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A study on pharmacokinetic parameters of glimepiride in experimental diabetes mellitus induced rats

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Abstract
An experimental study was conducted to evaluate the interaction of *Gymnema sylvestre* extract with insulin and glimepiride in diabetic Sprague dawley rats. Rats were randomly divided into seven groups of six rats each. In this experiment pharmacokinetic interaction of glimepiride with *Gymnema sylvestre* extract was assessed. The pharmaco kinetic study revealed the values of half-life, Absorption rate constant, Elimination rate constant and time to achieve maximum concentration of glimepiride were significantly varied in *Gymnema sylvestre* pre-treated rats compared to normal rats administered with glimepiride.

Keywords: pharmacokinetic study, glimepiride, diabetes mellitus, sprague dawley rats

Introduction
Diabetes mellitus (DM) is a multifactorial metabolic syndrome resulting from defect in insulin secretion, insulin action or both [1]. DM is the one of the most frequent chronic diseases worldwide being among the top five main causes of death in developing countries as per the world health organization, 2012. Glimepiride is a sulfonylurea agent that reduces blood glucose concentrations to satisfactory levels with once-daily dosing [2, 3] and has a rapid onset [4, 5] and prolonged duration of action, together with a low risk inducing hypoglycaemia [5, 6]. Once-daily dosing of glimepiride results in improved patient adherence [7, 8] and satisfactory control of blood glucose concentrations [13]. In an open-label, randomized study carried out in patients with type 2 DM, the combination of metformin and glimepiride showed significantly greater reductions in case of fasting blood glucose, total cholesterol, serum triglyceride and low-density lipoprotein cholesterol as compared to the metformin and glibenclamide group [10]. Gymnema sylvestre is effective in reducing blood glucose level and HbA1c when taken orally by patients with type 1 or 2 diabetes mellitus.

Materials and Methods
The experimental study was conducted on male Sprague dawley rats of uniform age (3 months) and weights. These were procured from National Centre for Laboratory Animal Sciences (NCLAS), National Institute of Nutrition (NIN), Hyderabad. Feed and water were provided *ad libitum* throughout the experiment. Animals were housed in polypropylene cages in an air-conditioned animal house with 12h-12h light-dark cycles. The experimental protocol was approved by the Institutional Animal Ethics Committee (Lr. No: I/6/2012; dated: 06/01/2012). Rats were randomly divided into 7 groups of 6 rats.
Pharmacokinetic analysis from the concentration-time data of glimepiride was performed by using PK Functions, mathematical basis [11] for these functions and built-in pharmacokinetic functions for Microsoft Excel. The pharmacokinetic data were statistically analyzed by applying paired sample t-test. Remaining data were subjected to statistical analysis by applying one-way ANOVA using statistical package for social sciences (SPSS) version 15.0. Differences between means were tested using Duncan's multiple comparison test and significance level was set at 0.05.

Results
The plasma levels of glimepiride as a function of time in six rats after single oral administration of glimepiride (4 $mg.kg^{-1}$). The plasma concentrations of glimepiride at various time intervals were determined by incorporating the peak areas of the chromatograms obtained after injecting plasma samples into the HPLC system, in the regression equation of the standard calibration curve obtained after plotting the peak areas versus corresponding plasma

standards of glimepiride (Fig 1). The mean C_{max} of glimepiride was 35.31 ± 4.05 µg.mL^{-1}. Mean plasma concentration of glimepiride was presented graphically in Fig 2. The peak plasma level for glimepiride was observed at a mean t_{max} of 3.2 ± 0.25h. The glimepiride was detectable up to 12 h.

Various pharmacokinetic parameters estimated basing on the plasma concentrations of glimepiride after single oral administration was summarized in Table 1. The mean absorption rate constant (K_a) for glimepiride was 2.92 ± 0.14 h^{-1}. The mean elimination rate constant (K_e) was 0.71 ± 0.09 h^{-1} with a corresponding mean elimination half-life ($t_{½\beta}$) of 5.30 ± 0.14 h. The average values for area under plasma drug concentration-time curve (AUC), area under the first moment curve (AUMC), volume of distribution ($V_{d(B)}$), and total body clearance (Cl_B) were 86.10 ± 5.2 µg.h.mL^{-1}, 154.63 ± 4.07 µg.h^2.mL^{-1}, 2.83 ± 0.13 L.kg^{-1} and 0.093 ± 0.005L.kg^{-1}.h^{-1}, respectively.

The plasma levels of glimepiride as a function of time in six rats after single oral administration of glimepiride (4 mg.kg^{-1}) following *Gymnema sylvestre* (400 mg.kg^{-1}) pretreatment. The mean C_{max} glimepiride was 26.10 ± 5.17 µg.mL^{-1} Mean plasma concentration of glimepiride were presented graphically in Fig 2. The peak plasma level for glimepiride was observed at a mean t_{max} of 2.42 ± 0.14 h. The glimepiride was detectable up to 12 h.

