World Inventia Publishers

Journal of Pharma Research

http://www.jprinfo.com/

Vol. 6, Issue 8, 2017 ISSN: 2319-5622 USA CODEN: JPROK3

Research Article

INVIVO STUIDES FOR GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF GLICLAZIDE

Mangulal Kethavath [1]*, Mujeeb Ur Rahman [2]

*[1] Research Scholar, Department of Pharmaceutics, Sunrise University, Alwar, Rajasthan, INDIA.

[2] Department of Life Science, Sunrise University, Alwar, Rajasthan, INDIA.

Received on: 18-07-2017; Revised and Accepted on: 02-08-2017

ABSTARCT

The aim of the present study was to develop non effervescent floating tablet formulation of Gliclazide to maintain constant therapeutic levels of the drug for over 9 hrs for the treatment of diabetis. Various grades of poly methacrylate polymers and accrual were employed as polymers. Gliclazide dose was fixed as 80 mg. Total weight of the tablet was considered as 500 mg for Gliclazide. Polymers were used in the concentration of 10, 20 and 30 mg concentration and accrual concentration used in the formulations were optimized according to the floating properties of the formulations . All the formulations were passed various physicochemical evaluation parameters like hardness, bulk density, friability, weight variation etc. and they were found to be within limits and also the drug and excipient studies showed that there is no incompatibility between pure drug and excipient. Whereas from the dissolution studies it was evident that the optimized formulations (F6) showed better and desired drug release pattern i.e., 91.17 % in 9 hours. It followed zero order release kinetics mechanism.

KEYWORDS: *Gliclazide, Floating tablets, HPMC K 100M, HPMC K15M, HPMC K4M, Accrual.*

INTRODUCTION

Gastro retentive Drug Delivery Systems:

Dosage forms that can be retained in stomach are called Gastro retentive Drug Delivery Systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site thus ensuring its optimal bioavailability [1-7].

The approaches that have been pursued to increase the retention of an oral dosage form in the stomach include Bioadhesive systems, swelling and expanding systems, High density systems and Low density (Floating) systems [8-13].

Factors Controlling Gastric Retention of Dosage Forms:

The gastric retention time(GRT)of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes)and administration of drugs such as pro kinetic agents (cisapride and metoclopramide) [14, 15].

1. Density of dosage form
2. Size of dosage form
3. Food intake and nature of food
4. Effect of gender, posture and age

MATERIALS AND METHODS

Gliclazide, HPMC K4M, HPMC K15M,HPMC K100M, Accural, Mag.Stearate, Talc, MCC Ph 102, HPMC E5,HPMC E50 all the chemicals were lab grade.

***Corresponding author:**

Mangulal Kethavath

Research Scholar,

Department of Pharmaceutics,

Sunrise University, Alwar, Rajasthan, India.

** E-Mail: mangupharmacist@gmail.com*

***Invivo* studies for Gliclazide non effervescent floating tablet:**

Introduction:

The present chapter deals with the description related pharmacokinetic studies of GLZ optimized compression coated tablets (DT4) for non effervescent floating. The main aim to conduct the pharmacokinetic studies in healthy rabbits was to demonstrate the time course of GLZ concentrations in blood in mathematical expressions, consequently to compare these with the marketed preparation of GLZ immediate release tablets. Pharmacokinetic of drugs following their administration from dosage forms is an integral part of part of research investigations in order to obtain vital information with respect to bioavailability of the newly developed dosage forms [16, 17].

The success of controlled drug delivery system depends on the ability to prolong the drug release for extended period of time. From the *invitro* dissolution studies of various GLZ non effervascent floating formulations explained in chapter 2, formulation DT4 i.e., HPMC K4M-cross povidone compression coated tablets was identified for *in vivo* evaluation in healthy rabbits. Since this formulation exhibited least amount of GLZ release up to 18 hrs in a controlled manner it is selected for this study. To substantiate these results, *in vivo* pharmacokinetic studies were designed. Hence the present investigation was planned to carry out *in vivo* studies and compare with *in vitro* results to prove the sustained drug delivery of GLZ from the optimized formulation [18, 19].

Experimental Methodology:

Analytical method development: HPLC method:

In order to estimate the GLZ content in the plasma samples, HPLC method was developed. For estimating the GLZ, a calibration curve was constructed by analyzing the plasma samples containing different concentrations of GLZ. In the present study Mobile phase was prepared by mixing 300ml (30%) 0.1M phosphate buffer pH 3.5 and 700ml (70%) of Acetonitrile. The mixer was degas in ultrasonic water bath for 5 minutes and filtered through 0.45 µ filter under vacuum. The Gliclazide samples were detected in ultra violet spectrum at 297 nm. Mobile phase was used as diluent.

Preparation of standard solutions:

Accurately weighted 10mg GLZ (working standard) was transferred into a 10 ml volumetric flask.7ml of diluent was added and

sonicated to dissolve the powder drug completely and finally volume was made up to the mark with the same solvent (stock solution). Further 1.0 ml of the above stock solution was pipetted into a 10ml volumetric flask and diluted up to the mark with diluent. Finally the preparation was filtered through 0.45µm filter.

Different concentrations (1, 10, 20, 30 & 40 µg/ml) were prepared for Linearity test.

Method of GLZ extraction from rabbit plasma sample:

In vivo study was performed in Albino Rabbits weighing 2 Kg.

***A. Groups for the Invivo Study*:**

In vivo study was carried out making three groups of healthy Albino rabbits. Each group consists of six rabbits (n=6).

