INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS
VOL.5 ISSUE 12, 2017; 498 – 507; http://ijpda.com; ISSN: 2348-8948

Research Article

Formulation Development And Evaluation Of Colon Targetted Matrix Tablets Of Gliclazide

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Date Received: 13th December 2017; Date accepted: 22nd December 2017; Date Published: 23rd December 2017

Abstract

Gliclazide was formulated as a hydrophobic matrix sustained release tablet employing HPMC using different grade materials and the sustained release behavior of the fabricated tablet was investigated. Sustained release matrix tablets containing 60 mg Gliclazide were developed using different grade of HPMC combinations with coated enteric coating polymers like Eudragit L100 and S100 were used as coating materials. The tablets were prepared by wet granulation technique. The physical properties were found to be satisfactory for all the formulae.The formulation was optimized on the basis of acceptable tablet properties and in vitro drug release. The resulting formulation produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. Statistically significant differences were found among the drug release profile from different HPMC combination matrices. The in vitro study revealed that combining of HPMC (Methocel K100LV-CR Premium (IF10805), HPMC K4M and use of Dibasic Calcium Phosphate as filler sustained the action more than 12 h. The developed sustained release matrix tablet of improved efficacy can perform therapeutically better than a conventional tablet.

Key words: Gliclazide, sustained release, HPMC, *in vitro* dissolution

INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of variety of bowl diseases such as ulcerative colitis, cirrhosis disease, amoebiasis, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug in route to the colon i.e. drug release and absorption should not occur in stomach as well as small intestine, and neither the bioactive agent should be degraded either of the dissolution sites, but only released absorbed once the system reaches the colon[1].Formulations for colonic delivery are also suitable for delivery of drugs, which are polar and / or susceptible to chemical and enzymatic degradation in upper GIT; in particular, therapeutic proteins and peptides are suitable for colonic deliveries[2].

Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systematically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors and antibiotics, which are useful in treatment of IBD and GI infections respectively. Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. A colonic targeted approach found to be effected in minimizing uncertain side effects[3]

Diabetes mellitus is one of the major causes of death and disability in the world. Although the prevalence of both type-I and type -II diabetes is increasing worldwide, the prevalence of type -II diabetes is expected to rise more rapidly in future because of sedentary lifestyle, increasing obesity and reduced activity levels. In United States of America (USA),about 90% of all diabetic patients have type -II diabetes[4] .

Gliclazide is a second generation sulphonylurea

which acts as a hypoglycemic agent. It stimulates β cells of the islet of Langerhans in the pancreas to release insulin. It also enhances peripheral insulin sensitivity. Overall, it potentiates insulin release and improves insulin dynamics and is one of the most widely used agents against type II diabetes. Sulfonylureas increase both basal insulin secretion and meal-stimulated insulin release. Medications in this class differ in their dose, rate of absorption, duration of action, route of elimination and binding site on their target pancreatic β cell receptor. Sulfonylureas also increase peripheral glucose utilization, decrease hepatic gluconeogenesis and may increase the number and sensitivity of insulin receptors. Gliclazide has been shown to decrease fasting plasma glucose, postprandial blood glucose and glycosolated hemoglobin (HbA1c) levels (reflective of the last 8-10 weeks of glucose control). Gliclazide is extensively metabolized by the liver; its metabolites are excreted in both urine (60-70%) and feces (10-20%). Gliclazide is used for patients with type II diabetes who have failed diet and exercise therapy. Gliclazide is a strong acid (pKa = 4.07), practically insoluble in water and acidic environment, and highly permeable (Class IV drugs in accordance to Biopharmaceutics Classification System, BCS).

In the present investigation, gliclazide matrix tablets were prepared by blending of excipients and wet granulation method. Matrix tablets were characterized by physicochemical evaluation , Fourier transform infrared spectroscopy (FTIR), in vitro drug release and stability studies. The objective of the investigation was to develop a sustained release system for the low solubility/low dose drug gliclazide, an oral anti-diabetic.