Various pharmacokinetic parameters estimated basing on the plasma concentrations of glimepiride after single oral administration following *Gymnema sylvestre* pretreatment were summarized in Table 1. The mean absorption rate constant (K_a) for glimepiride was 8.2 ± 0.25 h^{-1}. The mean elimination rate constant (K_e) was 0.42 ± 0.03 h^{-1} with a corresponding mean elimination half-life ($t_{½\beta}$) of 4.30 ± 0.19 h. the average values for area under plasma drug concentration-time curve (AUC), area under the first moment curve (AUMC), volume of distribution ($V_{d(B)}$), and total body clearance (Cl_B) were 76.85 ± 5.39 µg.h.mL^{-1}, 175.25 ± 27.62 µg.h^2.mL^{-1}, 2.95 ± 0.28L.kg^{-1}, and 0.10 ± 0.006 L.kg^{-1}.h^{-1}, respectively.

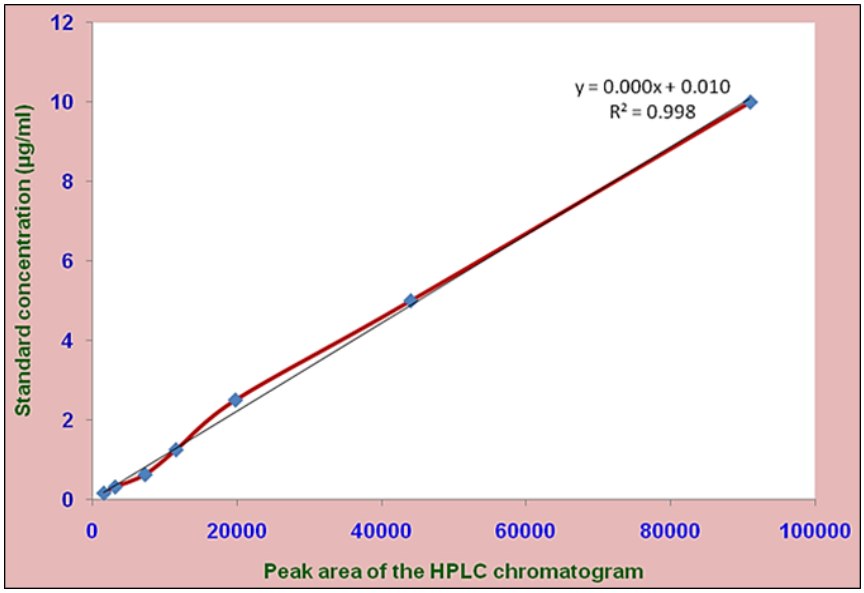

Fig 1: Calibration curve of glimepiride

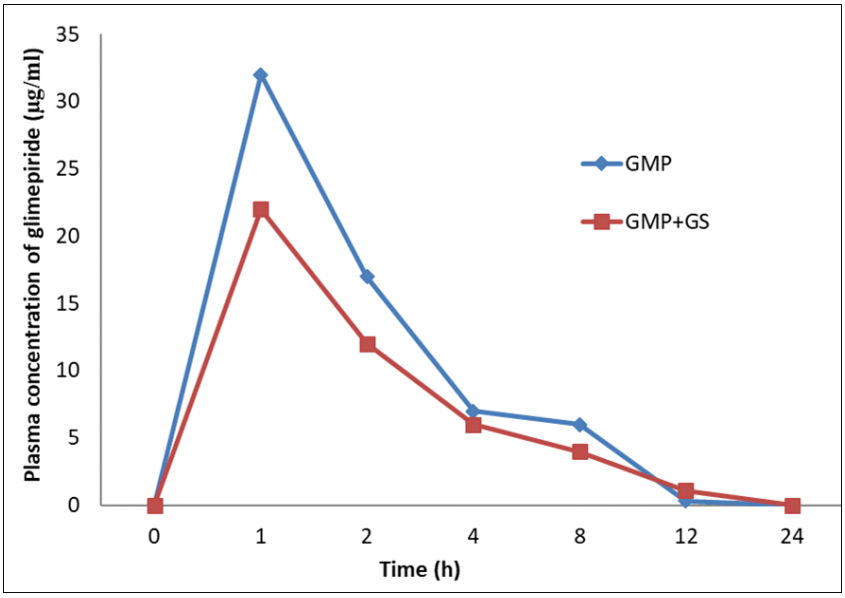

Fig 2: Semi logarithmic plot of mean concentrations of glimepiride in plasma versus time after single oral administration of glimepiride (4 mg.kg^{-1}) in rats with or without *Gymnema sylvestre* pretreatment.