Group I: Control (with drug)
Group II: Positive Control (pure drug tablet, marketed)
Group III: Formulation (Formulation tablet)

Preparation of sample solutions:

All rabbits were fasted overnight. To Group I, Tablet without drug, to Group II, Pure Gliclazide drug and to Group III, Gliclazide formulation - were administered by oral route.20 ml of water was given to rabbits immediately after the administration of tablet, for easy swallowing. Rabbits were placed in metabolic cages and blood samples were collected by using 27 gauge needle from the marginal ear vein into heparinized tubes at time intervals of 0.5,1,2,4,6,8,12,24 hours. Xylene was applied to the shaved marginal ear vein, which causes blood vessel to dilate. The samples were subjected to centrifugation by adding 50µl of Acetonitrile cyclomix at 8000 rpm for 20 mins and the supernatant was collected by using micropipette. After filtration 20 µl sample was injected into the HPLC system.

Conditions of Analytical Instrument & Method:

Rabbit Plasma Sample's Concentration of GLZ was found out by formerly described USP Method with minor modifications. waters hplc (2695 Seperation Module), With pda detector using hypersil ODS C_{18} Column (150 mm X 4.6 mm, 5 µm). Reverse phase chromatography utilized for estimation Of GLZ. The column and instrument temperature maintained at room temperature. Mobile phase was acetonitrile: phosphate buffer pH 3.5 (70:30 v/v), With A Flow Rate Of 1 ml/min, volume Of injection is 20 µl. the detection wavelength was 297 nm, temparature was mainted at 25 ^{0}C ± 2^{0}C.

HPLC method Validation:

10µl of drug free blank plasma and GLZ drug solutions were injected to determine specificity. The linearity was estimated using 0.2 to 1 µg/ml of GLZ. The chromatograms were developed by injecting 20 µl solution and the peak area was calculated for each drug solution and plotted the standard graphs and calculated correlation coefficient. To determine the inter and intraday precision repeated this study for six times. Method was validated for robustness, LOD, LOQ and accuracy.

Pharmacokinetic Evaluation in Rabbits:

Animal Ethical committee Approval:

The proposed protocol of the GLZ SR tablets in healthy Rabbits accepted by Animal Ethical committee of SICRA Labs Pvt Ltd. Andhra Pradesh, India with Registered No 769/2011/CPCSEA. Praposal no. 249.

Subjects:

2.0 to 2.5 kg, sound healthy, 18 male New Zealand white rabbits were utilized in the current pre clinical study. Animals were observed 10 days prior to study.

Study Design:

In the present research parallel study was utilized for determination of bioavailability parameters or pharmacokinetic parameters. White rabbits were randomly split into two groups, for each group comprising 6 animals. Composition of *invivo* CR tablet was shown in Table 4.

Half of the tablets of marketed conventional GLZ 10 mg tablets were given to one group and another group received laboratory prepared 40 mg GLZ CR tablets (The equivalent Dose was 12.97 mg). These 40 mg CR tablets were prepared from the blend of DT-4 (Optimized formulation), which were compressed into half of the tablet weight.

To prevent chewing of the tablet, it was placed under the tongue. Food was not given to the rabbits before 12 hrs and after 24 hrs of administration whereas free access to water in the entire study period. Rabbits were placed in metabolic cages and blood samples were collected by using 27 gauge needle from the marginal ear vein into heparinized tubes at time intervals of 0.5, 1, 2, 4, 6, 8, 12, 24 hours. Xylene was applied to the shaved marginal ear vein, which causes blood vessel to dilate. The samples were subjected to centrifugation by adding 50µl of acetonitrile cyclomix at 8000 rpm for 20 mins and the supernatant was collected by using micropipette. After filtration 20 µl sample was injected into the HPLC system.

Analysis of Pharmacokinetic Parameters:

Non compartmental method was used for the estimation of pharmacokinetic parameters of GLZ test and controls plasma concentration vs. time data. Test Biphaic (CR & IR) tablet) and control (Markted IR tablet) pk parameters were estimated by KINETICA 5.0 software.

Statistical Analysis:

With the help of Graph Pad Prism 6 software data was statistically analyzed. For comparison of PK parameters of test and control samples paired t-test was used and a value of $p<0.05$ was considered to be significant. ANOVA was used to determine any differences PK parameters obtained in a group (in six animals).

In vivo results and discussion:

Analytical Method Development: HPLC:

The HPLC method was developed, validated and adjusted the run time to 8 min. GLZ showed acccurate linearity in between 0.2-1µg/mL concentration and calibration curve showed splendid coefficient of correlation of 0.999 (Fig.1). GLZ retention time was observed at 5.428 mins .

Table No. 1: Linearity Results of Gliclazide

S NO	Linearity Level	Concentration	Area
1	**I**	0.2 µg/ml	9704
2	**II**	0.4 µg/ml	19409
3	**III**	0.6 µg/ml	29114
4	**IV**	0.8 µg/ml	38818
5	**V**	1 µg/ml	48523
Correlation Coefficient			**0.999**

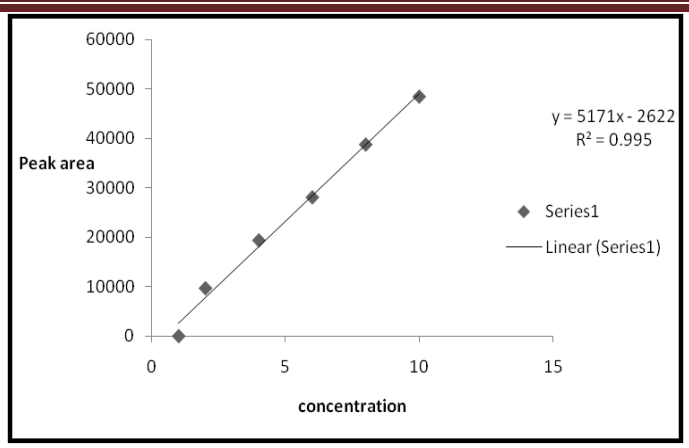


Fig. 1: Standard Linearity curve of Gliclazide

Validation of HPLC method:

This study confirmed that there was no GLZ peak in the blank plasma sample while it is present in the chromatogram of drug solution, established the specificity of method. Recoveries of standard drug were found to accurate at three different levels. The % recovery was obtained in range of 99.0-100.1% for each level % RSD of all six assays was found to be 0.64% for GLZ i.e., below standard value of 2%Linear regression coefficient of GLZ was found to be of 0.995 (Fig.1).

