

## FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE AND GLICLAZIDE SUSTAINED RELEASE BILAYER TABLETS: A COMBINATION THERAPY IN MANAGEMENT OF DIABETES

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### ABSTRACT

**Objective:** The main objective of the present investigation is to develop a sustained-release (SR) formulation to optimize the postprandial elevation of glucose level in type 2 Diabetic subjects using combination therapy. In the present research work, bilayer sustained release formulation of metformin hydrochloride (MFH) and gliclazide (GLZ), based on monolithic-matrix technology was developed and evaluated.

**Methods:** The formulations of metformin hydrochloride layer and gliclazide layer that contain polyox WSR coagulant and different viscosity grades of hydroxyl propyl methylcellulose (HPMC) as sustained-release matrix were prepared by direct compression and wet granulation method respectively. The bilayer tablets were prepared after carrying out the optimization of metformin layer and evaluated for various pre-compression and post-compression parameters. For the best formulation selected on basis of *in vitro* evaluation of tablets, Fourier-transform infrared spectroscopy (FT-IR) studies and comparison of *in vitro* dissolution profile of developed formulation with the innovator were performed.

**Results:** Metformin hydrochloride and gliclazide showed sustained release of drug by diffusion mechanism and followed first-order kinetics. The best formulation of metformin hydrochloride (M7) and gliclazide (G8) show 99.93% and 99.65% of drug release in 24 h respectively. The similarity factor (*f*<sub>2</sub>) was 79.95 for metformin hydrochloride and 73.62 for gliclazide when compared with the innovator.

**Conclusion:** The monolith diffusion-controlled bilayer tablets of metformin hydrochloride and gliclazide offer improved patient compliance and convenience with better postprandial hyperglycemic control with once-a-day dosing. The sustained release of the drug up to 24 h regulate antidiabetic activity round the clock with minimal side effects.

**Keywords:** Bilayer tablet, Sustained-release, Metformin hydrochloride, Gliclazide and type 2 diabetes mellitus

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### INTRODUCTION

Insulin is an anabolic hormone responsible for the maintenance of glucose homeostasis in the human body. It helps in the uptake of glucose molecules into the tissues and results in the utilization of glucose moiety into energy by various biochemical mechanisms [1]. However, lack of adequate insulin levels in our body leads to several chronic metabolic disturbances of carbohydrate, fat, and protein that is often termed as diabetes mellitus (DM) which is a serious and lifelong condition [2]. There are two principal forms of diabetes: type 1 diabetes, in which the pancreas fails to produce insulin, and type 2 diabetes, which results from the body's inability to respond properly to the action of insulin produced by the pancreas [3]. The prevalence of diabetes has increased globally over the years and it has been noted as one of the leading causes of high mortality and morbidity rate [4]. About 422 million people worldwide have diabetes and 1.6 million deaths are directly attributed to diabetes each year [5]. According to the IDF statistics, adults with type 2 diabetes (T2 DM) outnumber those with type 1 diabetes [6]. Type 2 DM is a heterogeneous disorder characterized by multiple problems in the pancreatic  $\beta$ -cell, liver, and peripheral tissue such as skeletal muscles and adipose tissue. These multiple complications are well managed by combination therapy using two antidiabetic drugs. Combination therapy is more advantageous than monotherapy in minimizing problems such as dose-dependent side effects, dosing frequency, etc. A low-dose combination of two different drugs reduces dose-related risks and minimizes the clinical and metabolic side effects that occur with the maximal dosage of individual components as in monotherapy, and thus dosage of the single components can be reduced [7, 8]. Diabetes needs much attention as glucose levels that tend to increase after a meal, have to maintain for the whole day for proper activity of the body [9]. To combat such conditions, sustained-release (SR) formulations that regulate antidiabetic activity round the clock need to develop to optimize the postprandial elevation of glucose levels [10].

Metformin hydrochloride, an oral biguanide first-line choice of drug and gliclazide (GLZ), the second-generation sulphonylurea provides good hypoglycemic excellence by increasing both basal and meal-stimulated insulin secretion along with enhancement of peripheral insulin sensitivity, ultimately leading to declining in fasting, postprandial glucose, and glycosylated hemoglobin (HbA1c) levels [11]. Bilayer technology is one of the suitable approaches for the successful development of sustained-release formulations that provide a way of successful drug delivery. A bi-layer tablet is suitable for the fabrication of sustained release dosage form (tablet) consisting of two drugs in combination in two different layers and sequentially release the drugs [12]. The present research aimed to develop a sustained release bilayer formulation using combination therapy, which provides better postprandial hyperglycemic control with a daylong duration and reduces the economic burden in management of diabetes compared to the expenses in marketing new drug entities. The objective of the present investigation is to design and evaluate sustained release bilayer tablets containing metformin hydrochloride and gliclazide.

