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Formulation and Characterization of Gliclazide Controlled Release Tablets

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ABSTRACT

Gliclazide is a second generation sulphonyl urea used worldwide in the treatment of type 2 diabetes. It is a weak acid with good lipophilicity and pH dependent solubility. The gliclazide matrix tablet will significantly improve the patient compliance, especially under the situations of prolonged use of drug and also reduce the total dosage of administered drug and consequently reduce the side effects.HPMC-K100LV and HPMC-K4M were used as rate controlling polymers and microcrystalline cellulose, lactose are used as diluents. Seven formulations (six formulations containing two polymers of three different proportions 30, 60 and 120mg respectively and one formulation without rate controlling polymer) were prepared by wet granulation method. The formulated tablets were compared with the marketed sample. The granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and hausners ratio. The granules showed good flow character. Tablets were evaluated for various parameters such as thickness, hardness, friability, drug content, weight variation, IR studies, in-vitro dissolution studies and stability studies. The different proportions of the polymers showed significant differences in the release of drug.

Keywords: Gliclazide, HPMC K 100LV, HPMC K4M, Povidone k 30 controlled matrix tablets.

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INTRODUCTION

Development of oral controlled release systems has been challenge to formulation scientists because of their inability to restrain and localize the system in the targeted area of the gastrointestinal tract. Controlled / Sustained release preparations using alternative routes have been formulated but the oral route still remain preferable. Controlled release formulations in many cases provide further significant advantages, including improved therapeutic effect, increased patient compliance by reducing dose frequency and decrease in incidence and / or intensity of adverse effect by a constant blood concentration [1].

The drug selected under study was gliclazide, a second generation sulphonyl urea is very useful for lowering sugar level in type 2 diabetes. It is almost completely absorbed from gastrointestinal tract after oral administration. The onset of action is about 1-2 hours and peak plasma concentration occurs about 4-6 hours after an oral dose. Hydroxy propyl methyl cellulose (HPMC) is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems [2].

When HPMC contacts with gastrointestinal fluids, it swells, forms a gel and finally dissolves slowly [3]. The swelling rate of polymer and dissolution rate as well as the corresponding drug release rate found to increase with either higher proportion of drug loading or with use of lower viscosity grades of HPMC [4].

MATERIALS AND METHODS

MATERIALS

Gliclazide was received as gift sample from Micro Labs Hosur. All other chemicals used in this experiment were of analytical grade obtained commercially.

Preparation of Controlled release matrix tablets of Gliclazide

Various formulations (F_1-F_7) were prepared by taking appropriate quantities of the ingredients as mentioned in Table no: 1

Table 1: COMPOSITION OF GLICLAZIDE CONTROLLED RELEASE TABLETS

Weight of each tablet 250mg.

S.NO	INGREDIENTS	Formulation Code (mg)						
		F_1	F_2	F_3	F_4	F_5	F_6	F_7
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

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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 mesh. HPMC-K_{100}LV, Lactose DCL-15 and iron oxide red were sifted through sieve no#40 and 100 mesh and mixed with dried granules for 10 minutes 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 compressed.

EVALUATION OF GRANULES

ANGLE OF REPOSE [5]

The angle of repose was determined by funnel method. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\emptyset = \tan^{-1}(h/r)$$

Where h and r are the height and radius of the powder cone

BULK DENSITY [6]

Bulk density is the ratio between a given mass of the powder and its bulk volume.

$$\text{Bulk density} = \frac{\text{Mass of Powder}}{\text{Bulk volume of the powder}}$$

An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and tapped volume (Vo) was measured . The cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume)was obtained (Vf). The bulk density was calculated by using the formula

$$\text{Bulk density} = \frac{W}{Vo}$$

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TAPPED DENSITY [7]

Tapped density is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Tapped density = mass of the powder/ tapped volume

COMPRESSIBILITY AND THE HAUSER RATIO ARE CALCULATED AS FOLLOWS [8]

Two most commonly used measures of the relative importance of the interparticulate interaction are the compressibility and the Hausner ratio.

