



Research Article

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Design and *in vivo* Evaluation of Controlled Release Gliclazide Trilayer Matrix Tablets in the Management of Diabetes Mellitus

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ABSTRACT

The purpose of the present study was to develop and optimize multi-layered matrix tablets of Gliclazide trilayer tablets to achieve zero-order drug release for sustained plasma concentration. Gliclazide tablets were prepared by direct compression and consist of middle active layer with different grades of hydroxypropyl methylcellulose (HPMC K 4M, K 15M and K100M), Guar gum and Eudragit L 100. The tablets were also evaluated for physicochemical characteristics and release kinetics. The physicochemical characteristics of the prepared tablets were satisfactory. The developed drug delivery systems showed prolonged drug release rates over a period of 24 h. *In vivo* bioavailability studies were carried out on the optimized formulation (EF14), mean time to attain peak drug concentration (T_{max}) was 6.00 ± 0.14 and 4.02 ± 0.12 h for the optimized and marketed product respectively, while mean maximum drug concentration (C_{max}) was 124.80 ± 1.02 ng/ml and 95.12 ± 1.05 ng/ml respectively. $AUC_{0-\infty}$ 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 EF14 was shown significant plasma concentration with controlled release and maintained for 24 hours with patient compliance by reducing the dosage frequency, when compared with marketed product in the efficient management of Diabetes mellitus.

Keywords: Gliclazide, Trilayer matrix tablet, HPMC, Guar gum, Pharmacokinetic studies.

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INTRODUCTION

Controlled release pharmaceutical systems have been developed and studied to improve the performance of drugs and to increase their pharmacological effect and reduce any side effect. [1] Several design options are available to control or modulate drug release from a

drug delivery system. Most oral controlled release dosage forms fall in the category of matrix, reservoir or multi-layer systems. Lately, multi-layer matrix systems are gaining importance in the design of oral sustained drug delivery systems. 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. [2] The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate. [3] In the device, the coat layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length is counter balanced by the simultaneous increase of the area available for drug release. [4]

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] Guar gum is soluble in water; it swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse and is used for the fabrication of matrices with uniform drug release characteristics. [6]

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. [7]

Gliclazide is an oral hypo glycaemic second-generation sulfonyl urea drug which is useful for a long-term treatment of non-insulin dependent diabetes mellitus (NIDDM). Previous studies showed that gliclazide possesses good general tolerability, low incidence of hypo glycaemia and low rate of secondary failure. Rapid absorption from the GIT is required for the oral hypoglycaemic drug for effective therapy. However, the absorption rate of Gliclazide from the GIT is slow and varied among the subjects. Slow absorption has been suggested to be due to either poor dissolution of Gliclazide due to hydrophobic nature of drug and poor permeability of drug across the GI membrane. [8-9] By incorporation of Gliclazide in the trilayer tablet may control its absorption from GI tract and overcome the variability problems. Thus, this study was undertaken to develop controlled release trilayer matrix tablets of Gliclazide using release retardant and HPMC polymers up to 24 h.

MATERIALS AND METHODS

Materials

Gliclazide (80 mg) film coated tablets were purchased from Orion Pharma Ltd, Mumbai. Gliclazide pure drug

was generous gift from Aurobindo Pharma Limited, Hyderabad, India. Sodium carboxyl methyl cellulose, HPMC K 4 M, HPMC K 15 M & HPMC K 100 M were obtained from Rubicon labs, Mumbai. Kondagogu gum, Eudragit L 100 and Carnauba wax were gifted from MSN Labs Ltd. Hyderabad. All other chemicals used were of analytical grade.

Methods

The following Pre-compression parameters were conducted: Angle of Repose [10], Carr's compressibility Index [11], Bulk Dentistry, Tapped Density [12], Hausner's Ratio. [13]

Formulation of controlled release Gliclazide trilayer matrix tablets

The trilayered matrix tablets of Gliclazide 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 12 hours. 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) so as 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, Kondagogu gum, Sodium CMC, DCP. All the formulations were varied in concentration of polymers, talc (1.5 mg) & magnesium stearate (1.5 mg) 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 12 mm 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. carnauba wax the swelling erosion modelling fillers which include water soluble DCP, EC and Kondagogu gum. The procedure tried to make the compacts was via direct compressions. For the first procedure the wax, Kondagogu gum and the filler was mixed in motor and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted.