### MATERIALS AND METHODS

#### Materials

Metformin hydrochloride and gliclazide were supplied as a gift sample from Cipla Pharmaceuticals Ltd., Mumbai. Desai chemicals Ltd remained as a main supplier for the polyox WSR coagulant, HPMC polymers of grade K4M, K15M, K100M and all other excipients used in the study. HPLC grade acetonitrile, potassium dihydrogen phosphate, orthophosphoric acid AR grade purchased from Lotus Chem. Mumbai, India. Waters e 2695 separation module with high pressure liquid chromatographic instrument provided with an RP-Select B C18 column (250 mm x 4.6 mm; 5 $\mu$ ) and 2489 UV-Visible detector, auto-injector, an autosampler with Empower 2 software from Waters Corporation, Milford USA was employed in the study.

## Methods

### Experimental method

#### Drug-excipient interaction study

It is a critical primary concern for any dosage form to study the compatibility of drug, polymer and other excipients; therefore, it is necessary to confirm that the drug does not interact with polymers and excipients under experimental conditions and affects the shelf life of the product. The drug excipient compatibility has done by physical observation of mixtures for one month and FT-IR study. The drug has mixed with excipients in a different ratio. These mixtures were kept in 5 ml glass white-colored vials and packed properly. These vials were exposed to room temperature and 40°C/75 % RH. 2 to 3 g of the blend was prepared and filled in three vials. Observations for any physical change in appearance were performed at zero weeks to one month [13].

#### FTIR spectroscopy

Fourier transform infrared spectroscopy (FT-IR) investigations were used to detect possible drug-drug and drug-excipient interactions by using an FT-IR spectrometer-430 (Jasco-Japan). The Potassium Bromide pellets, an infrared transparent matrix, were prepared on KBr press on grounding the solid powder sample with 100 times the quantity of KBr in a mortar [14]. The spectra were recorded at a resolution of 4 cm<sup>-1</sup> over the wavenumber of 4000 to 400/cm.

### Analytical method

#### Preparation of stock and working standard solution of metformin hydrochloride and gliclazide

A mixture of pH 6.6 phosphate buffer and acetonitrile in the ratio 60:40 % v/v filtered through 0.45µm membrane filter used as mobile phase for preparing the working solution of the drug. About 500 mg of metformin hydrochloride and 60 mg of gliclazide were accurately weighed and transferred into a 100 ml volumetric flask, the solution was sonicated and the resulting solution was diluted with the mobile phase to obtain a primary stock solution. 10 ml of this stock solution was further diluted to 100 ml using mobile phase to obtain 500 µg/ml metformin hydrochloride and 60 µg/ml gliclazide. From this solution, suitable working solutions of different concentrations were prepared.

#### Construction of calibration curve of metformin hydrochloride and gliclazide

Linearity of the peak area response was determined by measuring working standard dilution of metformin hydrochloride and gliclazide in the range of 125-750 µg/ml and 20-120 µg/ml respectively. Triplicate of the 20-µl quantity of each dilution injected each time into the column. The drug in elutes was monitored at 261 nm and the corresponding chromatograms were obtained. From these chromatograms, a plot of amount and response was constructed. The regression equation (fig. 1 and 2) obtained was used to estimate the amount of drugs present in a pharmaceutical dosage form.

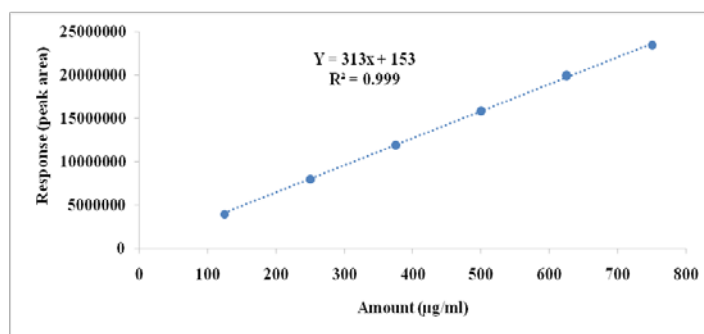


Fig. 1: Calibration curve of metformin hydrochloride

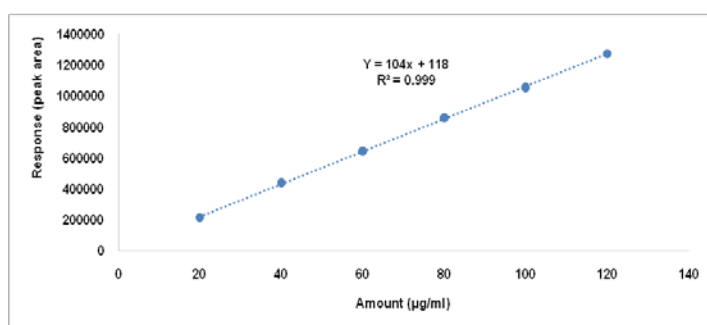


Fig. 2: Calibration curve of gliclazide

#### Formulation development of bilayer tablets

Development of bilayer tablets of metformin hydrochloride and gliclazide was carried out in two stages. Blends of the SR layer of metformin hydrochloride (layer 1) and gliclazide (layer 2) were prepared and initially compressed separately for preliminary evaluations. After optimization of an individual layer, the bilayer tablet was prepared using selected formulas.