The compressibility and the Hausner ratio may be calculated (using measured values of bulk density and tapped density) as follows

$$\text{Compressibility index} = \frac{\text{bulk density} - \text{tapped density}}{\text{Bulk density}} \times 100$$

$$\text{Hausner's ratio} = \text{bulk density} / \text{Tapped density}$$

Evaluation of Gliclazide Controlled release Matrix tablets

Hardness test or crushing strength [9]

Hardness which is now more appropriately called crushing strength determinations are made during tablet production. The hardness of tablets (kg\cm^2) was carried out by using Monsanto type hardness tester.

Weight variation test [10, 11]

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 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:

$$\text{Percentage deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Friability Test [10, 11]

Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed.

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The percentage friability was determined using the formula,

Percentage friability = Initial weight - Final weight/Initial Weight × 100

Estimation of Drug Content [12]

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 weighed and transfered 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 using Phosphate buffer pH 7.4 as blank.

IR spectral Analysis [13]

It is used to determine the interaction between the drug, polymer and excipients. The drug and polymer must be compatible with one another to produce a product stable, efficacious and safe.

The KBR disc method was used for preparation of sample and spectra were recorded over the wave number 4000 to 400cm^{-1} in a SHIMADZU FT-IR Spectrophotometer. The IR spectral analysis for drug and polymer was carried out. If there is no change in peaks of mixture when compared to pure drug, it indicates the absence of interactions.

IN-VITRO DISSOLUTION STUDIES

Dissolution study was carried out using USP dissolution apparatus Type II using pH-7.4 phosphate buffer for 2^{nd} hour, 4^{th} hour, 8^{th} hour and 12^{th} hour. The drug release study was performed at the above time intervals as per the method of Kranthi Kumar[13] and the drug release was estimated by HPLC method.

HPLC Experimental Method [14]

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 and measurements were made at 228nm. 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.

Preparation of mobile phase

The mobile phase was prepared by mixing acetronitrile and phosphate buffer pH7.4 in the ratio 60:40 v/v. The buffer contains 3ml Triethylamine and 3ml Phosphoric acid per 900ml. The solution was passed through 0.45µm membrane filter and sonicated.

Preparation of standard stock solution

Standard stock solution of pure drug was prepared by dissolving 30mg of gliclazide dissolved in 20ml of methanol in 100ml volumetric flask and further make up the volume with methanol. From this 10ml was pipette out and transferred to 50ml volumetric flask and make up the volume with phosphate buffer pH7.4.

Preparation of sample solution

Five tablets were weighed and the average weight was determined then powdered. The powder was transferred into 1000ml volumetric flask. To this 20ml methanol was added and allowed to sonicate and 400ml of phosphate buffer pH7.4 was added and make up the volume with buffer. Then the solution was allowed to cool. From this 10ml was pipette out and make up to 50ml with phosphate bufferpH7.4. The solution should be filtered before injecting into HPLC chromatogram.

Estimation method

20µL of solution was injected into HPLC system and the measurement was made at 228nm and the concentration of the drug released was determined.

$$\frac{\text{Peak area of test solution}}{\text{Peak area of standard solution}} \times \frac{Ws}{100} \times \frac{10}{1000 \times 50 \times Aw \times Ps}$$

Stability studies [15]

The optimized formulation F_7 was taken for stability studies. The tablets were stored in a bottle and kept at 45º c ± 2º c (RH75 ± 5%) for a period of three months. The tablets were observed physically for any color change. The tablets were taken at the end of three months for drug content and in-vitro release studies.

RESULTS AND DISCUSSION

Precompression Parameters

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Evaluation of Granules

The angle of repose for all the formulations was within 35ºindicates all the formulations have good flow property. The compressibility index and Hausner's ratio was 11.76 to 14.54 and 1.13 to 1.17 indicating good flow character of the granules. All the results are within the prescribed limits. It indicates all the formulations have good flow property.