Formulation of Gliclazide 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 (12 mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (500 mg). Then the pre-weighed amount of powder equivalent to bottom layer (125 mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and 250 mg of the drug containing middle active layer optimized formulation (F14) 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 (125 mg) 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 tests of trilayer matrix tablets performed by Hardness, Friability [14], Weight variation, Drug content / Assay [15], Swelling & Erosion studies. [16]

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 7.2 at $37 \pm 0.5^\circ\text{C}$ temperature. The amount of drug release was determined by UV visible spectrophotometer (Shimadzu UV 1800) at 229 nm.

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 $40^\circ\text{C}/75\% \text{ RH}$ for the best formulations for 6 months. The tablets were characterized for the hardness, friability, drug content and cumulative % drug release during the stability study period.

Pharmacokinetic study

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°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: 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 six animals. The group A was received prepared Gliclazide matrix Tablets (80 mg), marketed product (80 mg) was administered group B with equivalent dose of animal body weight. Blood samples (approximately 0.5 ml) were obtained with syringes by marginal ear vein at 0, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours 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 5 min to 10 minutes and stored frozen at -20°C until analysis.

HPLC method

For HPLC C8 column with $5\mu\text{m}$ particle size and the mobile phase consisted of acetonitrile and water (pH = 2.5 ± 0.2 adjusted with phosphoric acid) (55:45 v/v), and delivered at a flow rate of 1 ml/min. The eluted peaks were detected by a UV detector was set at wavelength of 230 nm. Internal standard glipizide was used. The retention times of gliclazide and glipizide (IS) were around 6.1 and 3.8 respectively. [18]

Table 1: Formulation trails for middle active layer

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Gliclazide	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80
HPMC K 4M	60	65	70	---	---	---	---	---	---	30	35	35	---	---	---	---
HPMC K 15M	---	---	---	60	65	70	---	---	---	30	30	35	---	---	---	---
HPMC K 100M	---	---	---	---	---	---	60	65	70	---	---	---	60	65	70	75
Eudragit L 100	32	40	42	32	40	42	32	40	42	32	40	42	32	40	42	42
Guar gum	20	22	25	20	22	25	20	22	25	20	22	25	20	22	25	25
Sodium carboxy methyl cellulose	25	15	10	25	15	10	25	15	10	25	15	10	25	15	10	15
Dibasic calcium phosphate	30	25	20	30	25	20	30	25	20	30	25	20	30	25	20	20

Table 2: Composition of Gliclazide trilayer matrix tablet

Ingredients	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14
Middle Active Layer (F14) (mg)								
Gliclazide	80	80	80	80	80	80	80	80
HPMC K 100M	65	65	65	65	65	65	65	65
Eudragit L 100	40	40	40	40	40	40	40	40
Guar gum	22	22	22	22	22	22	22	22
Sodium carboxy methyl cellulose	15	15	15	15	15	15	15	15
Dibasic calcium phosphate	25	25	25	25	25	25	25	25
Upper And Lower Layer (mg)								
Carnauba wax	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

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 stream 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 $t_{1/2}$ 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.

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

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 AF14 to HF14 showed good flow properties, the results are summarized in table 3.

TRILAYER TABLETS

Preparation of middle active layer

The matrix tablets of Gliclazide were prepared without the barrier layers. All the formulation trails were subjected to *in vitro* dissolution to determine the release profiles. From the above results, among all the

formulations the formulation F14 was decided as optimized formulation for active layer based on the highest drug release i.e. 99.60 ± 5.25 within 12 hours when compared with other preparations (table 4, 5 & figure 4, 5). Formulation F14 was chosen as active layer for further studies.