#### Formulation of metformin hydrochloride layer (layer-1)

Metformin hydrochloride is a very moisture-sensitive drug. Hence, various formulations of metformin hydrochloride were prepared by non-aqueous wet granulation (M1-M4) and direct compression (M5-

M7). In formulations, (M1-M4) HPMC K100M was used as a retardant. All the ingredients passed through a 60-mesh sieve. A blend of all ingredients was mixed thoroughly in a rapid mixer granulator resulting in phase homogenization and granulated manually with a binder solution, which was prepared by dissolving povidone K30 in isopropyl alcohol. The wet masses were passed through a 12 mesh sieve and the wet granules produced was initially air-dried for 10 min and finally at 45-50 °C in a tray dryer for 2 h until the LOD (Loss on drying) of granules reached moisture limit between 2-3% w/w. The dried granules sieved by 16 mesh sieve were lubricated with magnesium stearate (which was sifted through 60 mesh) and compressed to tablets. Formulations (F5-F7) were prepared using polyox WSR coagulant as retardant along with other

excipients. The ingredients passed through a 60-mesh sieve, mixed thoroughly in a rapid mixer granulator, lubricated and compressed. Before compression, the final blend was evaluated for its flow and compressibility characteristics. All the tablets compressed using Cadmach single punch tablet compression machine with 12 mm concave punch were stored in airtight containers for further study [15, 16]. The composition of the metformin hydrochloride sustained release layer is mentioned in table 1.

#### Formulation of gliclazide layer (layer-2)

Various formulations of gliclazide (G1-G9) were prepared with different ratios of Hydroxy Propyl Methyl Cellulose of different grades like HPMC-K4M, HPMC-K15M, HPMC-K100M and other ingredients by taking appropriate quantities as mentioned in table 2. The granules were prepared by the wet granulation method. The ingredients passed through a 60-mesh sieve. A blend of all ingredients except glidant and lubricant mixed thoroughly in a rapid mixer granulator resulting in

phase homogenization and granulated manually with a binder solution prepared by dissolving povidone K30 in isopropyl alcohol. The wet masses were passed through a 12 mesh sieve and the wet granules produced was initially air-dried for 10 min and finally at 45-50° in a tray dryer for 2 h until the LOD (Loss on drying) of granules reached moisture limit between 2-3% w/w. The dried granules sieved by a 16 mesh sieve were lubricated with magnesium stearate (which was sifted through 60 mesh) and compressed to tablets. Before compression, the granules were evaluated for pre-compression parameters. The composition of the gliclazide layer is mentioned in table 2.

#### Characterization of the powder blend

Precompression parameters of the metformin hydrochloride and gliclazide powder blends such as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined for their micromeritic properties before compression of the tablet were mentioned in table 3 and 4 respectively.

Table 1: Composition of metformin hydrochloride layer

Ingredients (mg)	Formulation code						
	M1	M2	M3	M4	M5	M6	M7
Metformin hydrochloride	500	500	500	500	500	500	500
HPMC K100M	120	160	200	240	-	-	-
PolyoxWSR coagulant	-	-	-	-	160	220	210
MCC	140	100	60	20	-	-	-
Mannitol	-	-	-	-	95	35	45
PVP K 30	25	25	25	25	25	25	25
IPA	qs	qs	qs	qs	qs	qs	qs

HPMC: Hydroxypropylmethylcellulose, MCC: Microcrystalline cellulose, PVP: Polyvinyl pyrrolidone, IPA: Isopropyl alcohol, qs: quantity sufficient. Total weight per tablet: 800 mg

Table 2: Composition of gliclazide layer

Ingredients (mg)	Formulation code							
	G1	G2	G3	G4	G5	G6	G7	G8
Gliclazide	60	60	60	60	60	60	60	60
DCP	90	70	50	90	80	70	90	80
HPMC K4M	20	30	40	-	-	-	-	-
HPMC K15M	-	-	-	20	30	40	-	-
HPMC K100M	-	-	-	-	-	-	20	30
PVP K30	6	6	6	6	6	6	6	6
Iron oxide yellow	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
SA	20	20	20	20	20	20	20	20
IPA	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium stearate	4	4	4	4	4	4	4	4

DCP: Dicalcium phosphate, HPMC: Hydroxy Propyl Methyl Cellulose, PVP: Polyvinyl pyrrolidone, IPA: Isopropyl alcohol, SA: Sodium alginate, qs: quantity sufficient. Total weight per tablet: 200 mg

#### Evaluation of marketed formulation exermet GZ 560

The marketed product (Exermet GZ 560) was evaluated to determine thickness, weight and dissolution profile following the standard method of testing. The values of these properties are given in table 5.

