Volume 3 (3), 2015, Page-794-802
CODEN (USA)-IJPRUR, e-ISSN: 2348-6465

PHS Scientific House
PHARMAHEALTHSCIENCES

International Journal of Pharma Research and Health Sciences

Available online at www.pharmahealthsciences.net

Original Article

Formulation and Characterization of Metformin Hydrochloride and Gliclazide Bilayer Tablets

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ARTICLE INFO

Received: 05 May 2015
Accepted: 28 Jun 2015

ABSTRACT

In the present work bilayered tablets of metformin hydrochloride and gliclazide were prepared by using different concentration of polymers of various grades of HPMC, Carboxy methyl cellulose, Calcium phosphate dibasic anhydrous, Micro crystalline cellulose, PVP, Lactose monohydrate All the granules from seven formulations posses good flow property as angle of repose of Layer-I granules (Metformin HCl) was found between32.33° to 34.43° and Layer II granules (Gliclazide) was found between 32.05° to 34.52° which specified within the limit of 31° to 35° and the flow type is good.. In all the formulations weight variation was within the I.P limits.(± 5%). The hardness of the different formulations ranged from 9-11 kg/cm^2. All the formulations exhibited less than 1% friability. The drug content analysis of Metformin and Gliclazide in all formulations was found within the I P limits (±5%) which indicate that the drug was uniformly distributed in the tablets. The in-vitro dissolution study was performed for layer I (Metformin) upto 10hrs (1hour,2 hour,6 hour and 10hours) and for layer II (Gliclazide) upto 12hrs (2hour,4hour,8hour and 12hour) . The bilayer tablet contributing initial loading dose and dissolves rapidly, the remainder of the drug in the extended release was constant rate till the end of the dissolution process.The I.R spectra proved that there was no interaction between the polymer/ excipients and Metformin, Gliclazide. The stability study of Formulation F7 showed after three month that there was no degradation and the drug was stable under accelerated and real time stability conditions.

Key words: Bilayered, Metformin, Gliclazide, Sustained release.

1. INTRODUCTION

Combination therapy have various advantages over monotherapy such as problem of dose dependent side effects are minimized.[1, 2] A low dose combination of different agents reduce the dose related risk, the addition of one agent may counteract some deleterious effect of other. Using low dose of different agents

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minimizes the clinical and metabolic side effects that occur with maximal dosage of individual component of tablet and thus dosage of single component can be reduced in the form of combination therapy[3].

Bilayer tablets are type of multiple compressed tablets. Tablets are composed of two layers of granulation and have similar actions or support the action of one layer with another layer prepared by compression. Bilayer tablets require fewer material than compression coated tablets, which weigh less and may be thinner. Bilayer tablet is suitable for sequential use of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is as initial dose which releases the drug slightly faster rate when compared to another layer and second layer is maintenance dose.

The present study aims to develop and evaluate to provide a combined therapy through a single tablet in which combination of Metformin hydrochloride and Gliclazide were used. Metformin hydrochloride belongs to biguanide group. Gliclazide is a second generation of sulphonyl urea. Hence the combination of Metformin and Gliclazide may help in the treatment of Non Insulin Dependent Diabetes Mellitus (NIDDM).

Depends upon the severity of the conditions of the patients, the dose of Metformin hydrochloride is 500mg to 4gm, daily orally and Gliclazide is 40mg to 160mg daily orally. Due to raising problems with conventional tablet resulting fluctuations of drug plasma levels, bilayer tablets of Metformin HCl 500mg and Gliclazide 60mg in a single unit having different release profile which improves patient compliance and prolong the drug action resulting in effective therapy along with better control of plasma drug levels.

In the present study Metformin HCl and Gliclazide bilayer tablets were formulated consisting of two layers. Metformin [Layer 1] granulation was prepared by using Hydroxy Propyl Methyl Cellulose (HPMC-15cps, HPMC-K_4M) and sodium carboxy methyl cellulose and Gliclazide [Layer -2] granulation was prepared by using HPMC –K_{100}LV and iron oxide red showing differentiation between two layers with the aim to attain once daily dosage from to enhance the bioavailability of the drug. Both granules were prepared by wet granulation method using povidone K-30 solution (Povidone K-30 in distilled water) as binders and granulating agent.