MATERIALS AND METHODS

Materials

Gliclazide was provided as a gift sample by Bal Pharma, India. Eudrajit L 100 D 55, Eudrajit S 100 were purchased from Loba chemicals, Mumbai. Other materials used in the study such as dibasic Calcium phosphate, povidone, aerosil 200, talc and Magnesium sterate were of pharmacopoeial grade. All the other chemicals were of analytical grade.

Methods

Formulation of Gliclazide SR tablet

Step I: Core Tablets

Stage 1: Sifting

Sifted the Gliclazide, Poly ethylene Glycol 6000 and Aerosil 200 through 40 # SS sieve in double lined polybag separately and sifted the HPMC (Methocel K100LV-CR Premium (IF10805), HPMC K4M and Dibasic Calcium Phosphate through 40 # SS sieve in double lined polybag.

Stage 2: Mixing :

The sifted material of step 1 are mixed for 5 minutes in the double lined polybag at unidirectional flow for uniform mixing.

Stage 3: Preparation of Binder solution (Granulation solution):

Povidone K-90 (Plasdone K-90) was dissolved into purified water under continuous stirring until to get lumps free clear solution.

Stage 4: Wet Granulation:

The prepared binder solution was slowly added to dry mixed materials of stage 2 till to get uniform wet granules. The wet mass was sifted using 12 mesh sieve.

Stage 5: Drying of granulesof stage 4

The sifted wet mass from stage 4 was transferred to lab model FBD (Retsch) , fixed the product container properly and dry the granulated mass at an Inlet temperature of 50-60° C and Product temp 35-45° C. Checked the LOD at this stage using Moisture Balance. LOD Limit: NMT 1.0-3.0 % (at 105 °C for 5 minutes) and Continued the Drying till required LOD is reached.

Stage 6: Sifting and milling of dried materials

The dried granules of stage 5 was sifted through quadro co-mill fitted with 0.457 (018 R) screen at a speed of 1000 RPM.

Stage 7 : **Lubrication:**

Add the Sifted Talc and Magnesium Stearate through # 40 mesh Sieve to stage 6 and mixed of 2 minutes in a double polylined bag.

Stage 8: **Compression:**

The lubricated blend of stage 7 was compressed using 9.5 mm normal concave circular punches , Cadmach Mini Rotary Tablet Press (Cadmach Machinary Co Pvt. Ltd).

Step – II: Coating

The optimized formulation of tablet was coated using a combination of Eudragit L 100 and S100 by using a fluidized bed coating apparatus. Coating solution was prepared by dissolution of 500 mg of Eudragit polymers (L-100 and S-100; 1:1) in ethanol: acetone (2:1) to give 10% coating. PEG 4000 (1% w/v) was used as a plasticizer. Coating solution was applied until there is no drug release in simulated gastric fluid. A 10% w/w increase in the coating level was selected as an optimum coating percentage level[5].

Table 1: Composition of Tablet formulations with different ratios and different grade of HPMC polymers

Ingredients(mgs)	GLZ-1	GLZ-2	GLZ-3	GLZ-4	GLZ-5	GLZ-6
Gliclazide -IP	60.000	60.000	60.000	60.000	60.000	60.000
Dibasic Calcium Phosphate IP	70.000	70.000	65.000	65.000	58.000	56.500
Colloidal silicondioxide IP(Aerosil 200)	20.000	14.000	12.000	8.000	8.000	7.500
Polyglykol 6000 PF	65.000	64.000	63.000	60.000	60.000	60.000
HPMC(Methocel K100 Premium LVCR	24.000	36.000	48.000	60.000	68.000	72.000
HPMC IP K4M (HPMC K4M)	30.000	26.000	22.000	20.000	20.000	18.000
Povidone (Plasdone K90)ISP	25.000	24.000	24.000	20.000	20.000	20.000
Purified water IP	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc -IP	3.000	3.000	3.000	3.000	3.000	3.000
Magnesium stearate -IP	3.000	3.000	3.000	3.000	3.000	3.000
Target weight / Tablet(mg)	300.000	300.000	300.000	300.000	300.000	300.000

Preformulation studies

Fourier transforms Infrared spectroscopy

FT-IR spectra of Gliclazide and physical mixture of Gliclazide were recorded at room temperature condition using KBr pellet technique. KBr pellets were prepared by applying a pressure of 5-7 tons. IR spectrum was recorded using Perkin Elmer Spectrum GX FT-IR, measured at the maximum at 4000 cm-1 using methanol as a blank.