Evaluation of trilayer matrix tablets of Gliclazide

The Gliclazide trilayer matrix tablets are shown in figure 3. Sustained release tablets generally have hardness in the range of 7-10 kg/cm². In case of trilayer tablets the hardness of the tablets was found to be 7.2 to 7.8 kg/cm². 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 6. In phosphate buffer pH 6.8, HPMC showed good swelling property. In trilayer tablets of Gliclazide, EF14 showed highest degree of swelling index 219.43%, where as in EF14 showed leased swelling with a swelling index of 134.68%.

Table 3: Powder flow properties of Trilayer tablets

Powder properties	Bulk density (g/cc)	Tapped density(g/cc)	Angle of repose (o)	Carr's index
AF14	0.715 ± 0.04	0.787 ± 0.10	33.69 ± 0.63	8.09 ± 0.91
BF14	0.712 ± 0.46	0.790 ± 0.93	34.93 ± 0.66	8.02 ± 0.93
C F14	0.512 ± 0.02	0.629 ± 0.17	33.12 ± 0.63	9.49 ± 0.51
D F14	0.705 ± 0.14	0.767 ± 0.2	31.89 ± 0.43	8.29 ± 0.91
E F14	0.714 ± 0.56	0.795 ± 0.93	24.39 ± 0.66	8.35 ± 0.94
F F14	0.684 ± 0.78	0.746 ± 0.82	33.09 ± 0.27	7.62 ± 0.58
G F14	0.695 ± 0.02	0.781 ± 0.048	28.15 ± 0.02	7.28 ± 0.33
H F14	0.704 ± 0.56	0.796 ± 0.93	26.39 ± 0.66	8.15 ± 0.94

Table 4: Dissolution profile of different formulations Gliclazide active layer (F1-F8)

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	15.18 ± 0.95	18.19 ± 0.98	17.24 ± 0.97	22.34 ± 1.05	19.03 ± 0.99	13.26 ± 0.93	16.14 ± 0.96	21.68 ± 1.02
2	32.20 ± 2.23	35.36 ± 2.24	21.36 ± 1.30	33.67 ± 2.20	28.56 ± 1.36	25.64 ± 1.38	24.38 ± 1.36	30.13 ± 2.01
4	40.38 ± 2.45	46.14 ± 2.65	30.18 ± 2.01	38.14 ± 2.19	37.28 ± 2.34	34.67 ± 2.12	32.47 ± 2.10	48.24 ± 2.69
6	52.64 ± 2.85	59.58 ± 2.96	48.27 ± 2.69	45.23 ± 2.62	50.12 ± 2.80	48.67 ± 2.68	47.56 ± 2.66	59.75 ± 2.96
8	64.38 ± 3.15	69.32 ± 3.32	59.46 ± 2.96	64.12 ± 3.18	68.14 ± 3.32	62.17 ± 3.10	57.52 ± 2.99	60.36 ± 2.97
10	77.29 ± 3.84	72.08 ± 3.80	75.04 ± 3.88	82.78 ± 4.51	89.24 ± 4.98	74.16 ± 3.88	76.61 ± 3.83	78.41 ± 3.95
12	89.44 ± 4.99	93.14 ± 5.03	91.21 ± 5.01	93.54 ± 5.10	95.12 ± 5.15	88.17 ± 4.89	92.32 ± 5.08	90.32 ± 5.01

Table 5: Dissolution profile of different formulations Gliclazide active layer (F9-F16)

Time (h)	F9	F10	F11	F12	F13	F14	F15	F16
0	0	0	0	0	0	0	0	0
1	14.20 ± 0.94	18.04 ± 0.98	20.78 ± 1.01	16.04 ± 0.96	19.24 ± 0.99	29.09 ± 1.40	17.29 ± 0.97	22.54 ± 1.08
2	25.34 ± 1.37	29.56 ± 1.97	28.57 ± 1.97	28.56 ± 1.58	22.38 ± 1.33	47.78 ± 2.79	26.30 ± 1.36	35.21 ± 2.15
4	38.30 ± 2.42	38.17 ± 2.40	37.64 ± 2.40	30.89 ± 2.50	36.19 ± 2.15	58.12 ± 2.96	35.48 ± 2.15	50.17 ± 2.81
6	46.38 ± 2.67	54.84 ± 2.70	50.32 ± 2.60	42.38 ± 2.60	58.27 ± 2.85	67.36 ± 3.78	58.51 ± 2.95	62.38 ± 3.12
8	69.74 ± 3.26	68.39 ± 3.25	60.19 ± 3.10	62.17 ± 3.83	74.54 ± 3.78	79.48 ± 3.97	75.27 ± 3.81	71.17 ± 3.80
10	75.96 ± 3.83	80.47 ± 4.32	75.27 ± 3.83	74.58 ± 3.51	80.67 ± 4.55	88.57 ± 4.98	85.66 ± 4.68	84.23 ± 4.62
12	89.30 ± 4.99	91.05 ± 5.02	93.28 ± 5.10	89.03 ± 4.99	90.24 ± 5.01	99.60 ± 5.25	92.30 ± 5.02	94.19 ± 5.12