2. MATERIALS AND METHODS

Metformin Hydrochloride IP and Gliclazide BP was olleted as gift samples from Wanbury Ltd, Mumbai and Zhejiang jiuzhou Pharma CO Ltd, Shanghai respetively. All the polymers and excipients are collected as gift samples from Cabot Sanmar Ltd,Chennai.

Preparation of Metformin Hydrochloride Granules (Layer -1)

Various formulations (F_1-F_7) were prepared with Hydroxypropylmethyl cellulose of different grades like HPMC-K4M, HPMC-15cps and Sodiumcarboxymethylcellulose polymers and other ingredients as mentioned in Table no: 1.

The granules were prepared by wet-granulation technique. Metformin Hydrochloride, HPMC-K_4M, HPMC -15cps, SCMC and Dicalcium phosphate were sifted through #40 mesh. The sifted blend was allowed to mix thoroughly in rapid mixer granulator for 15mints at slow speed. The binder solution was prepared by dissolving povidone in purified water. The prepared binder solution was added to mixed blend slowly and allowed to mix uniformly until to get granules. The resulting granules were allowed to dry in drier at 60°C until the LOD (Loss on drying) of granules was reached limit between 2-3%w/w. The dried granules were sifted through #16 mesh and the

granules was pre lubricated with colloidal silicon di oxide and talc for 5mints in RMG. The blend was finally mixed with magnesium stearate (which was sifted through # 60) for 2min in RMG. Final blend was collected and stored for compression.

Table 1: Composition of Various Trial Formulations Containing500mg of Metformin Hcl (Layer I)

S.no	Ingredients (mg)	Formulation code						
		F1	F2	F3	F4	F5	F6	F7
1	Metformin Hydrochloride	500.00	500.00	500.00	500.00	500.00	500	0.00 500.00
2	HPMC-K_4M	10.00	20.00	20.00	40.00	40.00	60.00	60.00
3	Sodium carboxy methyl cellulose	200.00	200.00	200.00	200.00	200.00	200.00	200.00
4	HPMC-15Cps	--	5.00	10.00	5.00	10.00	15.00	20.00
5	Dicalcium phosphate anhydrous	105.00	90.00	85.00	70.00	65.00	40.00	35.00
6	Povidone K-30	8.00	8.00	8.00	8.00	8.00	8.00	8.00
7	Purified water	qs	qs	q.s	qs	qs	qs	qs
8	Colloidal silicon dioxide	5.00	5.00	5.00	5.00	5.00	5.00	5.00
9	Talc	8.00	8.00	8.00	8.00	8.00	8.00	8.00
10	Magnesium stearate	9.00	9.00	9.00	9.00	9.00	9.00	9.00

Weight of Layer-I (Metformin HCl part):845mg

Preparation of Gliclazide Granules (Layer -2)

Various formulations (F_1.F_7) were prepared by taking appropriate quantities of the ingredients as mentioned in Table no: 2

Table 2: Composition of Various Trial Formulations Containing60mg of Gliclazide (Layer -2)

S.NO	Ingredients (mg)	Formulation Code						
		F1	F2	F3	F4	F5	F6	F7
1	Gliclazide	60.00	60.00.	60.00	60.00	60.00	60.00	60.00
2	Microcrystalline cellulose	75.00	70.00	65.00	55.00	45.00	45.00	40.00
3	Povidone –K-30	5.00	5.00	5.00	5.00	5.00	5.00	5.00
4	Purified water	qs	qs	qs	qs	qs	qs	qs
5	Lactose DCL-15	79.00	71.5	64.00	61.5	59.00	44.00	39.00
6	HPMC K100 LV	25.00	37.5	50.00	62.5	75.00	90.00	100.00
7	Magnesium stearate	3.00	3.00	3.00	3.00	3.00	3.00	3.00
8	Iron oxide red	3.00	3.00	3.00	3.00	3.00	3.00	3.00

The granules were prepared by wet granulation method. Gliclazide and MCC were passed through #40 mesh. The binder solution was prepared by dissolving the povidone in purified water. The sifted blend was mixed in rapid mixer granulator at 150 rpm for 15mints in slow speed. The binder solution was added to the blend and allowed to mix thoroughly until to get granules. The obtained granules was dried in fluidized bed drier at 60°C for 60mints until to get LOD of granules not less than 2%w/w. The dried granules were sifted through #20 meshes.HPMC-K_{100}LV, Lactose DCL-15 and iron oxide red were sifted through sieve no#40&100 mesh and mixed with dried granules for 10mints in RMG. The granules thus obtained was mixed with magnesium stearate (which was sifted through sieve no#60) for 2mints. Final blend was collected and stored for compression.