Evaluation of granules

Angle repose (Ø) of granules was determined by the funnel method. The diameter and height of the powder cone were measured and angle of repose was calculated using the equation[6], Tan Ø= h/r, where h and r are the height and radius of the powder cone. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. LBD and TBD were calculated using the equations[7] , LBD = weight of the powder/volume of the packing; TBD = weight of the powder/tapped volume. The compressibility index of the granules was determined by Carr's index[8] using the equation, Carr's index = [(TBD-LBD) X 100)]/TBD.

EVALUATION OF TABLETS

Tablet thickness

Thickness was measured using a Vernier calliper. Six tablets of each formulation were collected randomly and thickness was measured individually.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using digital hardness tester (electrolab). It is expressed in kg/cm2. Six tablets were randomly collected and hardness of the tablets was determined.

Friability

Friability of tablets was determined using Electrolab friabilator. Twenty tablets were weighed and placed in a chamber. The friabilator was operated at 25 rpm for four minutes (per 100 revolutions) and the tablets were subjected and the tablets were subjected for combined effect of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution[9]. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula,

$$F = Wi - Wf / Wi \times 100$$

Weight variation

Weight variation test was performed according to official method as per Indian Pharmacopoeia, 1996b[10].

Drug content(Assay)

Preparation of Buffer Solution:

Weigh about 5.75g of Ammonium dihydrogen phosphate and about 7.2g sodium lauryl sulphate in a 1000ml of beaker; added 700ml of water to dissolved and dilute to 1000ml with water. Adjust the pH of the solution to 5.5 ± 0.05 with ammonia solution. Filter through 0.45 µm nylon membrance filter and degas.

Preparation of Mobile Phase: Prepare the filtered and degassed mixture of buffer and Acetonitrile in the ratio of 550:450 v/v.mix well and degas.

Preparation of Reference Solution-1:

Weigh accurately about 60.0mg of Gliclazide working standard and into a 100ml volumetric flask, Add 70 ml of Methanol shake and sonicate to dissolved with intermittent shaking and make up the volume with mobile phase and mixed well. Pipette out 5 ml of this solution into a 50 ml volumetric flask make up the volume with the mobile phase and mixed well. Filter the solution through 0.45µm filter paper; collected the filtrate after discarding few ml.

Preparation of Reference Solution-2:

Weigh accurately about 60.0mg of Gliclazide working standard into a 100ml volumetric flask, Added 70 ml of Methanol shake and sonicate to dissolved with intermittent shaking and make up the volume with mobile phase and mix well. Pipette out 5 ml of this solution into a 50 ml volumetric flask make up the volume with the mobile phase and mix well. Filter the solution through 0.45µm filter paper; collected the filtrate after discarding few ml.

Preparation of Test Stock Solution-1:

Weigh and transfer 5 intact tablets into a 500 ml volumetric flask, add about 400 ml of Methanol and sonicate for 30minutes with intermittent shaking, to dissolved the contents. Cool the room temperature and make up the volume with methanol and mixed well. Centrifuge the solution at 3500rpm for 8 minutes and use clear supernatant solution and filter the clear supernatant solution through 0.45µm filter paper, collected the filtrate after discarding few ml of sample solution.

Preparation of Test Stock Solution-2:

Weigh and transfer 5 intact tablets into a 500 ml volumetric flask, add about 400 ml of Methanol and sonicate for 30minutes with intermittent shaking, to dissolved the contents. Cool the room temperature and make up the volume with methanol and mix well. Centrifuge the solution at 3500rpm for 8 minutes and use clear supernatant solution and filter the clear supernatant solution through 0.45µm filter paper, collected the filtrate after discarding the few ml of sample solution.

Preparation of Test Solution-1

Pipette out 5 ml of Test stock solution -1 into a 50 ml volumetric flask make up the volume with the mobile phase and mixed well.

Preparation of Test Solution-2

Pipette out 5 ml of Test stock solution -2 into a 50 ml volumetric flask make up the volume with the mobile phase and mixed well.