Table 6: Physical evaluation of Trilayer tablets

S. No	Tests	AF14	BF14	CF14	DF14	EF14	FF14	GF14	HF14
1	Hardness (Kg/Cm ²)	7.2 ± 0.15	6.1 ± 0.10	6.8 ± 0.24	7.1 ± 0.10	7.8 ± 0.26	7.5 ± 0.18	6.7 ± 0.23	7.3 ± 0.16
2	Friability (%)	0.15	0.28	0.26	0.30	0.35	0.18	0.23	0.24
3	Weigh variation (mg)	596 ± 20	599 ± 20	595 ± 20	594 ± 20	597 ± 20	595 ± 20	596 ± 20	600 ± 20
4	Assay (%)	97.51	96.82	96.24	97.07	98.96	97.41	96.12	95.14

Table 7 (a): *In-vitro* dissolution studies of Gliclazide Trilayer tablets

Time (h)	AF14	BF14	CF14	DF14	EF14
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	5.26 ± 0.35	8.26 ± 0.38	10.47 ± 0.48	12.24 ± 0.54	15.26 ± 0.95
2	18.29 ± 0.98	15.14 ± 0.95	13.36 ± 0.93	20.24 ± 1.01	28.45 ± 1.30
4	22.46 ± 1.08	25.26 ± 1.28	28.39 ± 1.30	30.36 ± 2.10	37.14 ± 2.18
6	34.67 ± 2.15	30.12 ± 2.10	32.64 ± 2.10	42.39 ± 2.67	46.39 ± 2.69
8	48.29 ± 2.70	42.34 ± 2.67	45.63 ± 2.68	54.14 ± 2.41	58.64 ± 2.45
10	54.67 ± 2.41	51.26 ± 2.38	58.47 ± 2.45	63.66 ± 2.60	67.39 ± 2.70
12	65.23 ± 2.63	63.40 ± 2.60	60.24 ± 2.58	71.29 ± 3.77	77.66 ± 3.85
16	74.28 ± 3.81	72.16 ± 3.78	76.29 ± 3.84	82.14 ± 4.32	89.24 ± 4.98
20	82.19 ± 4.34	84.39 ± 4.38	80.15 ± 4.30	89.45 ± 4.98	92.14 ± 5.04
24	92.14 ± 5.01	90.24 ± 5.00	94.39 ± 5.10	96.17 ± 5.15	98.26 ± 5.39

Table 7 (b): *In-vitro* dissolution studies of Gliclazide Trilayer tablets

Time (h)	FF14	GF14	HF14	COMPRID
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	11.29 ± 0.53	13.18 ± 0.93	7.38 ± 0.37	3.16 ± 0.30
2	14.14 ± 0.94	22.25 ± 1.08	24.15 ± 1.27	8.24 ± 0.38
4	18.28 ± 0.98	33.18 ± 2.14	35.64 ± 2.16	15.26 ± 0.95
6	25.16 ± 1.28	45.67 ± 2.68	40.19 ± 2.65	22.14 ± 1.08
8	37.14 ± 2.18	56.34 ± 2.45	53.28 ± 2.41	30.18 ± 2.10
10	48.67 ± 2.70	65.26 ± 2.63	60.28 ± 2.58	42.13 ± 2.67
12	52.39 ± 2.39	74.26 ± 3.81	73.14 ± 3.79	48.29 ± 2.70
16	68.17 ± 2.71	80.24 ± 4.32	85.16 ± 4.85	59.26 ± 2.48
20	75.36 ± 3.83	85.36 ± 4.38	87.29 ± 4.97	70.16 ± 3.75
24	89.28 ± 4.98	91.63 ± 5.01	93.64 ± 5.05	95.26 ± 5.15