Prior to compression, the granules are evaluated for their characteristic parameters such as bulk density, tapped density, compressibility index, angle of repose and Hausner's ratio.

Preparation of bilayer tablets

Bilayer tablet making machine consists of two hoppers and two feed frames separately without intermixing first and second layer of granules. Initially the die cavity was adjusted for proper die cavity filling and pressure adjustment was made to get proper hardness of tablet. Now granules are ready for compression of bilayer tablet.

Metformin HCl granules (Layer-1) were taken in one hopper and Gliclazide (Layer-2) was taken in another hopper. Metformin HCl granules (Layer-1) were compressed lightly. Over this compressed layer the required quantity of Gliclazide granules (Layer-2) was fed and compressed again. Second layer was differentiated by colored granulation.

The tablets are compressed using 19.2 x 8.9mm plain punch on 27 stations double rotary compression machine (Cadmech India Co Pvt Ltd). The final compressed bilayer tablet was hardness limit range 8-12Kg/cm^2 and thickness 5-8mm. The final tablet contains Metformin HCl 500mg and Gliclazide 60mg and the total weight of each tablet was 1095mg.

Evaluation Tests For Bilayer Tablets Of Metformin Hcl And Gliclazide

Tablet evaluation tests [4]

Hardness test or crushing strength

The tablet was placed horizontally in contact with the lower plunger of the Monsantro hardness tester and zero reading was adjusted. Then the tablet was compressed by forcing the upper plunger until the tablets breaks and this force was noted.

Friability test

Friability is the loss of weight of tablet in the container\ package due to removal of fine particles from the surface.

It is usually measured by Roche friabilator. Ten tablets are weighed initially (w_1) and placed in the in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After 4 minutes of this treatment or 100 revolutions, the tablets are weighed(w_2) and this was compared with the initial weight of the tablet. The loss of weight may be due to abrasion is a measure of a tablet friability. The value is expressed in percentage. A maximum loss of weight not greater than 1% acceptable for most of tablets. The friability was determined using the following formula

$$\text{Friability} = \frac{(W_1 - W_2) \times 100}{W_1}$$

Where

W_1 = weight of ten tablets before test.

W_2 = weight of ten tablets after test.

Weight variation test

Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablet was noted. Average weight was calculated from the total weight of the tablets. The individual weight was compared with average weight. The weight of not more than two tablets must not deviate from the average weight by more than the percentage given in the standard table and no tablet should deviate by more than double the percentage. The percentage deviation was calculated by using the formula

$$\text{Percentage deviation} = \frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \times 100$$

Estimation of drug content

1. For Metformin hydrochloride

To determine the amount of drug present in each formulation, 20 tablets were taken and crushed to powder with mortar and pestle. The powder equivalent to 100mg of Metformin hydrochloride was taken to a 1000ml volumetric flask and dissolved in 300ml of methanol and sonicated for 10minutes. Then 500ml of boiling water was added shaken well and sonicated for 20minutes. The flask was kept aside for some time until it reached to room temperature. Finally the volume was make up with with distilled water and allowed to settle for 20minutes. From this 2ml of supernatant liquid was taken and make upto 100 ml with distilled water. The amount of Metformin hydrochloride was calculated by measuring the absorbance at 233nm using distilled water as a blank UV spectrophotometer was used for the analysis.[5]

2. For Gliclazide

To determine the amount of drug in each formulation, 5 tablets were taken and crushed to powder by using mortar and pestle. The powder equivalent to 100mg of Gliclazide was weigh and transfer to 1000ml

volumetric flask and allowed to dissolve in 200ml methanol and sonicated for 5minutes. Then 400ml of buffer pH7.4 was added and warm the solution for 5minutes. The solution was stirred magnetically for 20minutes till the powder was completely dispersed. Then the solution was shaken well and cooled to room temperature and make upto 1000ml with buffer pH 7.4 and finally filtered. The absorbance of resulting solution was measured at 228nm using UV spectrophotometer.[5] Phosphate buffer pH 7.4 as blank.