Procedure:

Equilibrate the column with mobile phase for sufficient time until stable baseline is obtained, Inject 10 µL of Blank, Reference Solution 1and Reference Solution -2 as per the Sequence of injections Set – I and calculate the similarity factor. If the system suitability criteria meet the requirements then inject the Reference Solution-2 and Sample solution preparations as per the Sequence of injections Set – II, and recorded the chromatograms.

***IN –VITRO* DISSOLUTION STUDIES[11]**

The release rate of Gliclazide SR tablets were determined using USP dissolution testing apparatus I (basket type). The test was performed using 900 ml of 0.1 N HCl at 37 ± 0.5°C and 100 rpm for first 1 h. then replaced with 7.4 pH phosphate buffer and continued for 12 h. Aliquot volume of 5 ml was withdrawn at regular intervals and replaced with fresh buffer diluted. The samples were replaced with fresh dissolution medium. After filtration, the amount of drug release was determined from the standard calibration curve of pure drug.

STABILITY STUDIES

Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, color, odour, taste or texture of the formulation indicate the drug instability. Among the six formulations, GLZ6 was selected for stability studies based on the physicochemical characterization of coating films and release characteristics. The stability studies were carried out at 40 ± 2 °C with 75 ± 5%% RH

Chormatography Conditions	
Apparatus	HPLC system equipped with UV/PDA detector system
Column	Stainless steel C18 15cm x 4.6mm x5µ column (Inertsil is suitable or equivalent)
Flow Rate	1.0 ml / min
Detector wave length	230nm
Sample Cooling Temp	6°C
Injection volume	10 µl
Column Temp.	25°C
Run time	15 min
Retention time	About 7.7minutes

RESULTS AND DISCUSSION

IR studies

Drug polymer interaction when studied by FT-IR, showed no drug: excipient interaction. From the FTIR spectrum above interpretation it is understood that there is no major shifting in the frequencies of above said functional groups of Gliclazide was identified which indicates that there is no chemical interaction between Gliclazide and polymer which were used in the formulations. It is given in **figure 1 and 2.**

Micromeritic properties of granules

The micromeritic properties of various formulations granules are presented in table 2.The micromeritic properties of all the formulations granules were compared and it was found that GLZ-6 was optimal and within specified limits. Various formulations of granules were formulated using wet granulation for which the granules were subjected to different micromeritic parameters. Angle of repose ranged from 24.56° to 28.12° and the Carr's compressibility index ranged from 14.32 to 18.86. An angle of repose of less than 30 degrees indicates good flow properties [12]. This was further supported by the lower compressibility index. Granules with Carr's index values are considered to have good and excellent flow properties[12]. The bulk density and tapped bulk density of the prepared blend ranged from 0.468 to 0.578g/ml and 0.565 to 0.689 g/ml respectively. The results of angle of repose indicates good flow property of the powder and the value of Carr's compressibility index further showed support for the flow property (Table 2). All the formulation possessed good flow properties. Low value of angle of repose, Carr's index and Hausner's ratio (Table 2) revealed good micromeritic behavior of the granules. Since, the flow properties of the powder mixture are important for the uniformity of dose of the tablets; GLZ6 was found to be the best among all the tablet formulations due to low Hausner's ratio, Carr's index and angle of repose.

Physical properties

The physical properties of SR tablet of Gliclazide was presented in the table 3. The thickness of tablets was found to be between 9.51-9.54 mm. The hardness for various formulations was found to be between 4.6 to 6.0 kg/cm^2, indicating satisfactory mechanical strength. The friability of the uncoated tablets of various formulations were found in 0.48± 0.02 to 0.63± 0.03 and weight variation of uncoated tablets of different tablet formulations were found in compendial limits, i.e.302.42± 0.84 to 306.28± 0.45 respectively, which is an indication of

good mechanical resistance of the tablet. Drug content was found to be in the range of 97.54± 0.67 to 102.45± 0.23 % . All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial specifications for weight variation and friability (less than 0.7%)[13].