Table 8: Pharmacokinetic Parameters of Gliclazide optimized formulation and marketed product

Parameters	Gliclazide Optimized formulation	Marketed product
C _{max} (ng/ml)	124.80 ± 1.02	95.12 ± 1.05
AUC _{0-t} (ng h/ml)	330.65 ± 1.12	212.25 ± 1.02
AUC _{0-∞} (ng h/ml)	417.75 ± 1.14	328.14 ± 1.02
T _{max} (h)	6.00 ± 0.14	4.02 ± 0.12
t _{1/2} (h)	7.5 ± 0.014	5.15 ± 0.05

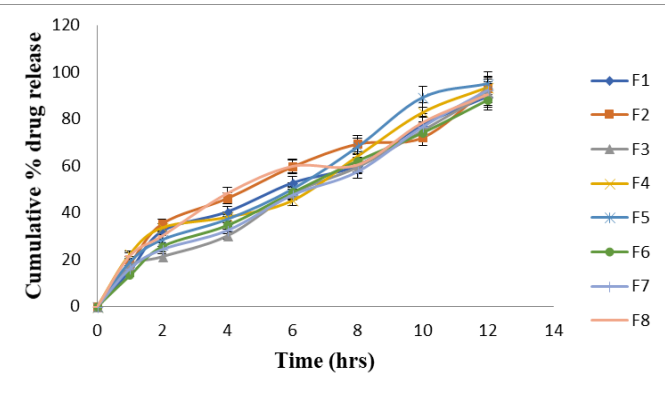


Fig. 1: *In vitro* Dissolution profile of F1-F8 Gliclazide active layer formulations

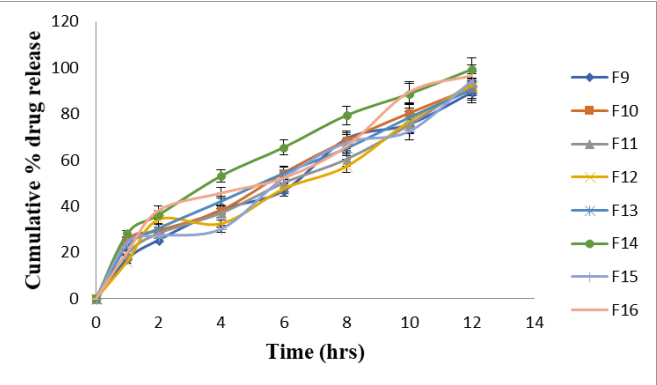


Fig. 2: *In vitro* Dissolution profile of F9-F16 Gliclazide active layer formulations