LOD results showed the signal to noise ratio (S/N) to 2.75 that stayed within the limits i.e., 3. In case of LOQ, the S/N ratio was found to be 9.84, which is less than 10 i.e., within the limits. From the results, the value of LOD and LOQ were found to be 0.0035 µg/ml and 0.018 µg/ml correspondingly. Change in flow rate and organic composition of mobile phase was not influenced the method. Hence it indicates that the method is robust at ±10% changes.

Table No. 2: Precision and Robustness results of Gliclazide

Precision Determination by injecting 0.6 µg/mL concentration		
Injection	**Peak area**	
Injection1	29114.2	
Injection2	28663.1	
Injection3	29056.2	
Injection4	28874.3	
Injection5	29172.8	
Injection 6	29004.1	
S.D	186.06	
RSD	0.64	
Intra Day and Inter Day Precision values		
Concentration	**Peak area**	
	Intra Day (n=3)	**Inter Day (n=3)**
0	0.00 ± 0.00	0.00 ± 0.00
0.2	9605.54 ± 3.112	9704.28 ± 4.136
0.4	19302.12 ± 6.002	19409.25 ± 6.008
0.6	29025.54 ± 5.119	29114.24 ± 2.196
0.8	38718.12 ± 5.106	38818.6 ± 6.186
1.0	48561.51 ± 2.162	48523.8 ± 2.121
Robustness		
S. No	**Parameter Change**	**System suitability results**
		USP plate count / **USP Tailing**
Change in Flow Rate (ml/min)		
1	**0.8**	3462 / 1.2
2	**1.0**	3504 / 1.4
3	**1.2**	3782 / 1.3
Change in the Organic Composition in the Mobile Phase		
1	**10% less**	5341 / 1.3
2	**Actual**	5022 / 1.5
3	**10% more**	5427 / 1.6