Table-2 Properties of the Gliclazide granules

Formula	Angle of repose (0)	Bulk density gm/ml	Tapped density gm/ml	Carr's index %	*Hausner's ratio*
GLZ-1	28.12± 0.29	0.534± 0.03	0.682±0.04	17.76±0.62	1.16±0.02
GLZ-2	27.55± 0.44	0.542± 0.07	0.668±0.06	17.62 ±0.34	1.11±0.03
GLZ-3	28.72± 0.22	0.484± 0.04	0.632±0.05	18.86±0.65	1.20±0.04
GLZ-4	25.67± 0.32	0.536± 0.05	0.656±0.04	18.12±0.56	1.12±0.03
GLZ-5	26.87± 0.52	0.524± 0.03	0.643±0.02	14.48±0.46	1.10±0.04
GLZ-6	24.56± 0.16	0.512± 0.02	0.636±0.02	14.32±0.38	1.09±0.05

All mean values are expressed of 3 determination ± standard deviation

Table-3 Physicochemical parameters of developed sustained release tablets of Gliclazide

Parameters	GLZ-1	GLZ-2	GLZ-3	GLZ-4	GLZ-5	GLZ-6
Hardness Kg/cm2	6.0± 0.62	5.8± 0.42	5.4± 0.52	5.2± 0.12	4.8± 0.48	4.6± 0.34
Friability (%)	0.48 ± 0.02	0.52± 0.04	0.58± 0.04	0.58± 0.05	0.64± 0.03	0.52± 0.04
Thicknessmm	9.52±0.02	9.53±0.04	9.54±0.02	9.25±0.04	9.51±0.04	9.51±0.04
Uniformity of Weight core tablets mg	304.24±0.22	305.54±0.36	306.28± .45	304.82± .62	306.28± 0.16	302.42±0.84
Uniformity of Weightcoated tablets (mg)	327.56± .34	328.54±0.22	329.65± .34	328.54± .24	327.34± 0.76	328.78±0.42
Drug content %	102.45±0.23	99.87± 0.65	97.54± 0.67	97.82± 0.56	98.76± 0.62	100.45±0.56