Table 1: Pharmacokinetic parameters of glimepiride in different groups of rats

Parameter	Unit	Glimepiride	Glimepiride + Gymnema sylvestre
$AUC_{(0-\infty)}$	$\mu g.h.mL^{-1}$	86.10 ± 5.2	76.85 ± 5.39
$AUMC_{(0-\infty)}$	$\mu g.h^2.mL^{-1}$	154.63 ± 4.07	175.25 ± 27.62
$t_{½\beta}$	h	5.30 ± 0.14	4.30 ± 0.19*
K_a	h^{-1}	2.92 ± 0.14	8.2 ± 0.25*
K_e	h^{-1}	0.71 ± 0.09	0.42 ± 0.03*
Cl_B	$L.kg^{-1}.h^{-1}$	0.093 ± 0.02	0.10 ± 0.06
$V_{d(area)}$	$L.kg^{-1}$	1.41 ± 0.18	1.77 ± 0.11
$V_{d(B)}$	$L.kg^{-1}$	2.83 ± 0.13	2.95 ± 0.28
C_{max}	$\mu g.mL^{-1}$	35.31 ± 4.05	26.10 ± 5.17
T_{max}	h	3.2 ± 0.25	2.42 ± 0.14*

Values are Mean ± SE (n = 6); One way ANOVA (SPSS).
*Significantly different (p<0.05) from respective values in a row.

Discussion

Effect of *Gymnema sylvestre* pretreatment on the plasma levels and pharmacokinetics of glimepiride was investigated by administering *Gymnema sylvestre* orally (400 $mg.kg^{-1}$) 40 min prior to the administration of glimepiride (4 $mg.kg^{-1}$).

Following oral administration of glimepiride in *Gymnema sylvestre* pretreated rats, a non-significantly lower peak plasma concentration (C_{max}) of 26.10 ± 5.17 $\mu g.mL^{-1}$ was observed, compared to the peak plasma concentration of 35.31 ± 4.05 $\mu g.mL^{-1}$ obtained in the group that received glimepiride alone and this might be due to enhanced first pass metabolism [12]. The absorption rate constant (K_a) for glimepiride in rats that received *Gymnema sylvestre* pretreatment was significantly higher (p<0.05) compared to the group that received glimepiride alone and this explains the shorter t_{max} for glimepiride in *Gymnema sylvestre* pretreated group. Significantly shorter elimination half-life ($t_{1/2}$) of 4.30 ± 0.19 h was observed for glimepiride in *Gymnema sylvestre* pretreated group compared to group receiving glimepiride alone. Important pharmacokinetic parameters did not vary significantly when glimepiride was used in combination with gymnema sylvestre leaf extract.

References

1. Beverley B, Eschwège E. The diagnosis and classification of diabetes and impaired glucose tolerance. In: Textbook of Diabetes 1 Ed: John C Pickup and Gareth Williams 2003, Chapter 2, 2.1-2.11.
2. Campbell R. Glimepiride: role of a new sulfonylurea in the treatment of type 2 diabetes mellitus. Annals of Pharmacotherapy 1998;32:1044-1052.
3. Rosenstock J, Samols E, Muchmore D, Schneider J. Glimepiride, a new once-daily sulfonylurea. A double-blind, placebo-controlled study of NIDDM patients. Diabetes Care 19 1996, 1194-1199.
4. Draeger E. Clinical profile of glimepiride. Diabetes Research and Clinical Practice 1995;28:139-146.
5. Schneider J. An overview of the safety and tolerance of glimepiride. Hormone Metabolism Research 1996;28:413-418.
6. Dills DSJ. Clinical evaluation of glimepiride versus glyburide in NIDDM in a double-blind comparative study. Glimepiride/Glyburide Research Group. Hormone and Metabolic Research 1996;28:426-429.
7. Paes A, Bakker A, Soe-Agnie C. Impact of dosage frequency on patient compliance. Diabetes Care 1997;20:1512-1517.
8. Lorenzati B, Chiara Z, Sara M, Federico L, Graziella B. Oral hypoglycemic drugs: Pathophysiological basis of their mechanism of action. Pharmaceuticals 2010;3:3005-3020.
9. Dr. Arshiya Masood Osmani, Shaikh Haseena. A possible correlation between low serum vitamin-D levels and type 2 diabetes mellitus. Int J Adv Biochem Res 2020;4(1):06-11.
   DOI: 10.33545/26174693.2020.v4.i1a.40
10. Shimpi RD, Patil PH, Kuchake VG, Ingle PV, Surana SJ, Dighore PN. Comparison of effect of metformin in combination with glimepiride and glibenclamide on glycaemic control in patient with type 2 diabetes mellitus. International Journal of Pharmacological Technique Research 2009;1:50-61.
11. Gibaldi M, Perrier D. Pharmacokinetics, 2nd ed. Marcel Dekker, New York 1982.
12. Xiao Dong S, Zhi Ping Z, Zhong Xiao W, Chong Shu C, Fattore C, Gatti G *et al*. Possible enhancement of the first-pass metabolism of phenacetin by ingestion of grape juice in Chinese subjects. British Journal of Clinical Pharmacology 1999;48:638-640.
13. Ramachandran A, Snehalatha C, Salini J, Vijay V. Use of glimepiride and insulin sensitizers in the treatment of type 2 diabetes. A study in Indians. Journal of Association of Physicians of India 2004;52:459-463.