#### Evaluation of post-compression parameters

##### Physicochemical properties of tablets

The compressed monolithic matrix tablets are characterized for post-compression properties like weight variation, friability, hardness and thickness as per IP and USP standard methods. The weight variation of the tablets was carried out with 20 tablets using an electronic balance (Shimadzu, Japan). Friability was determined using 10 tablets in a Roche friabilator (Pharma Lab, Ahmadabad, India) for 4 min at 25 rpm. For each formulation, the hardness of 10 tablets was evaluated using a hardness tester (Monsanto hardness tester). The thickness of 10 tablets was measured using Vernier Calipers [17, 18].

##### Drug content uniformity

Twenty tablets weighed accurately and finely powdered. The powder equivalent to 500 mg of metformin hydrochloride and 60 mg of gliclazide was transferred into a 100 ml volumetric flask. 50

ml of pH 7.4 buffer was added to the powder and sonicated to dissolve completely. Then the volume made up to 100 ml with buffer and filtered by Whatman filter paper. 1 ml of filtered solution was withdrawn and diluted to 100 ml using the buffer. The Peak area of the sample solution was measured at 261 nm to calculate the concentration of the drug in the sample [19].

##### In vitro dissolution profiles

The marketed and manufactured formulations were tested for *in vitro* drug release using USP Type II paddle dissolution apparatus (LAB INDIA 8000+). One matrix tablet was placed in each flask of the dissolution apparatus and dissolution was conducted for 24 h at 50 rpm at 37±0.5 °C. Initially, the study was performed in 900 ml of 0.1 N HCl for 2 h followed by 900 ml of pH 7.4 phosphate buffer 5 ml of sample was withdrawn at time intervals 2, 4, 6, 8, 10, 12, 16 and 24 h and the same volume was replaced to maintain sink conditions [20-21]. During sampling, samples were filtered through Whatman filter paper, suitably filtered and analyzed by the reported HPLC method at 261 nm using standard stocks. Each sample was injected six times and the sample retention times were observed in all cases. Retention time about 3.27 min for metformin hydrochloride and 6.12 min for gliclazide observed for stock solution.

### Dissolution data analysis

The dissolution profile comparison carried out using the model-independent or model-dependent method. A simple model-independent approach uses a difference factor ( $f_1$ ) and a similarity factor ( $f_2$ ) to compare dissolution profiles.

$$f1 = \left\{ \frac{[\sum_{t=1}^n |R_t - T_t|]}{[\sum_{t=1}^n R_t]} \right\} \times 100$$

$$f2 = 50 \times \log \left\{ \frac{1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2}{1 + (1/n) \sum_{t=1}^n R_t^2} \right\} \times 100$$

Where,  $R_t$  and  $T_t$  represent the average percent dissolved at time  $t$  for reference and test, respectively and  $n$  is the number of time points tested.

Dissolution profile considered satisfactory if  $f_1$  values lie below 50 (nearing zero) and  $f_2$  values lie more than 50 (nearing 100). If the  $f_2$  value is between 50-100, the value of the test and the reference are identical. The model-independent method is most suitable for dissolution profile comparison when three to four or more dissolution time points are available [23].

### Kinetic model fitting

Dissolution data of the above two methods were fitted in Zero order, First order and Higuchi equations. Based on the slope and  $r^2$  values obtained, the mechanism of drug release was determined.

### Accelerated stability studies

The accelerated stability testing was conducted to provide evidence on how the quality of a drug substance varies with time under influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions. The study was conducted by wrapping the bilayer tablets in aluminum foils and kept at 25 °C/60% RH and 40 °C/75% RH. Then the tablets were checked for appearance, thickness, and hardness. In addition, drug content and dissolution studies were performed periodically for 6 mo and compared with initials as per ICH guidelines [26].

## RESULTS AND DISCUSSION

### Drug-excipient interaction study

The compatibility of the pure drug with its excipients on physical observation exhibited no interaction; therefore, the excipients were selected for formulation. The distinctive melting points were observed for metformin hydrochloride at 224 °C and gliclazide at 182 °C and no evident melting point changes were noted indicating overall compatibility.

### FT-IR spectroscopy

The FT-IR spectrum of metformin hydrochloride and gliclazide in formulations was as shown in fig. 3C. FT-IR studies revealed that metformin hydrochloride showed two typical bands at 3371 and 3296/cm due to N-H primary stretching vibrations and a band at 3174/cm due to N-H secondary stretching, and characteristics bands at 624 and 1584/cm assigned to C=N stretching. No significant shifts of reduction in the intensity of the FT-IR bands of metformin hydrochloride were observed which indicates the absence of drug-drug interaction and drug-polymer interaction between metformin hydrochloride and Polyox WSR coagulant.

Hence, these two drugs were selected for the development of sustained-release bilayer tablets and polyox WSR coagulant was selected as a release-retarding agent. An IR spectrum of pure gliclazide shows two characteristic peaks. A peak at 3414.85  $\text{cm}^{-1}$  due to NH group and another peak at 1636.79  $\text{cm}^{-1}$  due to C=O as observed in fig. 3B showing no interaction indicating overall compatibility with the polymer HPMC K100M and excipients.