Evaluation of compressed tablets

Hardness of the tablets was in the range of 10.93 to 9.00 kg/cm2.This ensures good handling characteristics of all the batches. Weight loss in the friability test was less than 1% in all the cases, ensuring that the tablets were mechanically stable. All the tablets prepared contained the drug within 99.93 and 100.63±5% of the label claim. All the formulated tablets (F1 to F7) passed the weight variation test as the % weight variation was within the Pharmacopoeial limits of ± 5% of the average weight.

Drug content

The content of Gliclazide tablets were analyzed by the method as mentioned in the method and it was found that the percentage of Gliclazide in the formulationF_7 was found to be 100.63±0.53.

IR Spectral Analysis

Figure 1: FTIR Spectrum of Gliclazide

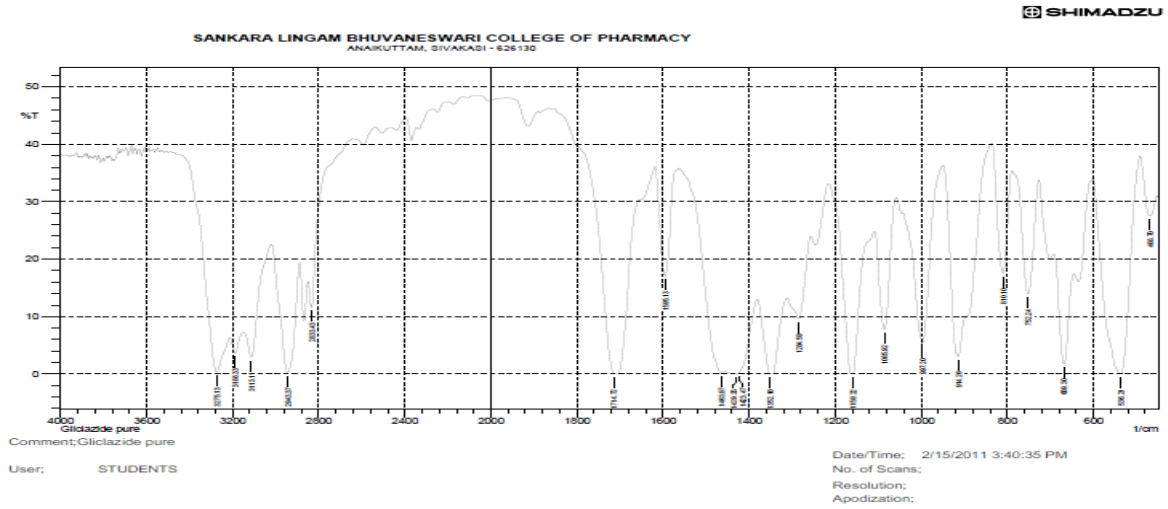

Figure 2: FTIR Spectrum of HPMC K100 LV

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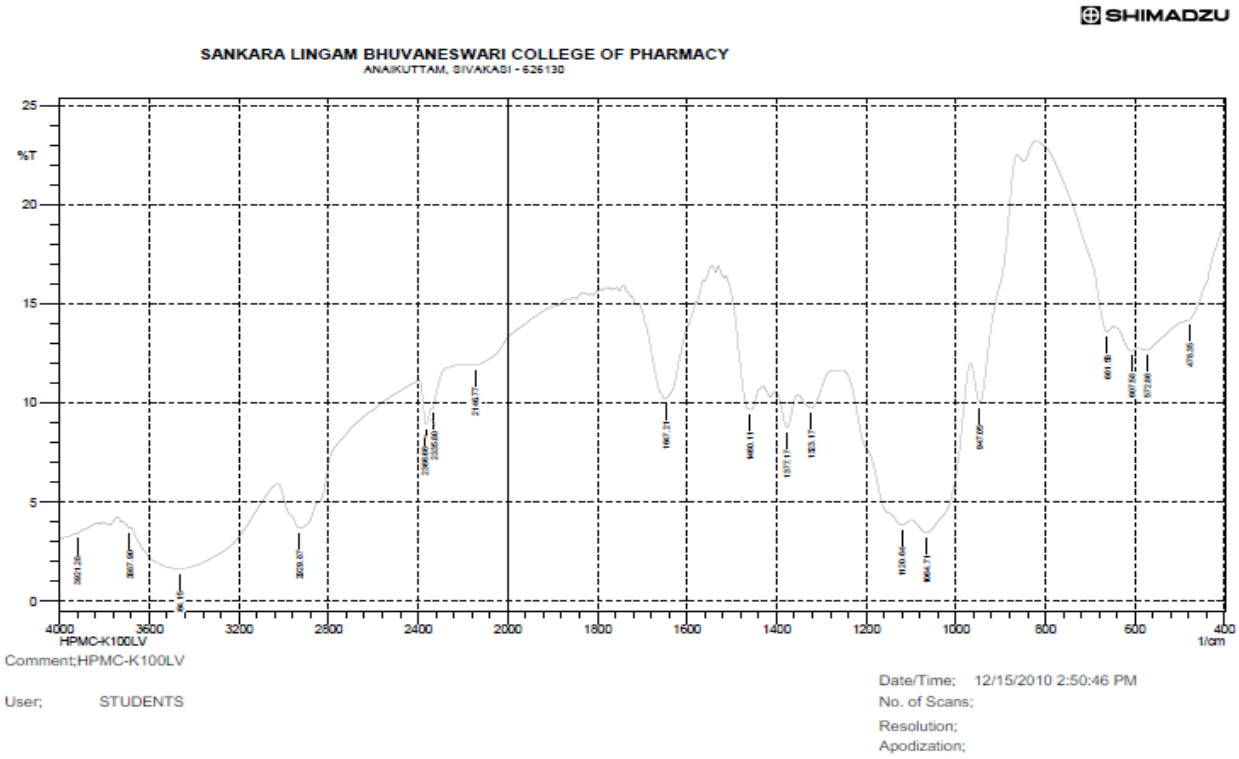

It is used to determine the interaction between the drug polymer and excipients. The drug, polymer and excipients must be compatible with one another to produce a product stable, efficacious and safe. The IR spectrums were represented in Figure no: 1 and Figure no: 2.

Dissolution release for Gliclazide

