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DRUG-DRUG INTERACTION BETWEEN GLICLAZIDE AND ROSUVASTATIN IN ANIMAL MODELS

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Abstract:

In the present work Rosuvastatin showed more influence the in blood glucose levels in diabetic group of rats than normal rats treated with Gliclazide. This enhanced anti hyperglycemic activity of Gliclazide may be due to inhibition of metabolizing enzymes like CYP 2c9, 3A4 by Rosuvastatin. Significant difference was observed in blood levels and pharmacokinetic parameters of Gliclazide when administered in the presence of Rosuvastatin compared to matching control in acute, chronic study of Gliclazide. Finally it is concluded that Rosuvastatin produced anti-hyperglycemic and enhanced the pharmacodynamic activity of Gliclazide with altering pharmacokinetics. The interaction was observed in two dissimilar species. it is likely to occur in human also. Hence the combination of Gliclazide (1/2TD), Rosuvastatin (TD) should be contraindicated / used with caution in clinical situation.

Key words: *Gliclazide And Rosuvastatin, Drug-Drug Interaction*

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INTRODUCTION:

Drug interaction can be defined as "It may arise either from alteration of Pharmacological response or effect due to Pharmacodynamic or Pharmacokinetic of one drug by the other or from combination of their actions or effects" [1].

In modern life today, numerous studies have demonstrated that many patients receive multiple drug therapy with recognized potential. As the number of drugs in patient's therapeutic regimen increases, the greater is the risk of occurrence of drug interaction [2]. It is known that the incidence of adverse drug reaction to drugs rise from 4.2% when five or fewer drugs are used to 45% when twenty or more drugs are used. This may lead to enhanced or diminished effect of concomitantly used drugs may be useful or harmful. The useful drug interaction is illustrated by synergistic combination of drugs such a antibiotics or antihypertensive .Harmful drug interactions are ,unfortunately ,more numerous [3].

These drug interactions may result in severe adverse drug reaction, exaggerated pharmacological responses, toxic effects or reduced efficacy of drugs.

The characterization of drug-drug interactions has been a standard part of drug development programs for the last two decades. Before release to the general public, a new drug entity must be tested for its ability to modulate the pharmacokinetic or Pharmacodynamic effects of co-prescribed medications, and for the reverse effects of the see established medications on the new drug entity. Many clinically important drug-drug interactions involved.

The modulation of drug metabolism or transport processes .However, until recently, there has been only limited emphasis placed on understanding and predicting the scope and mechanism of metabolically or transport-based drug interactions during the period of new dug development [4].

Clinically significant drug-drug interactions were uncommon and studies between the new drug development process and existing therapeutic agents were generally restricted to drugs ,such as warfarin and theophyllin ,with a narrow therapeutic index and proven susceptibility to metabolic inhibition of induction .In general ,interaction studies with a new drug entity were performed without much regard for the mechanistic basis for the interaction, resulting In much information on negative interactions and little specific guidance on the type of drugs that thought not to be administered together with the new drug entity [5].

Very often some life threatening adverse drug reactions also may be precipitated due to drug-drug interactions. According to one report, the drug interactions may be fourth to sixth leading cause of death in UnitedSates [4].

A study was conducted on drug-drug interactions in selected community pharmacies in which out of 1368 prescriptions, evaluated over a span of 3 months, 613 interactions are found in 516 prescriptions, out of which 16.15% were severe, 3.75% interactions were found where patient was receiving more than 8 drugs and 11.58 % interactions had a significant level [6].

Hence a concentrate effort is required to minimize the problem of drug-drug interactions while participating polypharmacy. Keeping the above statistics and severity of the problem in view, it is essential to understand the possible mechanism of drug-drug interactions and to generate scientific data on possible drug interactions.

Drug-drug interactions are basically of two types' pharmacodynamic interactions and pharmacokinetic interactions Pharmacodynamic type of interactions may be due to the similar or opposite pharmacological activities of concomitantly used drugs result in useful or harmful interactions. Pharmacokinetic type of drug drug interaction, one drug may interfere with theabsorption, distribution, metabolism and excretion of other drug and there by increasing or decreasing the potency, onset and duration of action .

MATERIAL AND METHODS:

Gliclazide Was Procured From Sun Pharma, Mumbai. Rosuvastatin Was Procured From MSN laboratories, Hyderabad.