IR Spectral analysis

The KBR disc method was used for preparation of sample and spectra were recorded over the wave number 4000 to 500cm^{-1} in a SHIMADZU FTIR Spectrophotometer. The IR spectral analysis for drug and polymer was carried out. The FT-IR studies of pure Metformin HCl, Gliclazide, HPMC K4M, HPMC 15cps, HPMC K100 LV, MetforminHCl+HPMC K4 M, MetforminHCl+HPMC 15cps, Gliclazide+HPMC K100LV,Metformin HCl+Gliclazide+HPMC K4-M+HPMC 15cps+ HPMC K100-LV(all polymers with higher proportions) and formulation of Metformin and Gliclazide bilayer tablet containing higher proportions of polymers were carried out to study the interaction between the drug and polymer.

In-Vitro Dissolution Studies

For Metformin Hydrochloride

Dissolution studies of Metformin HCl were carried out as per the USPNF 26 method with some modifications. Dissolution studies were performed in 900ml of distilled water using USP Type II paddle method at 75rpm and the temperature at 37±0.5°C. The first layer of Metformin HCl tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10hours.10ml of sample was withdrawn after 1st hour, 2nd hour, 6th hour and 10th hour.[130] The fresh dissolution medium was replaced every time with same quantity of dissolution medium. Collected samples were suitably diluted to 100ml with distilled water in 100ml standard flask and analysed at 233nm using distilled water as blank. The percentage drug release was calculated.[6]

For Gliclazide

In-vitro drug releases was performed as per the method described by Dhirendra kumar et al [6] with slight modification.

Dissolution study was carried out using USP dissolution apparatus Type II at pH-7.4 phosphate buffer for 2nd hour, 4th hour, 8th hour and 12th hour. The drug release study was performed at the above time intervals and the drug release was estimated by HPLC method.

HPLC Experimental Method

Chromatographic conditions

Mobile phase used for analysis consist of acetronitrile : buffer (pH 7.4) in the ratio of 60:40 (buffer containing 3ml Triethylamine and 3ml Phosphoric acid per 900ml). It was passed through 0.45µm membrane filter and degassed by ultrasonication. The flow rate was maintained at 20µL / min. The column and the HPLC system were kept in ambient temperature. Prior to the injection of the drug solution, the column was equilibrated for at least 30mints with the mobile phase flowing through the analytical column.

Stability Studies

The formulation F7 was packed in Alu-PVC Blister and kept at 40°C±2°C and 75%RH±5%. Samples were analysed for drug content and in-vitro dissolution studies in the intervals of 1,2,3 months. The real time stability studies were carried out at 30°C±2°C and 65%RH±5% for in-vitro dissolution studies.

3. RESULTS AND DISCUSSION

Evaluation of Powder blend of Metformin HCl and Gliclazide bilayer tablet formulation

The powder blend of Metformin HCl and Gliclazide were evaluated and the results are shown in Table No: 3.

Table 3: Evaluation Of Powder Blend Of Metformin Hcl (Layer 1) And Gliclazide(Layer 2) Granules

S. no	Formulaion Code	Bulk density (g/cm^3)		Tapped density (g/cm^3)		Angle of repose (θ)		Compressibility index (%)		Hausner's ratio	
		Layer 1	Layer 2	Layer 1	Layer 2	Layer 1	Layer 2	Layer 1	Layer 2	Layer 1	Layer 2
1.	F1	0.41±0.005	0.45±0.001	0.48±0.03	0.51±0.01	34.01±0.61	32.27±0.11	14.58±0.03	11.76±0.11	1.17±0.23	1.13±0.04
2.	F2	0.45±0.006	0.41±0.001	0.51±0.02	0.47±0.02	33.02±0.35	33.68±0. 18	11.76±0.24	12.76±0.004	1.13±0	1.15±0.02
3.	F3	0.39±0.002	0.48±0.003	0.45±0.002	0.54±0.02	32.45±0.20	32.05±0.34	13.33±0.02	11.11±0.02	1.15±0.002	1.12±0.01
4.	F4	0.43±0.003	0.44±0.001	0.51±0.01	0.51±0.06	34.43±0.19	34.04±0.31	15.01±0.13	14.90±0.47	1.18±0.02	1.15±.06
5.	F5	0.47±0.007	0.52±0.003	0.55±0.002	0.58±0.007	32.33±0.15	32.85±0.18	14.54±0.11	11.34±0.38	1.17±0.01	1.11±0.01
6.	F6	0.38±0.004	0.41±.005	0.45.±0.002	0.47±0.006	33.46±0.20	34.52±0.15	13.03±0.04	12.76±0.19	1.18±0.02	1.14±0.21
7.	F7	0.51±0.003	0.42±0.001	0.58±0.003	0.48±0.02	32.98±0.34	32.83±0.16	12.76±0.07	12.49±0.06	1.13±0.02	1.14±0.02

