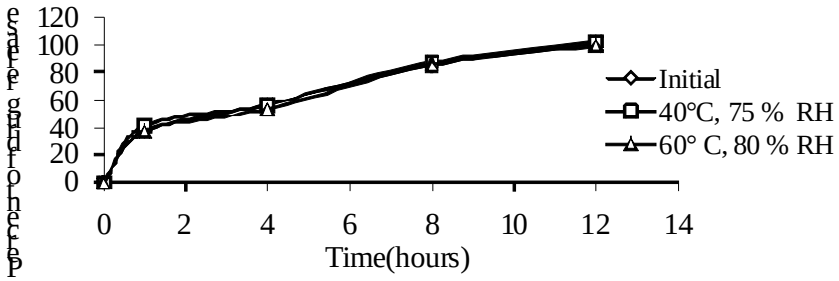

Fig. 17: Comparative release of metformin hydrochloride of initial and accelerated stability condition after one month storage

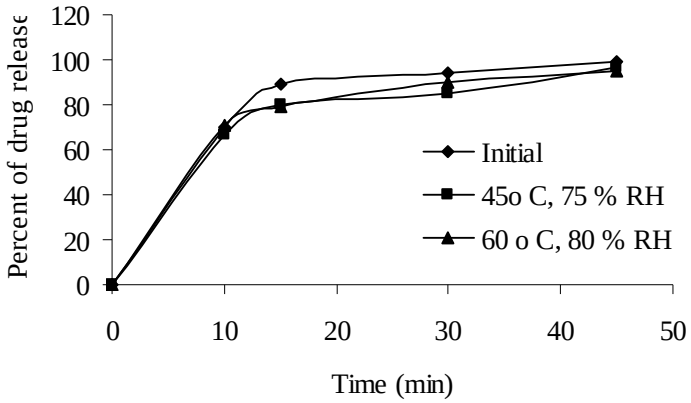

Fig. 18: Comparative release of glimepiride of initial and accelerated stability condition after one month storage

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.

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Table 5: 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 f_2 = 80.10	f_1 = 1.79 f_2 = 84.29	f_1 = 2.84 f_2 = 78.12	f_1 = 3.69 f_2 = 68.77

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