Seven formulations of Gliclazide tablets were prepared with different proportions of release retarding polymer HPMC K100LV and In-vitro dissolution study was conducted.

Table 2: In-Vitro dissolution study of Gliclazide

S.NO	Parameters	F_1	F_2	F3	F4	F_5	F_6	F_7
1	2-hour	43.27±0.02	40.21±0.13	41.60±1.3	36.19±0.25	25.05±0.67	21.03±0.61	21.57±0.13
2	4-hour	55.46±0.26	54.54±0.02	44.56±0.15	38.20±0.11	47.43±0.20	58.76±1.38	41.52±0.13
3	8-hour	94.76±0.02	85.56±0.12	79.31±0.05	76.63±1.25	74.56±0.29	72.05±0.76	72.93±0.12
4	12-hour	101.30±0.12	95.42±0.02	92.48±0.45	90.31±0.03	87.24±0.14	86.10±0.15	86.63±0.13

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

The percentage drug release was 101.30%, 95.42%, 92.48%, 90.31%, 87.24%, 86.10% and 86.63% from the formulations F_1, F_2, F_3, F_4, F_5, F_6 and F_7 at the end of 12th hour. The result was presented in the Table no:2 More than 70% of Gliclazide was released from all the formulation at the end of 8^{th} hr of dissolution study. The drug release from formulation F_7 was 21.57%, 41.52%, 72.93%, and 86.63%. at the end of 2hrs, 4hrs, 8hrs and 12hrs. The formulation F_7 was compared with the marketed sample of Glizide MR 60mg. The drug release pattern of

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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 $F_7$was found to be comparable with that of marketed product. This release was represented in the figure no: 4 and figure no:5.