All mean values are expressed of 3 determination ± standard deviation

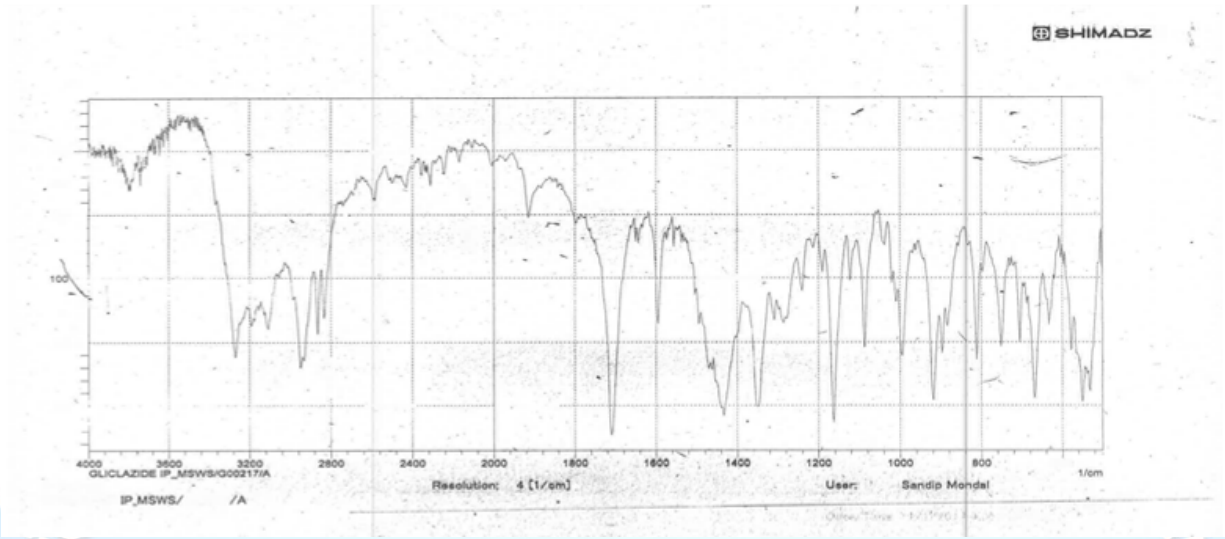

Fig-1 FTIR Spectrum of Gliclazide

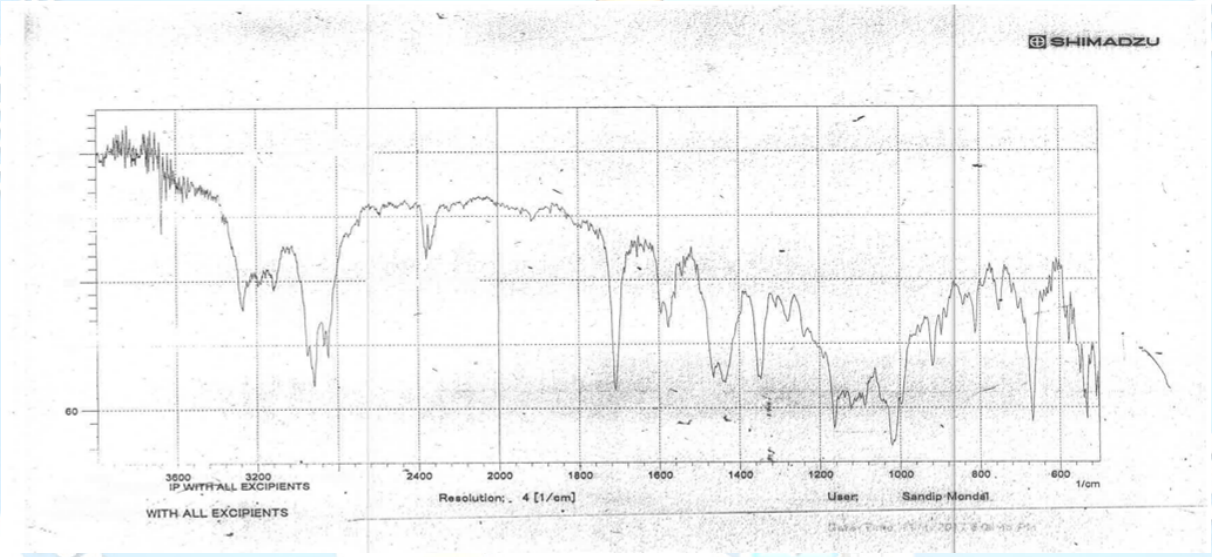

Fig-2 FTIR Spectrum of Gliclazide with all excipients

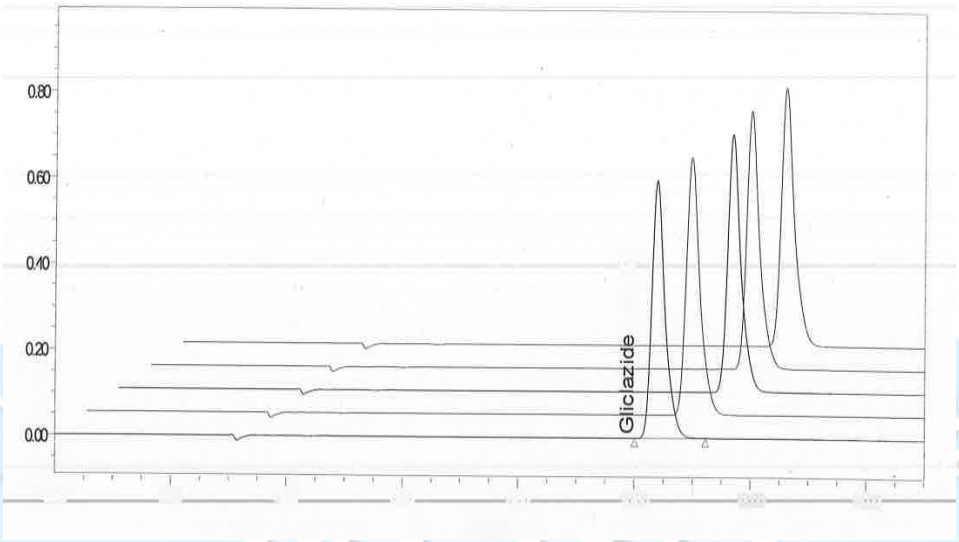

Fig 3 Gliclazide standard chromatogram(5 injection)