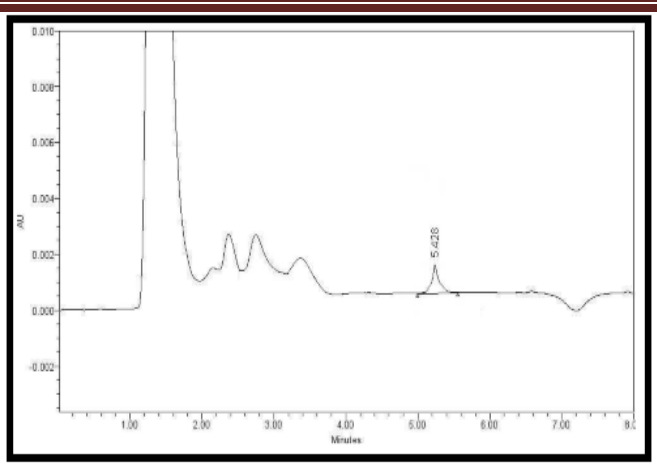


Fig. 2: showing chromatogram of GLZ standard curve at 0.2 µg/mL concentration

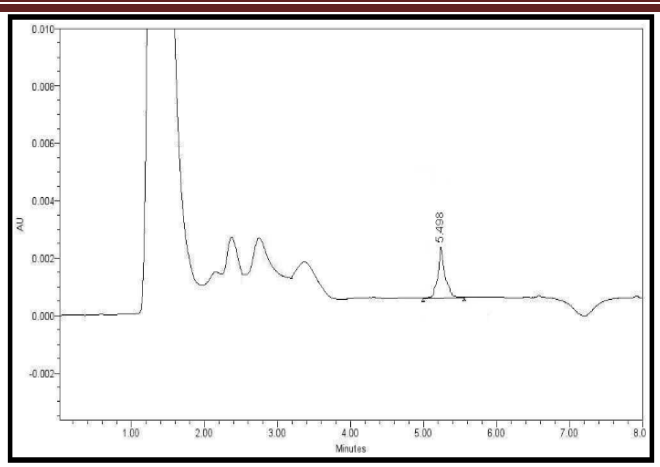


Fig. 3: showing chromatogram of GLZ standard curve at 0.4 µg/mL concentration

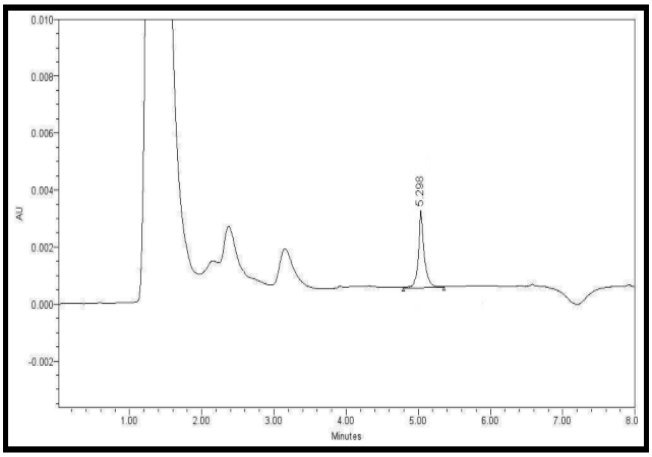


Fig. 4: showing chromatogram of GLZ standard curve at 0.6µg/mL concentration

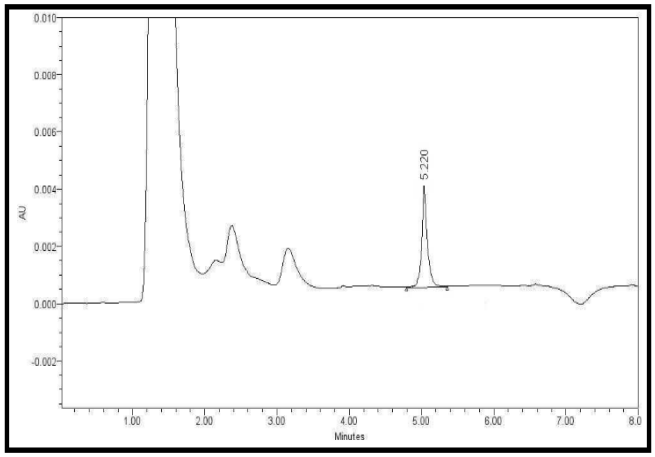


Fig. 5: showing chromatogram of GLZ standard curve at 0.8µg/mL concentration

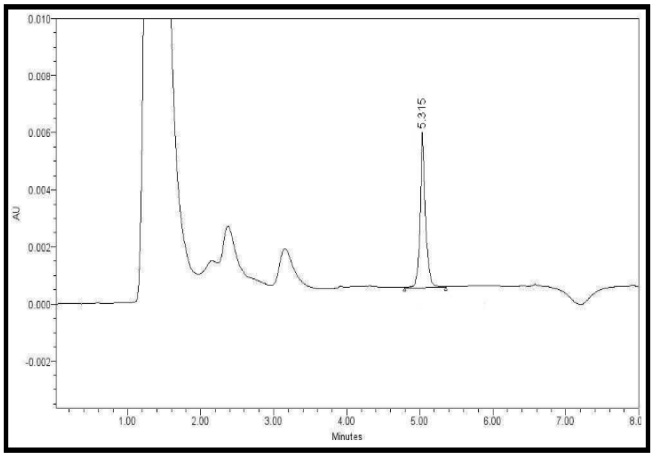


Fig. 6: showing chromatogram of GLZ standard curve at 1.0 µg/mL concentration

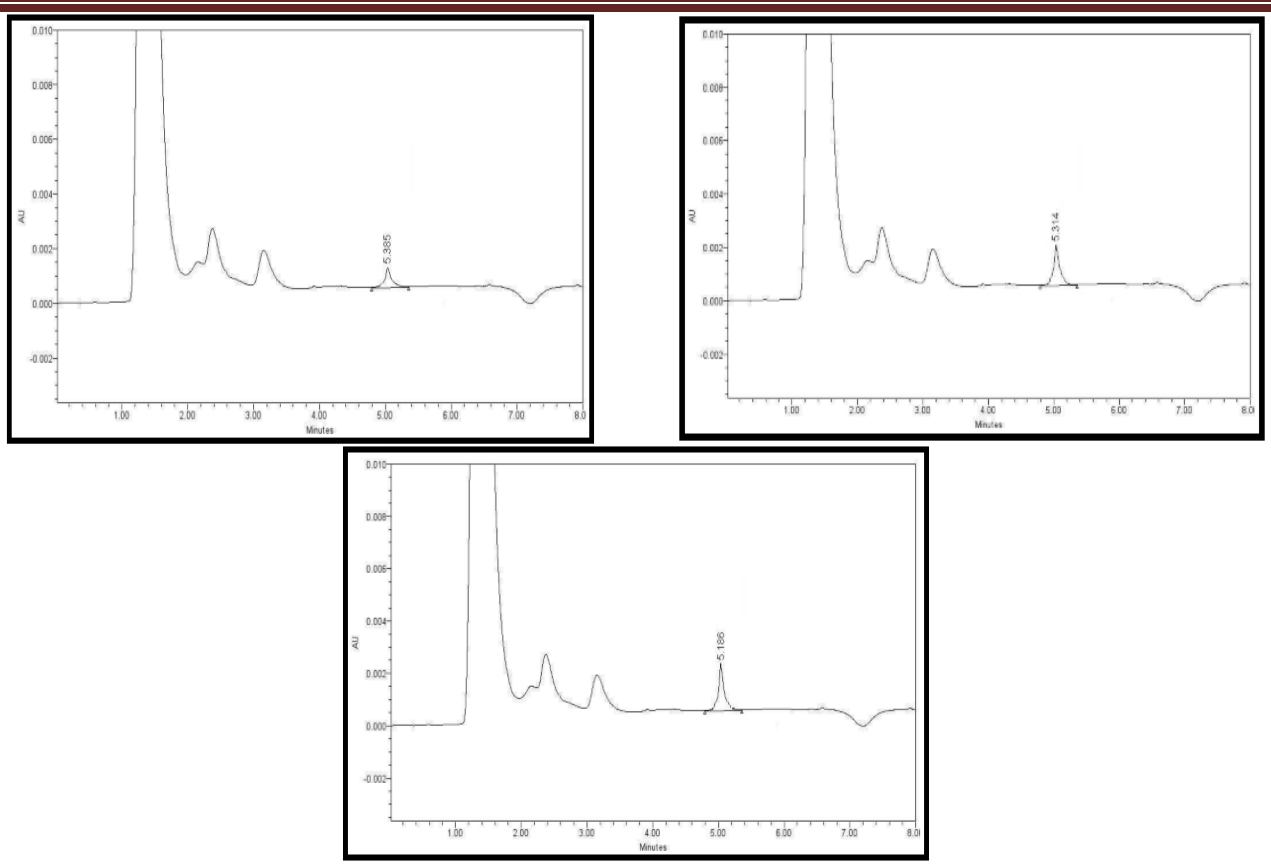


Fig. 7: GLZ test animal 6 (40 mg Compression coated tablet) sample HPLC chromatograms at1st, 2nd and 4th hrs.