Figure 3: FTIR Spectrum of Gliclazide and HPMC K100LV

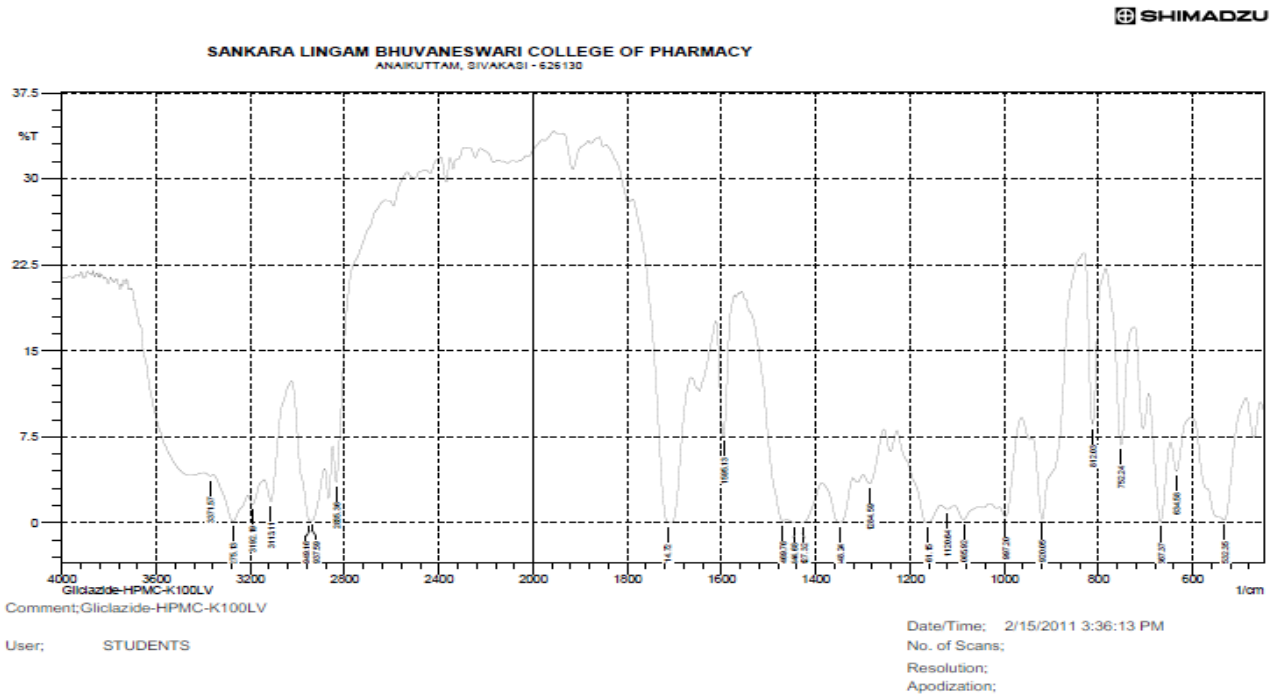

Figure 4:In-Vitro Dissolution Study of Gliclazide

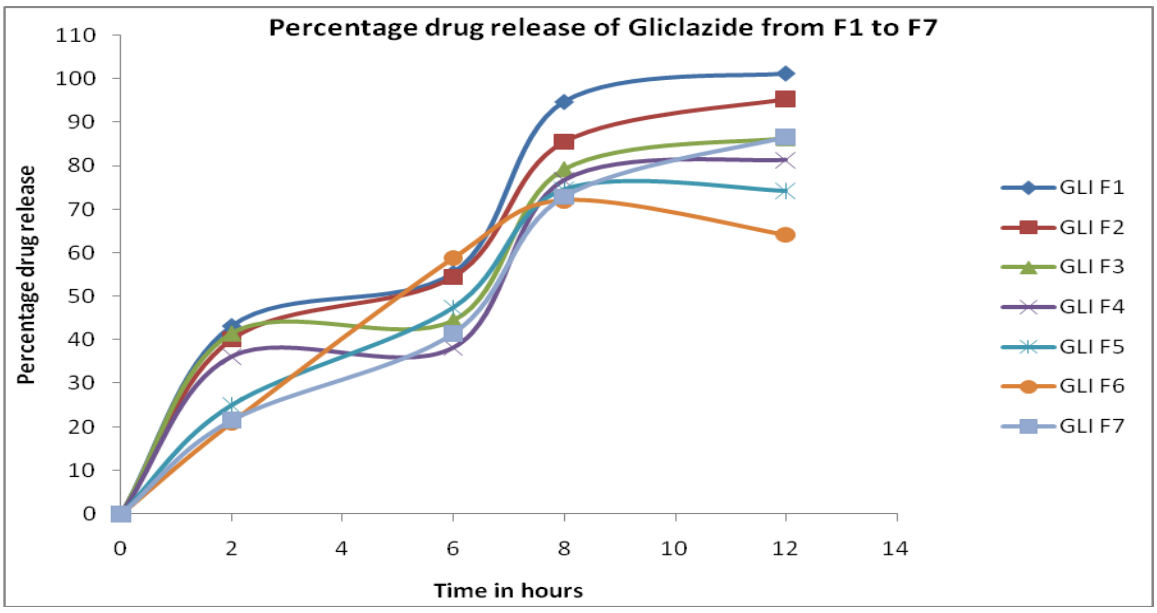

Figure 5: Comparative Dissolution Study of Gliclazide with Marketed Sample

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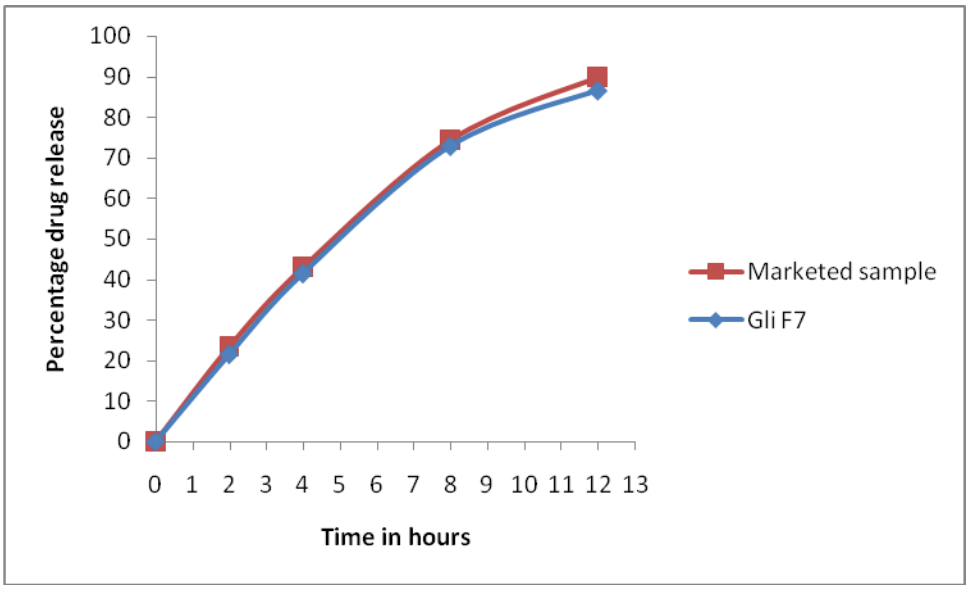

STABILITY STUDIES

The formulation F_7 was selected for stability study. Formulation F7 preparations were stored at 45°C±2°C in humidity chamber (RH 75%±5%) for 3months. At the end of three months, all preparations were analyzed for any physical changes such as color, thickness, diameter, drug content and percentage drug release, and results were analyzed. 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 3: Stability Study Report

Formulation	Time in hours	Percentage of 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
Gliclazide	2nd hour	21.57±0.04	21.54±0.84	21.52±0.19	21.49±0.75	21.55±0.93	100.63±0.53	99.21±0.33
	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		

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

CONCLUSION

From these results, it was found that all the preformulation characteristics of the formulation F1 to F7 were found to be within the specified limits. From the drug content, post compression parameters, in-vitro drug release studies it was found that among the various formulations, Formulation F_7 (Drug with HPMC-K100LV) was the found to be the best formation. The formulation is further taken for pilot scale up studies and stability studies.

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