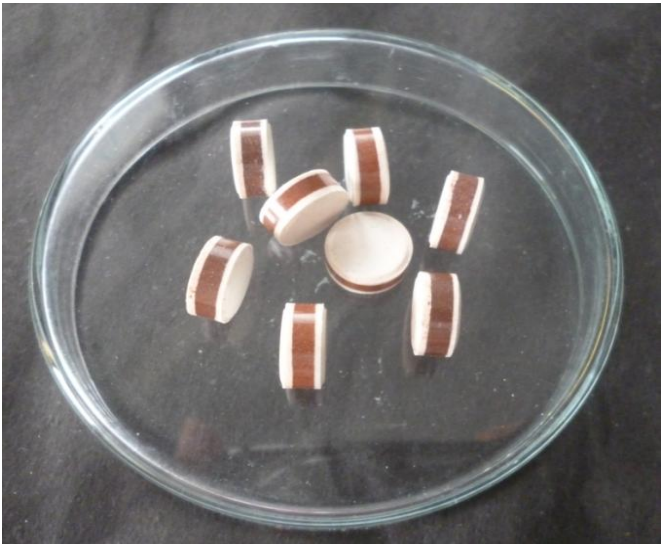


Fig. 3: Preparation of Gliclazide trilayer matrix tablets

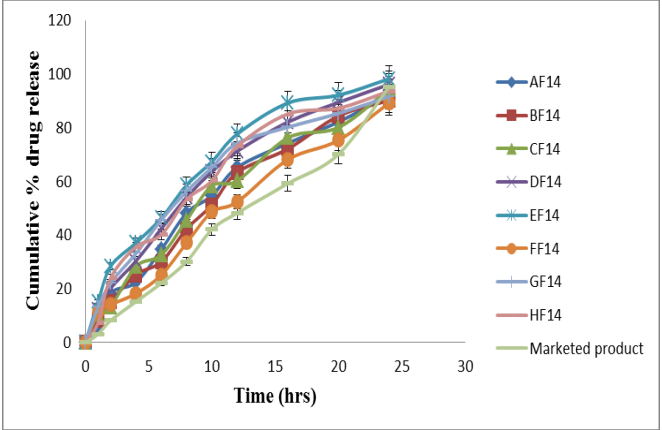


Fig. 4: *In-vitro* dissolution studies of AF14-HF14

In vitro dissolution studies of Gliclazide Trilayer tablets

The release of Gliclazide from different formulations was carried out in phosphate buffer pH 6.8 and the results are depicted in Tables 7(a) and 7(b). The trilayer tablets extended the drug release up to 24 hours. The highest drug release was found in the formulation EF14 i.e 98.29% within 24 h. EF14 was found to be optimized formulation based on the dissolution and other evaluation parameters. The comparison of marketed product Gliclazide (200 mg) film coated tablet and optimized formulation EF14 was shown in figure 4. The drug release from marketed product was 95.26% within 24 hours.