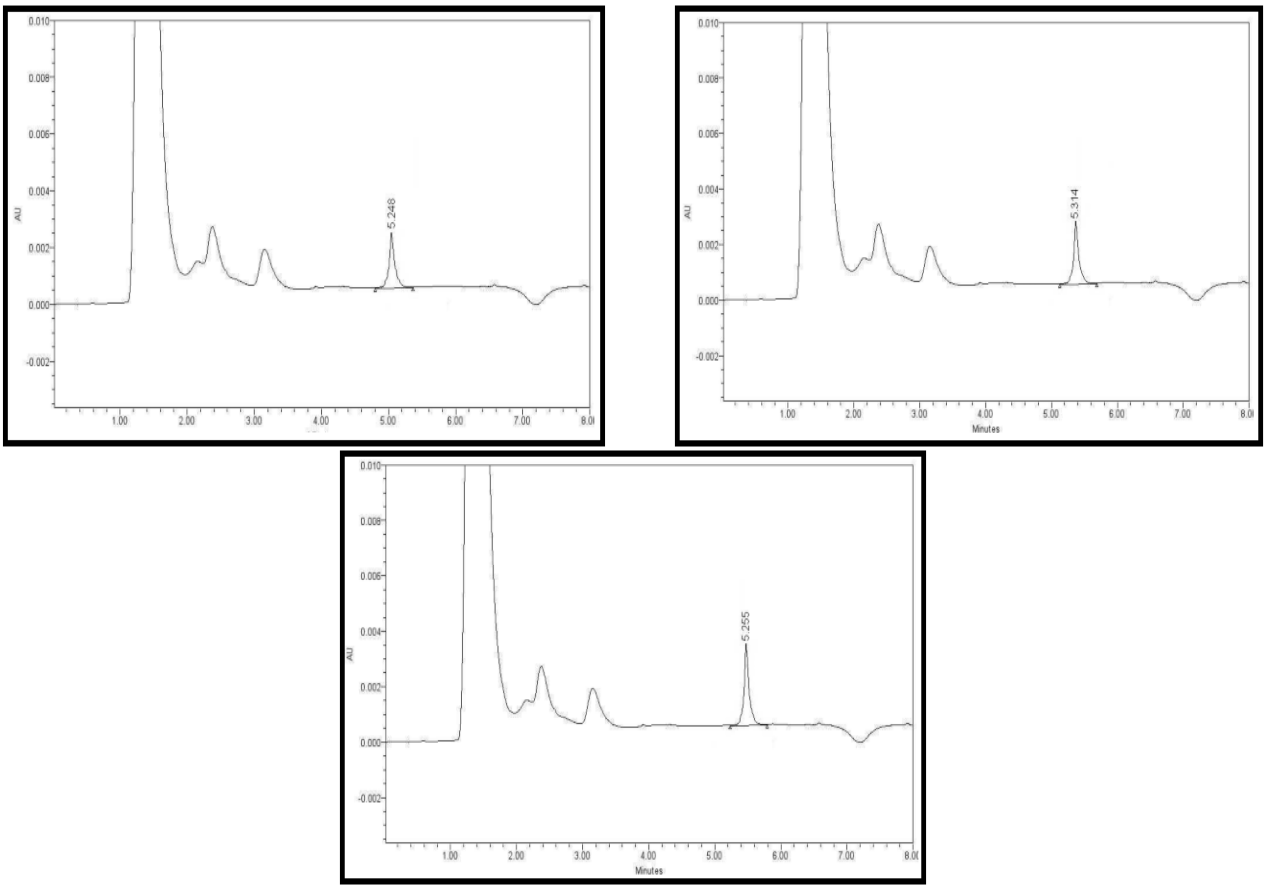


Fig. 8: GLZ test animal 6 (40 mg Compression coated tablet) sample HPLC chromatograms at 6th, 8th and 12th hr

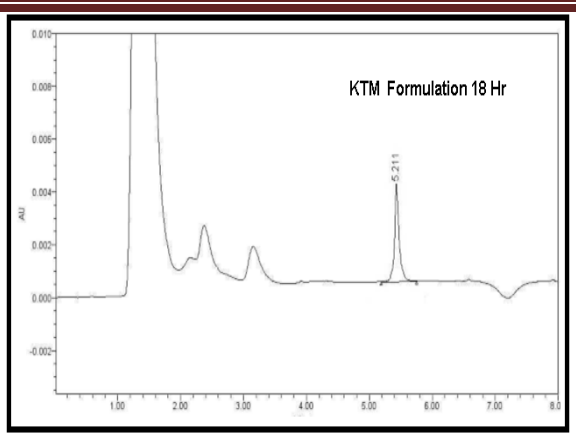
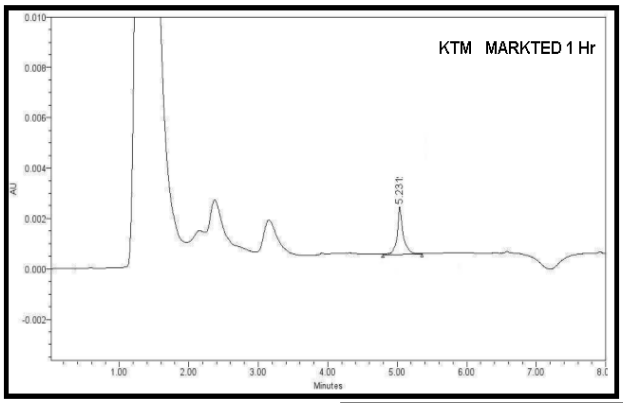
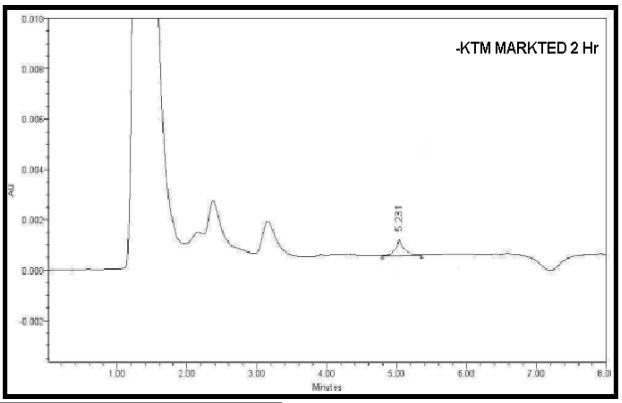