### Characterization of powder blend

The results of the pre compressional parameters such as bulk density, tapped density angle of repose, Hausner's ratio and compressibility index of all batches of SR blend containing metformin hydrochloride and gliclazide exhibited good characteristics. All the formulations showed good compressibility and flow properties than pure drugs. The precompression values of metformin hydrochloride and gliclazide blend were indicated in table 3 and table 4 respectively.

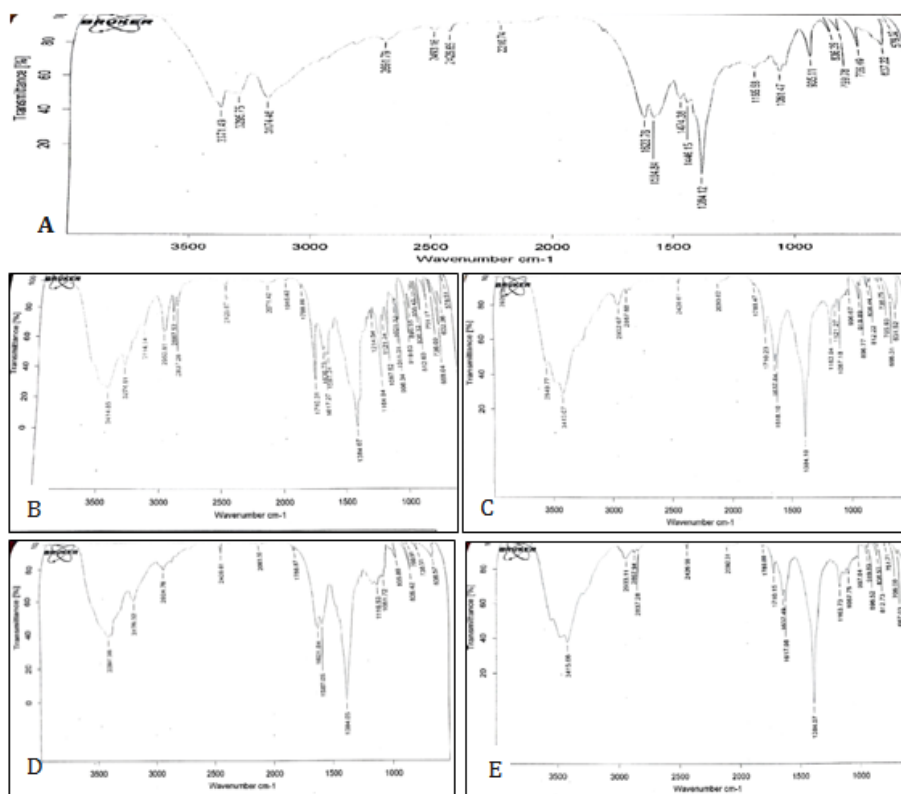


Fig. 3: Fourier transform infrared spectrum (A) Metformin hydrochloride (B) Gliclazide (C) Metformin hydrochloride+Gliclazide (D) Metformin hydrochloride+Polyox WSR coagulant (E) Gliclazide+HPMC K 100M

Table 3: Precompression parameters of metformin hydrochloride formulation M1-M7

Formulation code	Bulk density (g/cm <sup>3</sup> )	Tapped density (g/cm <sup>3</sup> )	Compressibility (%)	Hausner's ratio	Angle of repose (°)
M1	0.62±0.009	0.71±0.038	12.8	1.14	23
M2	0.72±0.012	0.85±0.0983	15.8	1.18	25
M3	0.68±0.018	0.78±0.027	13	1.14	25
M4	0.62±0.06	0.74±0.012	16.5	1.19	22
M5	0.61±0.053	0.79±0.042	22.2	1.28	28
M6	0.62±0.038	0.72±0.082	13.7	1.15	20
M7	0.66±0.039	0.72±0.013	9.14	1.1	18

mean±SD, n = 3 SD=Standard deviation

Table 4: Pre compression parameters of gliclazide formulation G1-G8

Formulation code	Bulk density (g/cm <sup>3</sup> )	Tapped density (g/cm <sup>3</sup> )	Compressibility (%)	Hausner's ratio	Angle of repose (°)
G1	0.65±0.072	0.79±0.082	17.6	1.21	20.6
G2	0.54±0.012	0.69±0.032	22	1.28	21.7
G3	0.57±0.019	0.71±0.015	19.6	1.24	19.7
G4	0.52±0.062	0.68±0.082	22.4	1.29	19.3
G5	0.53±0.083	0.68±0.029	22.5	1.29	22.6
G6	0.54±0.022	0.65±0.072	16.3	1.29	20.1
G7	0.56±0.014	0.69±0.012	19.8	1.24	18.7
G8	0.52±0.092	0.68±0.062	22.4	1.29	19.8

mean±SD, n = 3

Table 5: Physical evaluation of the innovator

Brand name	Exermet GZ 560
Manufacturer	Cipla
Composition	Metformin hydrochloride-500 mg Gliclazide-60 mg
Total weight of the tablet	1000 mg
Thickness	5.3 mm
Drug content	Metformin hydrochloride-99.97±0.11% Gliclazide 99.96±0.41 %