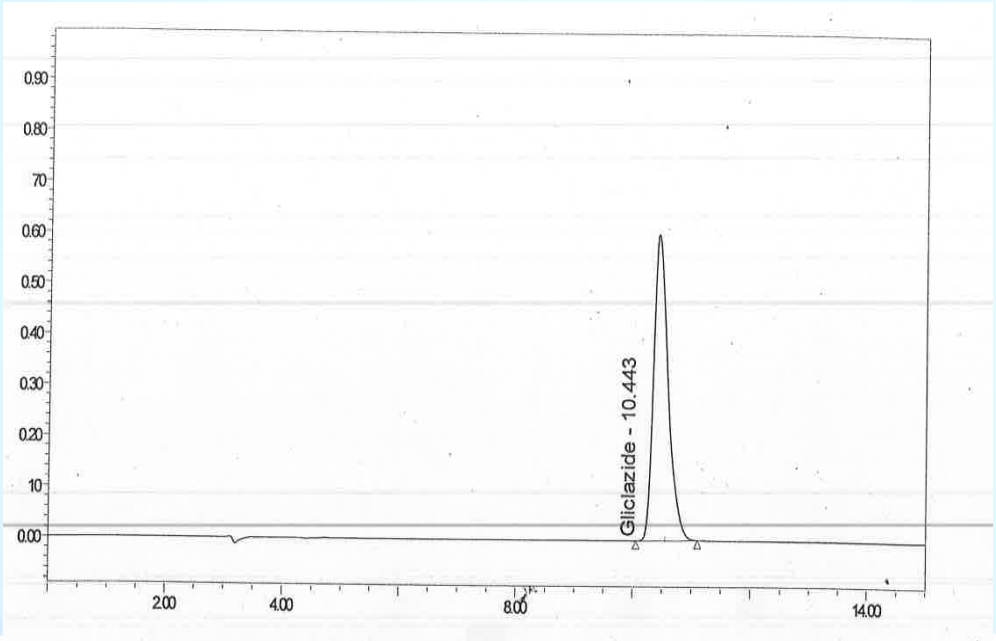

Fig 4 Gliclazide Tablet chromatogram

***IN VITRO* DRUG RELEASE STUDIES**

The cumulative percentage releases of different formulation of Gliclazide SR tablets were shown in Table 4 and Figure 5.The release of Gliclazide from SR tablets varied according to the types and proportion of polymers content in the various formulations. Formulation which shows most satisfactory result is GLZ6, where drug release started after 1 hrs, and released maximum 97.67 by 12 hrs. Remaining formulations were respectively, release started and reached maximum, GLZ1- 1hr in 15..24 and 99.34 in 8 hrs, GLZ2-14.62 in 1 hr and 98.42 in 10 hrs, GLZ 3-14.72 in 1hr and 98.22 in 10 hrs, GLZ4 13.98 in 1 hr and 98.42 in 10 hrs and GLZ5 7.04 in 1 hr and 98.37 in 10 hrs. Formulations GLZ1 to GLZ 6 contain hydroxyl propyl cellulose at different concentrations. As the concentration of hydroxyl propyl cellulose increases retardation nature also increased. The duration of drug release was slower with formulation GLZ6 which was about only 97.67 % in 12 hrs.

Stability studies

Among the six Formulations, Formulation GLZ6 was selected for stability studies based on the physicochemical characterization of coating films and release characteristics. The stability studies were carried out at 40 ± 2 °C with 75 ± 5%% RH . There were no significant changes in their physical appearance, average weight of tablets and hardness. It was observed that the initial drug content and the drug contents of the samples analyzed after 1,3 and 6 month of storage were similar. The release profile also not showed any significant changes indicating that there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence, it can be concluded from the results that the developed tablets were stable and retain their pharmaceutical properties over a period of 6 month.