Fig. 9: GLZ test animal 6 (40 mg Compression coated tablet) sample HPLC chromatograms at 18th hr





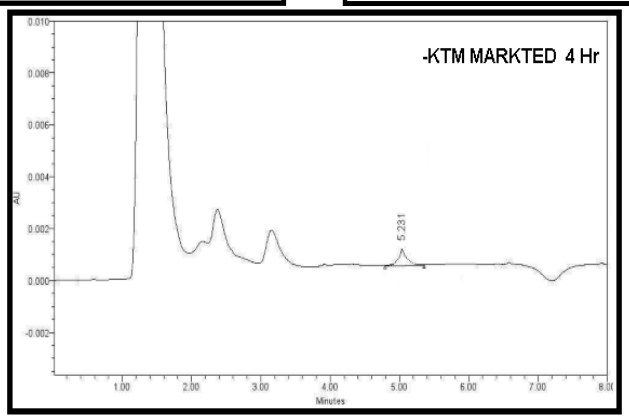
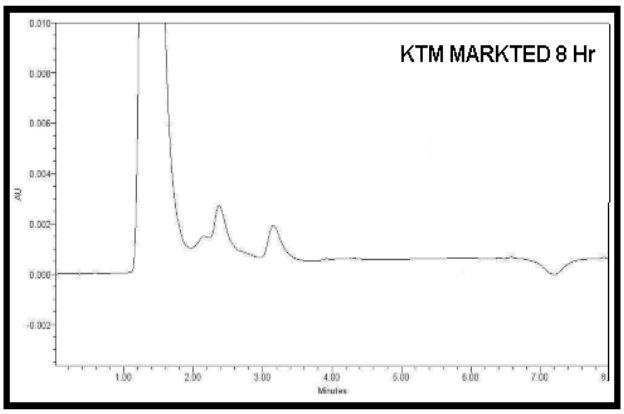


Fig. 10: GLZ control sample of animal 6 HPLC chromatograms at 1st, 2nd and 4th hrs



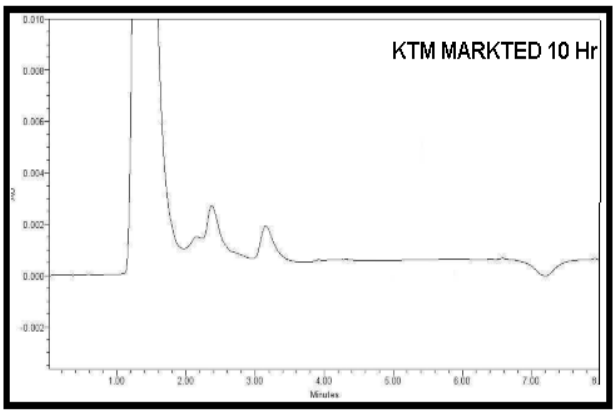


Fig. 11: GLZ control sample of animal 6 HPLC chromatograms at 8th and 10th hr

Table No. 3: Pharmacokinetic parameters of Markted tablet (Reference)

Pharmacokinetic Parameters											
Sub	T_{max} (h)	C_{max} (µg/mL)	$t_{1/2}$ (h)	MRT	Cl	Vd (mL)	AUC_{0-t}	AUC extrapolate	$AUC_{0-\infty}$	Total AUMC	K_{el}
1	0.5	0.8	3.62	0.08	420.3	5702	150.65	8.041	158.69	587.51	1.815
2	0.52	0.79	4.02	0.065	440.5	5603	170.79	14.76	185.55	938.11	2.189
3	0.5	0.8	3.21	0.084	490.2	6221	131.05	8.716	139.77	655.68	1.954
4	0.5	0.85	3.65	0.078	470.5	5882	132.23	0.341	132.23	444.32	0.907
5	0.5	0.77	4.25	0.072	425.2	5221	146.78	3.941	150.27	613.71	1.552
6	0.5	0.81	3.52	0.079	431.2	5773	130.47	3.742	134.22	522.52	1.483
Statistical Parameters											
N	6	6	6	6	6	6	6	6	6	6	6
Mean	**1.833**	**40.701**	**2.38**	**4.25**	**446.3**	**5733.6**	**143.66**	**6.59**	**150.12**	**626.975**	1.6504
SD	0.258	2.845	0.64	0.62	27.9	329.22	15.86	5.05	20.04	169.491	0.4471
Min	1.5	37.25	1.31	3.31	420.3	5221	130.47	0.341	132.23	444.32	0.9078
Median	2	39.91	2.43	4.29	435.8	5737.5	139.5	5.991	145.02	600.61	1.6839
MAX	2	45.35	3.16	5.05	490.2	6221	170.79	14.76	185.55	938.11	2.1898
%CV	0.141	0.07	0.271	0.147	0.063	0.057	0.11	0.766	0.134	0.27	0.2712

(CV= Coefficient of variation, SD=Standard deviation)

Table No. 4: Plasma concentrations tablet (T) of Optimized GLZ Compressed Coated Tablet at different Time intervals