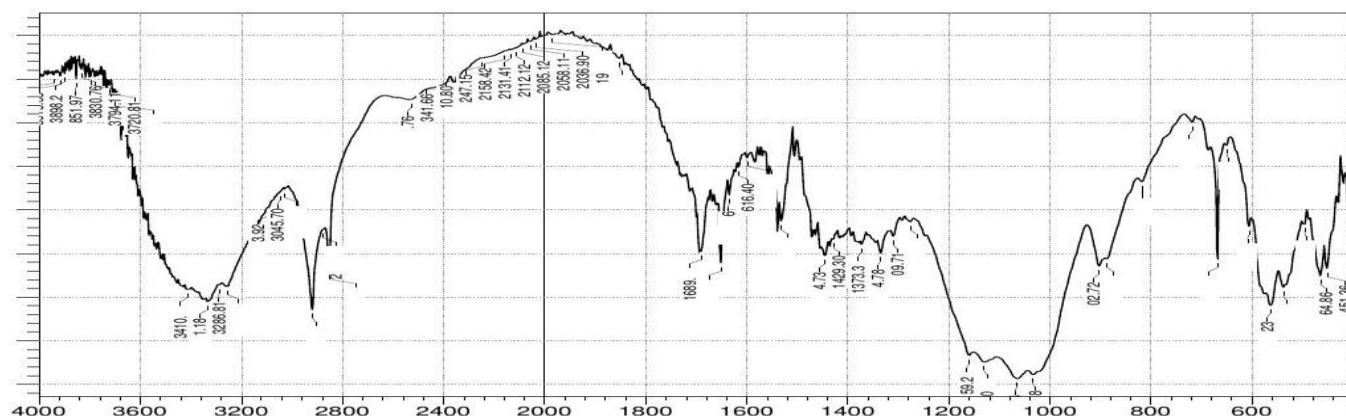


Fig. 7: FT-IR spectrum of pure drug Gliclazide

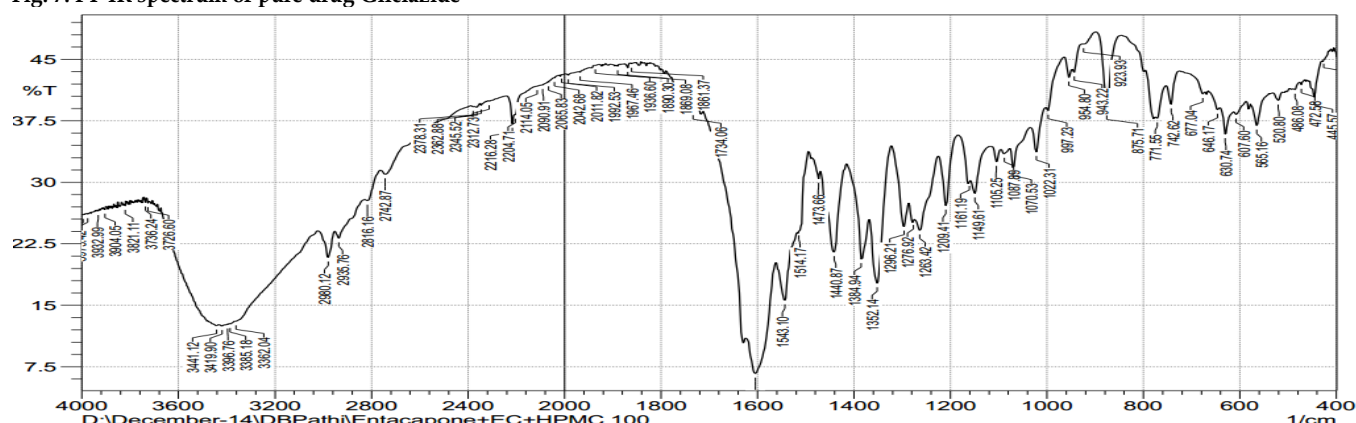


Fig. 8: FT-IR spectrum of pure drug and other polymers

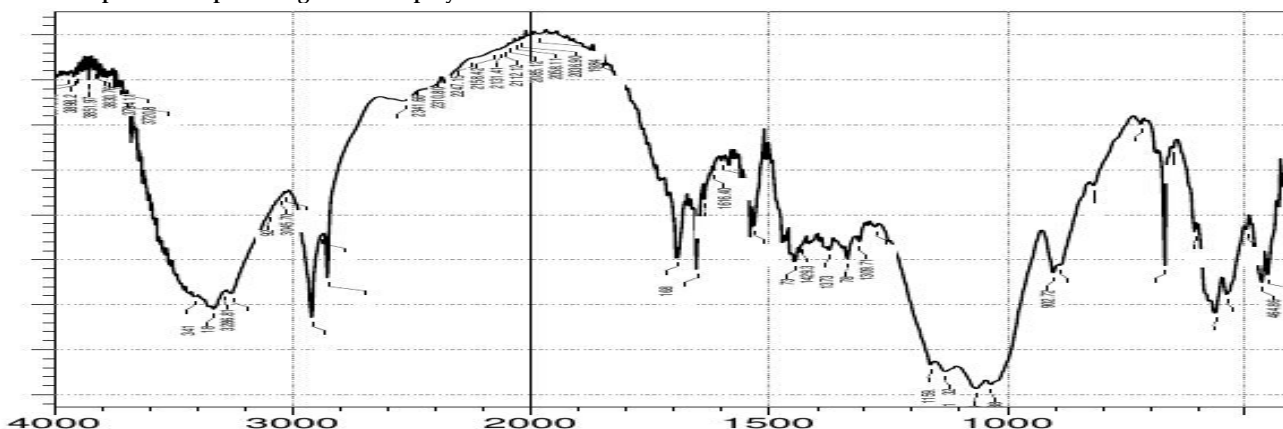


Fig. 9: FT-IR spectrum of optimized formulation EF14

In vitro dissolution studies of Gliclazide Trilayer tablets formulated in different trails

Characterization

FT-IR

Overall there was no alteration in peaks of Gliclazide 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

DSC was used to detect interaction between Gliclazide and excipients. The thermogram of Gliclazide exhibited a sharp endotherm melting point at 163°C. The thermo

gram of optimized formulation of Gliclazide exhibited a sharp endotherm melting point at 165°C. The DSC thermo gram retained properties of Gliclazide, 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

Optimized formulation was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences.