Table-4 The *In vitro* cumulative percentage release study of different formulation of Gliclazide SR matrix Tablets

Dissolution Media	Time (Hrs)	Formulations(cumulative percentage drug release)					
		GLZ-1	GLZ -2	GLZ -3	GLZ-4	GLZ -5	GLZ -6
Phosphate buffer pH 7.4	1	15.24	14.62	14.72	13.98	7.04	10.74
	2	36.45	33.43	32.82	28.88	29.54	23.70
	3	49.34	63.84	56.12	47.42	38.62	36.88
	4	70.12	78.74	78.46	61.68	58.54	50.44
	6	86.22	93.84	92.64	85.94	80.56	71.92
	8	99.34	97.62	96.86	96.78	91.92	85.31
	10	-	98.42	98.22	98.42	98.37	91.92
	12	-	-	-	-	-	97.67

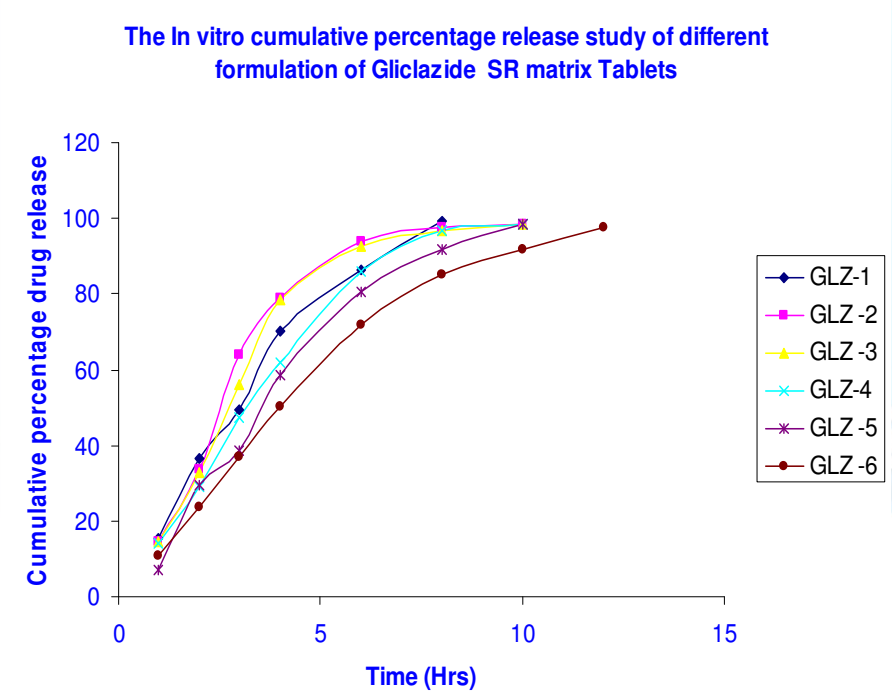

Table.5.Stability studies of Gliclazide SR Tablets formulation GLZ6

Evaluation parameters	Observation in month			
	Initial	1st month	3rd month	6th month
Physical appearance	white colour, circular tablets	white colour, circular tablets	white colour, circular tablets	white colour, circular tablets
Hardness (Kg / cm2) *	4.6 ± 0.42	4.6 ± 0.64	4.5 ± 0.24	4.5 ± 0.34
Drug Content (%)*	100.45 ± 0.45	99.98 ± 0.34	99.89 ± 0.86	99.76 ± 0.24

All values are expressed mean of 3 determination ± standard deviation

Conclusion

The colon targeted matrix tablets of gliclazide formulation system includes the drug delivery system that achieves slow and extended release of the drug over an extended period of time. It improves the bioavailability of the drug as well as its half life. Gliclazide different formulations were developed by using release rate controlling polymers like hydoxy propyl cellulose by wet granulation methods and then the tablets were enteric coated with Eudragit polymers (L-100 and S-100; 1:1) polymers. The different grade of HPMC as mucoadhesive polymers and coated with Eudragit polymers are best suitable in colon drug delivery system to provide necessary drug release of gliclazide to be absorbed in colon and protect it from SGF and SIF. As a result, colon delivery of gliclazide appeared to be a promising alternative to traditional drug administration routes.

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