All values are expressed as mean ± SD (n=3)

Evaluation of Metformin Hcl And Gliclazide Bilayer Tablets

The formulated bilayer tablets are evaluated and results are presented in Table: 4

Table 4: Evaluation of Bilayer Tablet of Metformin Hcl And Gliclazide Bilayer Tablets

S.no	Parameters	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	Hardness kg/cm^2	9.16±0.28	9.83±0.28	10.16±0.25	9.0±0.5	10.76±0.25	10.66±0.28	10.93±0.11
2	Friability (%)	0.13±0.05	0.15±0.05	0.22±0.01	0.13±0.03	0.18±0.03	0.23±0.02	0.15±0.04
3	Weight Variation (mg)	1094±1.0	1093.±4.04	1096±1.15	1095±2.51	1092±3.51	1096±2.0	1095±1.73
4	Diameter(mm)	8.9±0.07	8.8±0.06	8.9±0.05	9.0±0.01	8.9±0.02	8.8±0.01	8.9±0.03
5	Drug content	99.31±0.55	99.93±1.11	98.11±1.03	99.2±0.43	98.71±0.01	99.56±0.25	99.68±0.17
	a)Metformin	99.13±0.83	99.46±0.96	99.3±0.2	99.9±1.25	100.12± 1.62	99.26±0.90	100.63± 0.73
	b)Gliclazide							
6	Thickness(mm)	5.7±0.1	5.7±0.07	5.86°±0.05	5.93±0.05	5.86±0.05	5.8±0.1	5.86±0.05

IR Spectral Analysis

The signal (3271.57cm-1 to 3296.35 cm-1) of secondary amine of Metformin HCl and Gliclazide and OH of polymers merge with each other and appears as broad and short bands. In the region 1708.93 cm^{-1} and 1645.28cm^{-1} C=O stretching of Gliclazide, C=C stretching of Gliclazide and C=N of Metformin HCl, in the region of 1165 cm^{-1}, presence of CH_3 group of Metformin HCl and Gliclazide, in region of 734.88cm^{-1} to 540.07 cm^{-1} CH aromatic bending of Gliclazide were also present in the same regions of Formulation F7.

IR spectral analysis showed that the fundamental peaks and patterns of the spectra were similar both in pure drugs, higher proportions of polymers and with formulation of bilayer tablet. This indicated that there was no chemical interaction or decomposition of Metformin HCl and Gliclazide in the presence of polymers.The result showed in fig1-10 and in table 5-13.

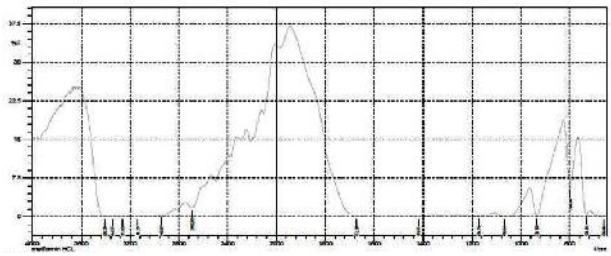

Fig 1:FTIR Spectrum of Metformin

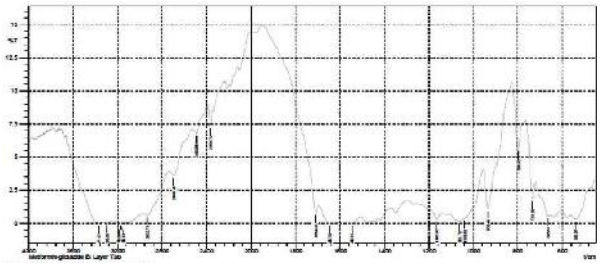

Fig 2: FTIR Spectrum of Metformin and Gliclazide Bilayer tablet

In-Vitro Release Studies

In vitro release of Metformin HCl

In all the formulations, the drug release was 109.32%,104.12%, 101.02,68.42%,95.35%,91.46%, and 90.60% respectively in 10hrs from formulations F1 to F7.