ANALYTICAL METHODS USED IN THE STUDY

Collection of blood samples from rats:

Materials:

1) Micro centrifuge tubes (1.5 ml capacity)
2) Micro capillary tubes (1 mm diameter).
3) Absorbent cotton

Blood was collected from the retro orbital plexus of rats. It is the best method, if small amounts

(0.1 to 0.5 ml) of blood samples are required. A fine capillary is inserted gently in the inner angle of the eye, and then the capillary was slided under the eye ball at 45 degree angle and over the bony socket to rupture the fragile venous capillaries of the ophthalmic venous plexus. The passage is about 10 mm. The tip of the capillary is slightly retracted and the blood collected in the orbital cavity flows out from the capillary which is collected in a micro centrifuge tube. After collecting the desired volume, capillary is removed with simultaneous release of pressure by forefinger and thumb. Any residual blood droplet around the eye ball is wiped off by absorbent cotton swab. In this study un-anaesthetized animals were used because, anesthesia causes hyperglycemia by various mechanisms. Ether increases blood glucose levels by glycogenolysis in liver [55]. Halothane increases blood glucose by inhibiting release of insulin from pancreas, inhibit the effect of insulin on tissues and decreased rate of glycogen synthesis in liver [56]. The same procedure was carried out for collection of blood samples from diabetic rats after induction of diabetic state by alloxan monohydrate.

Estimation of blood glucose in rats and rabbits

In this study the enzymatic; glucose oxidase-perixodase (GOD – POD) method [57] was used.

A. Glucose oxidase-peroxidase (GOD/POD) method

Glucose kit based on Trinder's method in which glucose oxidase (GOD) and peroxidase (POD) enzymes were used along with the chromogen 4-aminoantipyrine and phenol. This method is one step, simple and rapid.

PRINCIPLE:

Glucose is oxidized by glucose oxidase to gluconic acid and hydrogen peroxide. In a subsequent peroxidase catalyzed reaction the oxygen liberated is accepted by the chromogen system to give a red colored quinoneimine compound. The red colour quinoneimine dye so developed is measured using Ultra-violet spectroscopy at 520nm.

$$Glucose + H_2O \xrightarrow{Glucose\ oxidase} Gluconic\ acid + H_2O_2$$

$$H_2O_2 + 4 - Aminoantipyrene + P - hydroxybenzoate \xrightarrow{Peroxidase} \text{Quinoneimine dye}$$

REAGENTS:

Reagents Type	Reagent Name	Name Of The Chemical
Reagent-1	Glucose reagent (9 vials	Glucose oxidase, Peroxidase 4-aminoantipyrine,buffer, stabilizers,
Reagent-2	Glucose Diluent (1*450ml)	Diluent, Phenol Preservetive
Reagent-3	Glucose standard (1*3 ml	Dextrose, benzoic acid

Working reagent preparation: The contents of 1 vial of reagent-1 were transferred quantitatively to a clean black colored plastic bottle provided in the kit. The bottle was reconstituted with 50 ml of glucose diluent (Reagent-2).

Storage of working reagent: The working reagent is stable for 12 months from the date of reconstitution when stored at 2-8^{0}C.

Specimen collection: The collected blood was made to stand without adding any anticoagulant. The clot that is formed is disturbed using a glass rod and was then centrifuged at 3000 rpm for 10 min. The serum is separated and used for the analysis.

EQUIPMENT:

Programme: The basic assay parameters are:

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Mode	***Endpoint***
Wave length	505nm (490-550nm)
Temperature	37^{0}C
Blanking	Reagent Blank
Incubation	30min at 37^{0}C
Sample volume	20 l
Working reagent volume	1 .5ml
Concentration of standard	100 mg/dl
Linearity	up to 500 mg/dl
Stability of color	30min
Units	mg/dl

PROCEDURE:

Pipette into tubes marked	Blank	Standard	Test
Serum Glucose Standard Working glucose reagent	- - 1 .5ml	- 20□l 1.5 ml	20□l - 1.5 ml
Mix well. Incubate at 37 ^{0}C for 10 minutes.			

They were mixed well and glucose values were noted using UV spectroscopy at 520 nm

CALCULATION:

Percentage of blood glucose reduction was calculated by using the following equation.

$$\%\ Blood\ Glucose\ reduction = \left(\frac{Xdi - Xdf}{Xdi}\right) * 100$$

- Xdi = blood glucose level at zero hr.
- Xdf = blood glucose level at that time.

Note: Unused working glucose reagent should be refrigerated immediately.

B.Collection of blood sample from rabbits:

Blood samples were collected from the marginal ear vein of the rabbits for estimation of blood glucose and blood gliclazide. For this, rabbits were kept in wooden holders with their heads protruding out. The left ear, for convenience, was shaved and blood vessels were dilated either by warming the ears on a low voltage electric lamp or by rubbing with a cotton swab. The dilated blood vessel of left marginal ear vein was punctured with a sharp syringe (22-24guaze) in the direction of venous blood flow. The blood was collected in micro centrifuge tubes.