#### Evaluation of post-compression parameters of tablets

All tablets appeared smooth and oblong. The weight of the metformin hydrochloride layer was kept constant to 800 mg. All tablet batches qualify the tablet weight variation test and found variation 100±5 % within range; friability below 1%; drug content

90-110% within limit and deviation in thickness found less than 5%. Results of post-compression parameters of metformin hydrochloride tablets were observed in table 6. The optimized metformin hydrochloride formulation was further used to prepare bilayer tablets using different gliclazide formulations. Results of post-compression parameters of bilayer tablets were observed in table 7.

Table 6: Post compression parameters of metformin hydrochloride formulations M1-M7

Formulation code	Weight variation (mg)	Hardness (Kg/Cm <sup>2</sup> )	Thickness (mm)	Friability (%)	Content uniformity % (layer 1)
M1	800±0.19	7.5±0.23	5.1±0.21	0.41±0.002	99.28±0.57
M2	800±0.38	7.8±0.24	5.02±0.15	0.68±0.005	99.57±0.86
M3	800±0.79	8.5±0.23	5.04±0.23	0.53±0.005	99.75±0.36
M4	800±0.74	8.9±0.26	5.08±0.42	0.36±0.008	99.78±0.87
M5	800±0.56	8.3±0.93	5.11±0.33	0.86±0.002	98.68±0.28
M6	800±0.49	8.5±0.27	5.04±0.13	0.72±0.004	99.83±0.39
M7	800±0.68	8.4±0.23	5.03±0.26	0.93±0.007	99.95±0.26

mean±SD, n = 3

Table 7: Post compression parameters of gliclazide formulation G1-G8

Formulation code	Weight variation (mg)	Hardness (Kg/ Cm <sup>2</sup> )	Thickness (mm)	Friability (%)	Content uniformity (%) (Layer 2)
G1	200±0.67	7.5±0.23	2.11±0.03	0.54±0.0098	98.5±0.83
G2	200±0.29	6.7±0.28	2.01±0.83	0.67±0.0021	99.4±0.75
G3	200±0.57	7.4±0.83	2.13±0.12	0.49±0.0024	99.3±0.62
G4	200±0.75	8.5±0.26	2.17±0.08	0.81±0.0027	99.7±0.69
G5	200±0.38	8.5±0.73	2.04±0.42	0.32±0.0037	99.5±0.62
G6	200±0.32	8.8±0.27	2.08±0.16	0.65±0.0073	98.6±1.04
G7	200±0.61	8.5±0.74	2.04±0.28	0.87±0.0028	98.6±1.67
G8	200±0.85	8.6±0.51	2.03±0.34	0.62±0.0065	99.7±0.19

mean±SD, n = 3



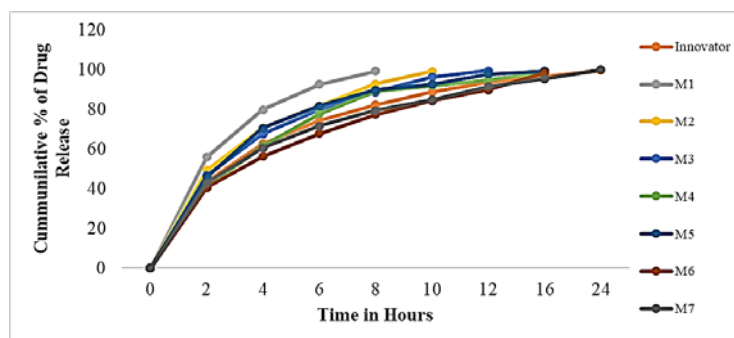
### ***In vitro* dissolution studies of the sustained-release layer containing metformin hydrochloride**

All the formulations subjected to *in vitro* dissolution studies revealed that tablets containing release modifiers exhibited sustained release of metformin hydrochloride and gliclazide. The dissolution profile of formulations containing metformin hydrochloride was represented in fig. 4. The dissolution profile of metformin hydrochloride formulation revealed that M1-M3 formulations released the drug completely by the end of 12 h, which is probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores

for the entry of solvent molecules. A suitable sustained-release formulation should release the required amount of drug in the initial hour, followed by slow release. Formulation M4 (30% HPMC K100M) exhibited the slowest dissolution profile which was consistent with USP specification. In contrast, the release of metformin hydrochloride from formulation M5-M7 prepared using polyox WSR coagulant was extended up to 24 h. Batch M7 prepared by direct compression method using polyox WSR coagulant (25%) exhibited a good drug release profile. Data of comparison of formulations M4 and M7 with innovator by similarity and dissimilarity factor represented in table 8 reveals that M7 is the promising batch and selected as the best formulation for further studies.