Subjects		Time (hrs)												
		0	**0.5**	**1**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**36**	**48**	**72**
1	Plasma Concentration	0	0.35	0.18	0.25	0.34	0.48	0.59	0.69	0.8	0	NA	NA	NA
2		0	0.36	0.16	0.28	0.38	0.45	0.6	0.72	0.82	0	NA	NA	NA
3		0	0.35	0.16	0.23	0.39	0.46	0.62	0.75	0.83	0	NA	NA	NA
4		0	0.34	0.2	0.28	0.38	0.49	0.65	0.74	0.81	0	NA	NA	NA
5		0	0.28	0.15	0.26	0.34	0.42	0.58	0.67	0.79	0	NA	NA	NA
6		0	0.35	0.18	0.27	0.34	0.46	0.6	0.72	0.85	0	NA	NA	NA
N	Statistical Parameters	6	6	6	6	6	6	6	6	6	6	*	*	*
Mean		**0**	**0.33**	**0.171**	**0.261**	**0.361**	**0.46**	**0.606**	**0.715**	**0.816**	0	*	*	*
SD		0	0.029	0.018	0.019	0.024	0.024	0.025	0.03	0.021	0	*	*	*
Min		0	0.28	0.15	0.23	0.34	0.42	0.58	0.67	0.79	0	*	*	*
Median		0	0.35	0.17	0.265	0.36	0.46	0.6	0.72	0.81	0	*	*	*
Max		0	0.36	0.2	0.28	0.39	0.49	0.65	0.75	0.85	0	*	*	*
%CV		0	8.65	10.68	7.417	6.639	5.324	4.126	4.219	2.64	0	*	*	*

(CV= Coefficient of variation, SD=Standard deviation)

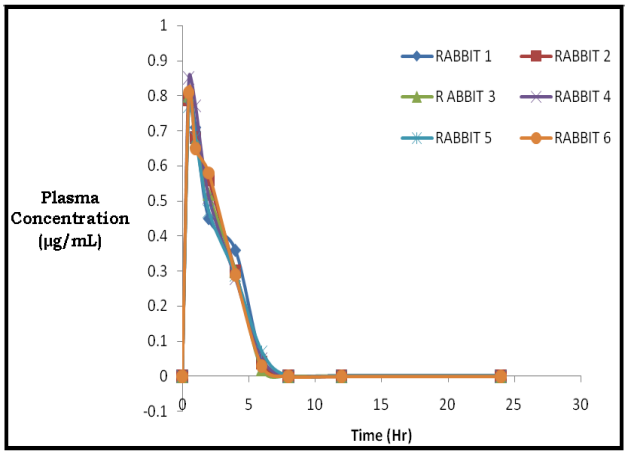


Fig. 12: Showing plasma concentration vs. time profile of Markted GLZ in rabbit plasma samples

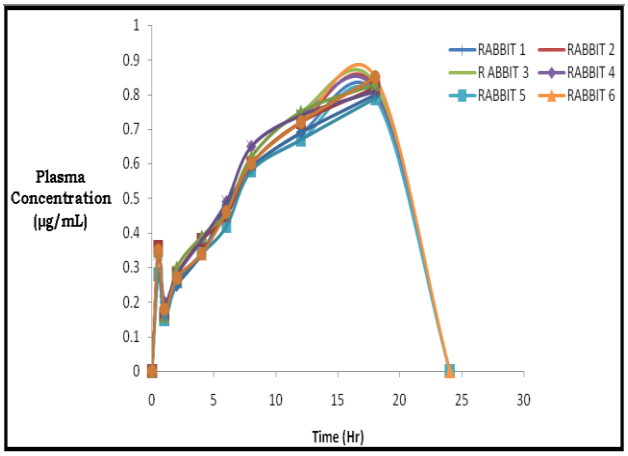


Fig. 13: Showing plasma concentration vs. time profile of Test GLZ compressed coated tablet in rabbit plasma samples

Pharmacokinetic Parameters Evaluation:

These parameters are compulsory for determination of bioavailability, such as maximum concentration of serum (C_{max}), time to reach the maximum conc. of serum (T_{max}), area obtained under the plasma-concentration time curve(AUC), Volume of distribution(V_d), half-life ($t_{1/2}$), mean residence time (MRT) and clearance(Cl_T). Showed HPLC chromatograms of reference GLZ in rabbit plasma samples. Showed HPLC chromatograms of test tablets in rabbit plasma samples. Plasma concentration values and bioavailability parameters of reference marketed formulation. Depicts plasma concentration values and bioavailability parameters of test extended release formulation.

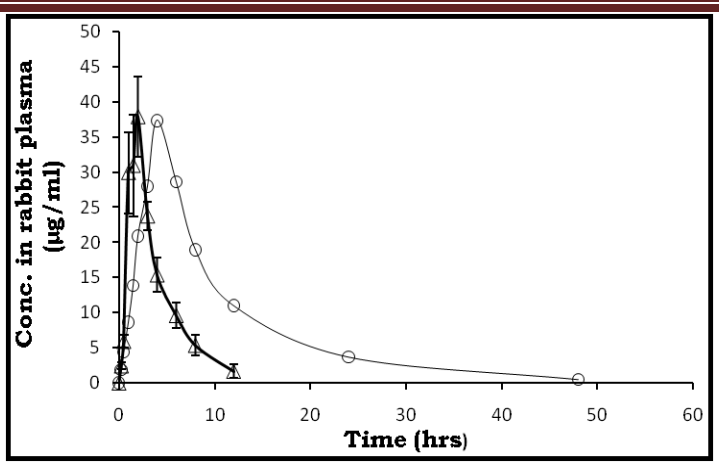


Fig. 14: Comparison curves of Plasma Conc. vs. time of Reference and test GLZ formulation

Table No. 5: Comparitive bioavailability parameters of reference and Test formulations

PK parameter	Reference Tablet	Test Tablet	't' test at 0.05
C_{max} (µg/mL)	0.81	0.84	Not significant
T_{max} (hrs)	0.52	18.20	Significant
$t_{1/2}$ (hrs)	4.26	6.41	Significant
MRT (h)	0.081	0.086	Significant
Total AUC (µg-hr/mL)	150.12	406.46	Significant
Total AUMC (µg-hr/mL)	626.9	4846.8	Significant
Cl (mL/min)	446.31	151.08	Significant
K_{el} (hrs^{-1})	1.65	8.09	Significant