Similarly the drug release was more than 50% from 1st hour onwards and in 6th hour the drug release was increased more than 75% from all formulations except formulation F6. It showed that the release rate was high in initial periods but the release rate may become slower as time goes on.

However the release profiles of drugs from formulations F1 to F6 were not found to be as per the specifications and time intervals quoted in USP NF26.

The standard limits of drug release in the prescribed time as per USP NF26 is 1 hour: 20-40%; 2 hours: 35-55%, 6 hours: 65-85% and in 10 hours Not Less Than 85%.

The drug release from formulation F7 was 38.78%, 49.72%, 78.23% and 90.60% in first hour, 2nd hour, 6th hour and 10th hour respectively. The time intervals and the release profiles of Metformin HCl complied with the limits specified in USPNF26. The result proved that F7 is the optimized formulation.

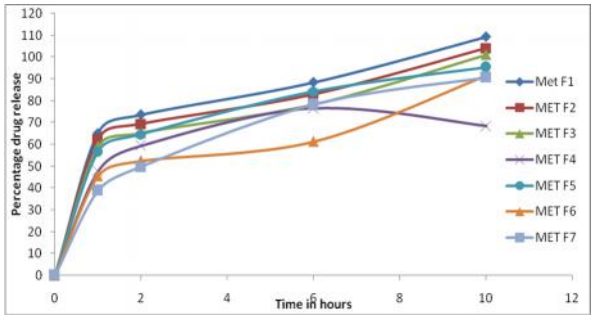

Fig 3: In-Vitro Dissolution studies of Metformin HCl

Dissolution release for Gliclazide

The percentage drug release was 101.30%, 95.42%, 92.48%, 90.31%, 87.24%, 86.10% and 86.63% from the formulations F1, F2, F3, F4, F5, F6 and F7 at the end of 12th hour. The result was presented in the Table no: 19. More than 70% of Gliclazide was released from all the formulation at the end of 8th hr of dissolution study.Many sustained release formulations shown high amount of drug was released initially followed by gradual release of additional amounts of drug over a predetermined period. This result is in conformity with the result of Aisha Khanum et al, Patel Geeta et al. Generally the release rate was found to be decreasing as the proportion of polymer HPMC K100LV was increased.

The drug release from formulation F7 was 21.57%, 41.52%, 72.93%, and 86.63%. at the end of 2hrs, 4hrs, 8hrs and 12hrs. (Table-19). The above study has shown that the in-vitro dissolution profile of formulation F7 was found to be comparable with that of marketed product.

There were no marketed bilayer sustained release tablets of same combination. So dissolution profile was compared with Obimat SR (Metfromin HCl 500mg) and Glizid MR (Gliclazide 60mg) separately.

The drug release of marketed sample of Metformin HCl (Obimet SR 500mg) was 39.13%, 51.96%, 82.90% and 93.63% at 1st hour,2nd hour, 6th hour and 10th hour respectively. It was almost similar with the formulation F7 (Metformin HCl) and comply with the specifications of USPNF 26.

The drug release pattern of marketed sample of Gliclazide (Glizid MR 60mg) was 23.42%,42.96%, 74.35% and 89.83% at 2nd hour, 4th hour, 8th hour and 12th hours respectively. The above study has shown that the in-vitro dissolution profile of formulation F7was found to be comparable with that of marketed product. This release was also in conformity with the reports of Margret Chandira et al and Kotta Kranthi Kumar et al.