**Table 8: Comparison of formulations with innovator by similarity and dissimilarity factor**

Formulation	$f_2$ value	$f_1$ value
M4	72.05	3.6
M7	79.95	2.36

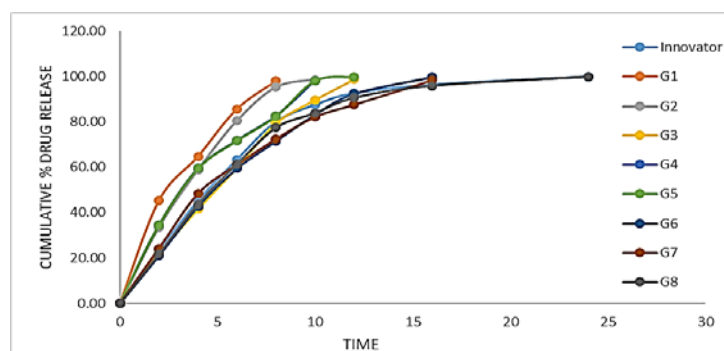


**Fig. 4: *In vitro* dissolution profile of Metformin hydrochloride formulation M1-M7 and innovator**

### **Sustained-release layer containing gliclazide**

The dissolution profile of gliclazide formulations was represented in fig. 5. Formulation G3 and G6 displayed a cumulative release of

nearly 98.7% and 99.6% in 12 h and 16h respectively where 40% of polymers HPMC K4M and K15M were employed. In contrast, the formulation G8 exhibited a better-controlled release profile of 99.8% at 24 h as represented in fig. 5.



**Fig. 5: *In vitro* dissolution profile of gliclazide formulation G1-G8 and Innovator**

Here, the polymer HPMC K100M showed a better rate of retardant ability than the above two variants at a lesser concentration. The hydration rate of HPMC increases with an increase in the Hydroxyl Propyl content and the solubility of HPMC is pH-independent [22]. The water-repelling property of higher variants of HPMC retarded the drug release from the matrix by preventing the penetration of solvent molecules. HPMC K100M was judiciously selected in preparation due to its profound ability to form a strong viscous gel on contact with aqueous media, which helps in controlling the delivery of highly water-soluble drugs [24].

### **Final compression of bilayer tablets**

Based on results of *in vitro* dissolution studies batch M7 of metformin hydrochloride and batch G8 of gliclazide were selected to

prepare bilayer tablets. Initially, the metformin hydrochloride blend was poured into the die cavity and compressed with moderate force. Then the upper punch was lifted and the gliclazide granules were poured in the die cavity, containing initially compressed layer 1 and compressed with full force to form a bilayer tablet of 1000 mg with a hardness of 7-8 Kg/Cm<sup>2</sup> using Cadmach single punch compression machine with 12 mm concave punch and die [26]. The dissolution profiles of the individual layer in the final formulation were compared with the innovator (Exermet GZ 560) and results were represented in fig. 6. From the graphs, it is evident bilayer tablet shows a similar release pattern as Exermet GZ 560 with a good similarity factor 79.95 and 73.62 for metformin hydrochloride and gliclazide respectively. The post-compression parameters of the bilayer tablets were found to be within the limits.

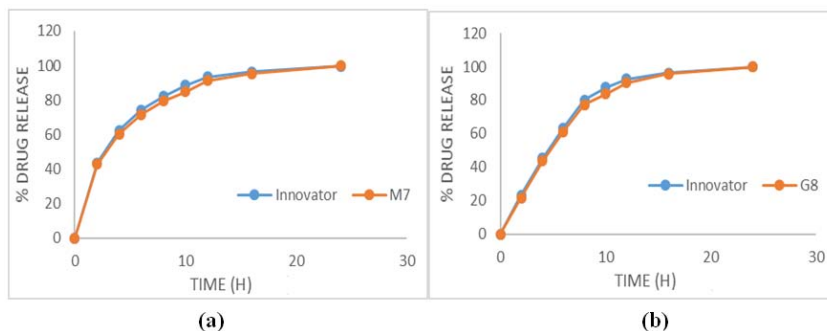


Fig. 6: Comparison of dissolution profiles of (a) Metformin hydrochloride in formulation M7 and Innovator. (b) Gliclazide in formulation G8 and innovator