C_{max} of GLZ and test formulations were 0.8 ± 0.1 µg/mL and 0.85 ± 0.02 µg/mL respectively with significantly no difference (P<0.05) and a P value of 0.0856. T_{max} values of GLZ, test were 0.533 ± 0.25 hrs, 18.33 ± 0.81 hrs respectively with significant variance (P<0.05) and a P value 0.0005. ETOVA and test $t_{½}$ values were 2.38 ± 0.645 hrs, 7.855 ± 1.71hrs respectively, with significant variance (P<0.05) and a P value is 0.0002. MRT values of ETOVA and test were 4.25 ± 0.624 hrs and 11.67 ± 2.28 hrs respectively with significant variance with a P value is 0.002. $AUC_{0-\infty}$values were 150.1 ± 20.04 µg-hr/mL, 406.5 ± 49.44 µg-hr/mL respectively for ETOVA and test with significant variance (P<0.05) and P value is <0.0001. Elimination rate constant of reference and test were1.650 ± 0.44 hr^{-1}, 8.09 ± 1.586 hr^{-1} respectively with significantly variant and P value is 0.0001.

Owing to the subjective variability there was variance in individual T_{max} and C_{max} values. This was ascertained in marketed and test samples also.

The results of pharmacokinetic parameter values designate that the marketed formulation and test formulation were entirely variant owing to the prepared formulation liberates the drug extended period of time.

CONCLUSION

In the present research work gastro retentive non effervescent floating matrix formulation of Gliclazide were formulated by using various hydrophilic polymers. Initially analytical method development was done for the drug molecules. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using HPMC K100M were unable to produce desired drug release, they were unable to retard drug release up to 9 hours. The formulations F6 prepared with HPMC K15M retarded the drug release up to 9 hours in the concentration of 80 mg. Hence they were considered. The optimized formulations (F6) dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed Higuchi mechanism of drug release.

REFERENCES:

1. Harekrishna roy, Anup Chakraborty, Bhabani Shankar Nayak, Satyabrata Bhanja, Sruti Ranjan Mishra, P. Ellaiah. Design and in vitro evaluation of sustained release matrix tablets of complexed nicardipine hydrochloride. Int J Pharma Pharma Sci **2014**;2(4):2014
2. Akhlak Ahmed, Narendra KR. Goyal and Pramod K. Sharma. Effervescent floating drug delivery system: a review. Global journal of pharmacology **2014**;8(4):478-485
3. Sarvesh D. Parsekar, Shruti Prabhu, Amitha Shetty, Mohd Azharuddin and AR. Shabaraya. A brief review on floating bilayer tablet as a convenient gastroretentive drug delivery system. **2014**;3(2).
4. Sevgi Güngör, M. Sedef Erdal, Buket Aksu. New formulation strategies in topical antifungal therapy. J Cosm, Dermatolog Sci and Appli **2013**;3:56-65.
5. Jadhav Mayur N, S. Shanmugam, K. Sundaramoorthy, T. Ayyappan and T. Vetrichelvan. Formulation and in-vitro evaluation of gastro retentive floating matrix tablets of famotidine. **2010**;1(4).
6. Ritesh Kumar. Development and in vitro evaluation of sustained release floating matrix tablets of metformin hydrochloride. IJPSR **2010**;1(8).
7. Gilman AG, Rall TW and Taylor P. Goodman and Gillman's the pharmacological basis of therapeutics. The mc graw-hill companies inc, new york, 10th edition **2001**.
8. Tripathi KD. Essentials of medical pharmacology. Jaypee brothers, New Delhi, fifth edition **2003**.
9. Singh BN and Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Cont Rel **2000**;63(1–2):235-259.
10. Bolton S. Pharmaceutical statistics practical and clinical applications. Marcel decker inc. New york, second edition **1990**.
11. Aulton ME. Pharmaceutics: the science of dosage form design. Churchill livingstone, new york, second edition **2002**.
12. Chawla G, Gupta P, Koradia V and Bansal AK. Gastroretention: a means to address regional variability in intestinal drug absorption. Pharm tech **2003**;27(7):50-68.

13. Remington. The science and practice of pharmacy. 20th edn, vol.i, pg.no.903- 913.
14. Lachman et al. Theory and practice of industrial pharmacy. 3rd ed philadelphia, **1991**;303-314.
15. RJ. Suryawanshi, U. Shah, and K. Vishnupad. Alternative granulation technique: melt granulation. Drug development and industrial pharmacy, **1996**;22(9-10)917–924.
16. JG. Hardman, LE. Limbrid, A. Goodman, PB. Molinoff and RW. Ruddon. The pharmacological basis of therapeutics, macgraw-hill, new york, ny, usa, 10th edition, **2001**.
17. Kirkwood J. Neill and E. Breden. Zolpidem modifiedrelease in insomnia. Neuropsychiatric disease and treatment **2007**;3(5):521–526.
18. M. Lue, FS. Nielsen, T. Magnussen et al. Using biorelevant dissolution to obtain ivivc of solid dosage forms containing a poorly-soluble model compound. Eur J Pharma and Biopharma **2008**;69(2)648-657.
19. Neha M. Dembla, Arun Pandian Maniyam and Surendra Agarwal. Formulation development and evaluation of gabapentin controlled release tablets. Pharma & Pharmacol Int J **2015**;2(3).

How to cite this article:

Mangulal Kethavath, Mujeeb Ur Rahman. INVIVO STUIDES FOR GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF GLICLAZIDE. J Pharm Res 2017;6(8):115-123.

Conflict of interest: The authors have declared that no conflict of interest exists.

Source of support: Nil