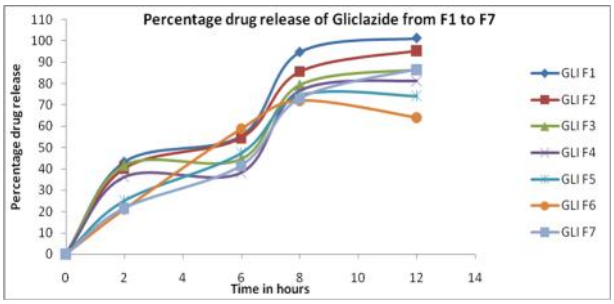

Fig 4: In-Vitro Dissolution Study of Gliclazide

Table 5: Comparative Dissolution Study of Metformin HCl with Marketed Sample

S.NO	Parameters	Optimized Formula (F7)	Marketed Sample (Obimet SR)
1	1st hour	38.78±0.51	39.13±0.25
2	2nd hour	49.72±1.11	51.96±0.61
3	6th hour	78.23±1.20	82.90±0.71
4	10th hour	90.60±0.06	93.63±0.83

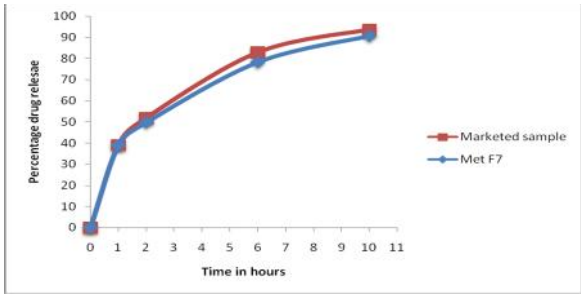

Fig 5: Comparative Dissolution Study of Metformin HCl with Marketed sample

Table 6: Comparative Dissolution Study of Gliclazide with Marketed sample

S.NO	Parameters	Optimized Formula (F7)	Marketed Sample (Glizid MR 60mg)
1	2nd hour	21.57±0.13	23.42±0.45
2	4th hour	41.52±0.13	42.96±0.61
3	8th hour	72.93± 0.12	74.35±0.95
4	12th hour	86.63±0.13	89.83±0.31

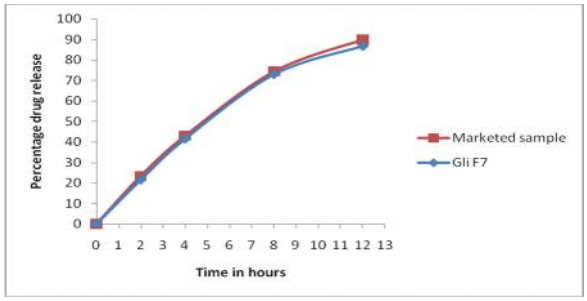

Fig 6: Comparative Dissolution Study of Gliclazide with Marketed Sample

Stability Studies

Formulation F7 preparations were stored at 40°C in humidity chamber (75%RH) for 3months. At the end of three months, all preparations were observed for any physical changes such as colour, thickness and diameter and percentage drug release, drug content were analysed and results were presented in Table 17. There was no physical change and also there was no change in drug content and percentage drug release. The result showed that the preparations are physically and chemically stable.

Table 7: Stability Study Report

Formulation	Time in hours	Percentage drug release						
		Accelerated stability (40°C /75%RH)				Real time Stability ((30°C/65%RH)	Assay	
		Initial	1 month	2 month	3 month	3 month	Initial	After stability
Metformin HCl	1st hour	38.78 ±0.51	38.75 ±0.47	38.71 ±0.87	38.69 ±0.74	38.74±0.43	99.68	98.74
	2nd hour	49.72 ±1.11	49.69 ±0.09	49.65 ±0.16	49.58 ±0.79	49.68±0.69		
	6th hour	78.23 ±1.20	78.18 ±0.14	78.14 ±0.93	78.11 ±0.91	78.21±0.38		
	10th hour	90.60 ±0.06	90.58 ±0.96	90.53 ±1.46	90.49 ±0.87	90.55±0.84		
Gliclazide	2nd hour	21.57 ±0.04	21.54	21.52	21.49	21.55	100.63	99.21
	4th hour	41.52 ±0.14	41.49 ±0.21	41.46 ±0.41	41.43 ±0.73	41.49±0.09		
	8th hour	72.93 ±0.37	72.91 ±0.53	72.89 ±0.72	72.86 ±0.63	72.90±0.12		
	12th hour	86.63 ±0.82	86.61 ±0.49	86.57 ±0.86	86.51 ±0.71	86.60±0.49		

4. CONCLUSION

From the above results, it is concluded that by adopting a systematic formulation approach delivery of two drugs from a single dosage form can be obtained which could improve patient compliance and give better disease management. Such type of bilayer tablets also reduced dosing frequently and increases bioavailability.

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Source of Funding: Nil

Conflict of Interest: None