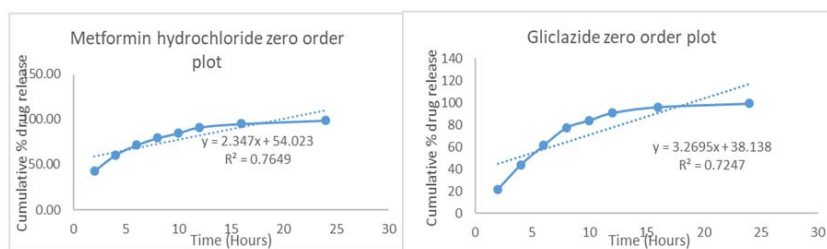


Fig. 7: Zero-order plot of drug release in an optimized bilayer tablet

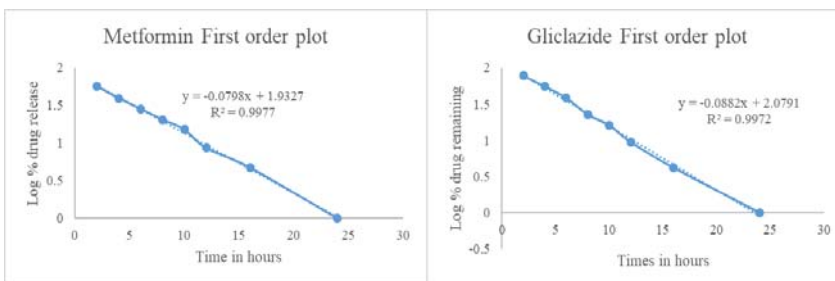


Fig. 8: First Order plot of drug release in an optimized bilayer tablet

**Drug release kinetics**

The release mechanism of metformin hydrochloride and gliclazide from bilayered optimized formulation was studied by fitting the data obtained from *in vitro* release studies into zero-order, first-order, Higuchi and Korsmeyer-Peppas models.

It is evident from fig. 8 that a linear relationship was obtained with 'r' value close to unity and higher than 'r' obtained from the zero-order equation for optimized bilayer formulation of metformin hydrochloride and gliclazide, showing that the release is an apparent first-order process. This indicates that the amount of drug released is dependent on the matrix drug load.

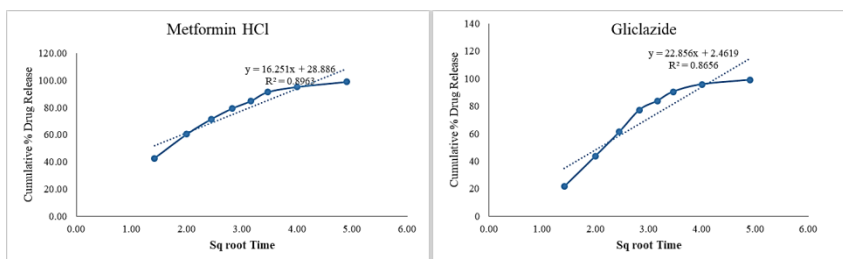


Fig. 9: Higuchi plot of optimized bilayer tablet

The linearity of the Higuchi plot indicates that the release process of metformin hydrochloride and gliclazide from the optimized formulation is diffusion controlled. The Slope values in the Korsmeyer-Peppas equation in fig. 10 indicate that the diffusion mechanism involved was Fickian in the case of metformin

hydrochloride and the Non-fickian in the case of Gliclazide in the final bilayer tablet. Thus, the sustained-release bilayer tablet formulation displayed the release of the required quantity of drug with predetermined kinetics to maintain an effective drug plasma concentration.

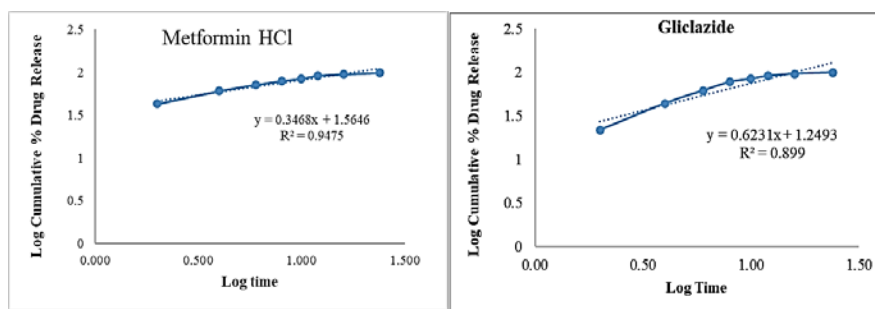


Fig. 10: Korsmeyer-peppas plot of optimized bilayer tablet

### Stability studies

Stability studies of sustained-release bilayer tablets developed in this investigation were carried out for 6 mo in specified conditions. The results reveal that there was no significant change in physical characteristics, % drug content and % drug release in 24 h. when stored at  $40 \pm 2$  °C/ $75 \pm 5$ % RH. Therefore, it has been considered that formulation having good stability.

### CONCLUSION

The monolith diffusion-controlled bilayer tablets of metformin hydrochloride and gliclazide were successfully developed using the lesser concentration of polyox WSR coagulant and HPMC K 100M as retardant polymers respectively. *In vitro* release profiles revealed that 99.93% of the metformin hydrochloride and 99.65% gliclazide were released from the final optimized formulation at the end of 24 h. The drug release follows first order and is diffusion controlled. Therefore, the designed formulation offers improved patient compliance and convenience with better postprandial hyperglycemic control with once-a-day dosing. The sustained release of the drug up to 24 h regulates antidiabetic activity round the clock with minimal side effects.

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### AUTHORS CONTRIBUTIONS

All authors have contributed equally.

### CONFLICT OF INTERESTS

The authors declare no conflict of interests.

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