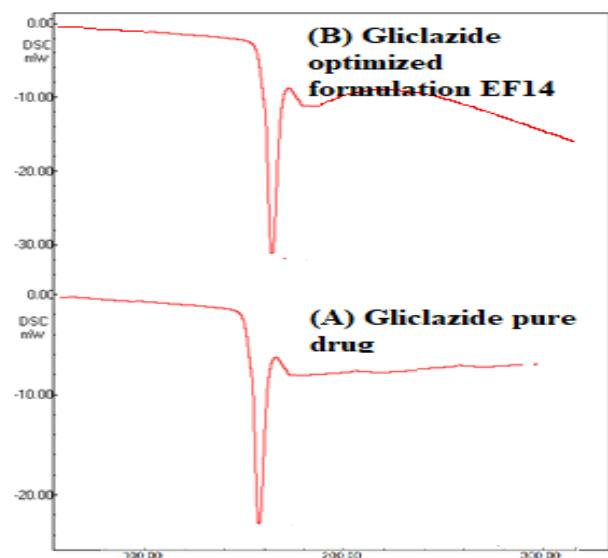


Fig. 10: DSC thermogram of Gliclazide pure drug (A) and optimized formulation EF14 (B)

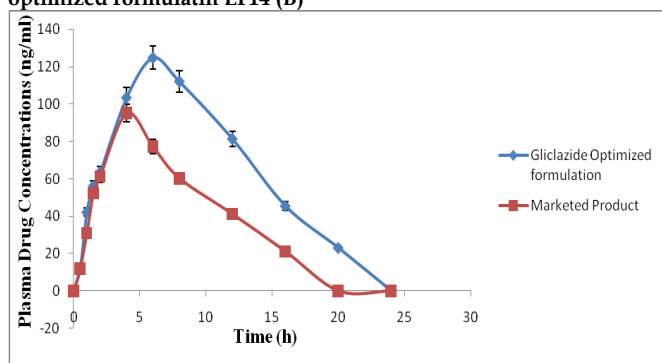


Fig. 11: Plasma concentrations of gliclazide Optimized formulation (EF14) and Marketed Product at different time intervals

Bioavailability Parameters

Mean plasma concentration profiles of prepared gliclazide optimized formulation and Marketed product are presented in figure 11. Gliclazide optimized formulation exhibited as sustained release *in vivo* when compared with Marketed product. All the pharmacokinetics parameters displayed in table 8. The release pattern of both marketed and test formulation showing sustained release pattern. The T_{max} of the optimized formulation was (6.01 ± 0.04 h) and Marketed Product T_{max} was (4.02 ± 0.12 h). 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 (95.12 ± 1.05 ng/ml) was significantly different from the test preparation (124.80 ± 1.02 ng/ml). However, the $AUC_{0-\infty}$ values for the two formulations were significantly different test formulation (417.75 ± 1.14 ng h/ml) and marketed (328.14 ± 1.02 ng h/ml). This suggests that the gliclazide contained in the test product was completely absorbed showing more bioavailability when compared with marketed Product.

It was concluded that Trilayer matrix tablets of Gliclazide can be successfully prepared by direct compression technique using different polymers combination. Based on the evaluation parameters, drug

dissolution profile and release drug kinetics EF14 was found to be optimized formulation. *In vitro* studies were conducted for optimized Gliclazide trilayer tablets and marketed product, the results were indicating that the optimized Gliclazide formulation was shown sustained release patterns where marketed product was shown immediate release. *In vivo* bioavailability studies were carried out on the optimized formulation (EF14), mean time to attain peak drug concentration (T_{max}) was 6.00 ± 0.14 and 4.02 ± 0.12 h for the optimized and marketed product respectively, while mean maximum drug concentration (C_{max}) was 124.80 ± 1.02 ng/ml and 95.12 ± 1.05 ng/ml respectively. AUC_{0-t} and $AUC_{0-\infty}$ 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 HF14 was shown significant plasma concentration with controlled release and maintained for 24 hours with patient compliance by reducing the dosage frequency, when compared with marketed product in the efficient management of Diabetes mellitus.

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