C. Estimation of gliclazide in serum of rabbit by HPLC

A simple, sensitive HPLC method was developed for estimating the serum gliclazide levels. For pharmacokinetic studies, a method that allows an accurate measurement of low concentrations of gliclazide in serum is needed. Various analytical methods using high performance liquid chromatography (HPLC) and colorimetric assay[67] have been developed for the determination of gliclazide in biological samples. Each HPLC technique has its own advantages and disadvantages.

The present method is simple, sensitive and accurate which enables the determination of gliclazide even at ng/ml level in serum.

Chromatography: Typical chromatograms corresponding to individual blank serum and gliclazide (1□g) and diltiazem (2□g) {internal standard (IS)} were shown in fig. No endogenous interfering peaks were visible at the retention times of gliclazide or diltiazem confirming the specificity of the analytical method. Both the analyte and the internal standard were well separated with retention times of 12.10 and 5.90 minutes, respectively. System suitability parameters for the method were as follows. Number of theoretical plates for gliclazide and IS were 4726.75 and 6124.34 respectively; tailing factor was less than 1.5 for both gliclazide and IS.

Quantification: The ratio of peak area of gliclazide to that of IS was used for the quantification of gliclazide in serum samples. The calibration curves were linear in the concentration range 50–1000 ng/ml. The calibration regression equation was y = mx+c, where y represents the peak area ratio of gliclazide to IS, x represents the concentration of gliclazide, m is slope of the curve and c is the intercept. The equation of the calibration curve obtained was y = 0.0112x ; (r^2=0.9995) and its

calibration curve was represented

Materials: Gliclazide pure sample was gifted by Microlabs, Bangalore, India and diltiazem, pure samples was gifted by Sun pharmaceuticals, Mumbai respectively. Acetonitrile (HPLC grade) was purchased from Qualigens chemicals, Mumbai, India. Orthophosphoric acid (AR grade) and methanol (HPLC grade) were purchased from SD fine chemicals, Mumbai, India and Loba chemie pvt. Ltd., Mumbai, India respectively. Triple distilled water used for HPLC was prepared in the laboratory.

Standard solutions: Primary stock solution of 1 mg/ml of gliclazide and diltiazem were prepared in methanol and stored at 4 ^{0}C. Appropriate dilutions of gliclazide were made in mobile phase to produce concentrations of 10, 1 µg/ml and 500, 200, 100, 50 ng/ml. These dilutions were used to spike serum in the preparation of calibration curves. The IS working stock solution (100ng/ml) was made from primary stock solution using mobile phase for dilution. Calibration samples were prepared by spiking 100 µl of individual blank serum with appropriate amount of drug on the day of analysis. Samples for the determination of recovery, precision and accuracy were prepared by spiking control rabbit serum in bulk of appropriate concentrations (50, 100,200, 500 and 1000 ng/ml) and stored at -4 ^{0}C.

Preparation of phosphate buffer (15Mm):

1. Solution A: Dissolve 2.04g of potassium dihydrogen phosphate in water to produce 1000ml.
2. Solution B: Dissolve 0.21g of disodium hydrogen phosphate in water to produce 1000ml.

Mix 95.4ml of solution and 3.6ml of solution B-pH5.5.

EXPERIMENTAL WORK:

Gliclazide (5g) sample obtained from Microlabs, Bangalore, India and by Rosuvastatin (3g) sample obtained by were used. Blood glucose kits (Auto span) manufactured by Span diagnostics Ltd, Surat, India were purchased from a diagnostic kits and suppliers. Gliclazide solution in distilled water was prepared by dissolving 50 mg of gliclazide in a few drops of 0.1N sodium hydroxide then made up to 10 ml with distilled water.

Animals Used in the Study:

Inbred adult Wistar albino rats of either sex were procured from Mahaveer Enterprises, Hyderabad, India. The prior permission for the study was obtained from our Institutional Animal Ethics Committee (IAEC). Standard animal pellet diet manufactured by Rayan's biotechnologies pvt Ltd, Hyderabad, India was used for feeding the animals

Procedure:

Albino rats of either sex weighing between 180-280 g were used in the study. They were divided into 3 groups each consisting of 6 rats. Rats were maintained on uniform diet and at room temperature with 12 h /12 h light and dark cycle. They were housed in polypropylene cages. Rats were fed with standard animal pellet diet and water *ad libitum.* The rats were fasted for 18 h prior to the experiment with water *ad libitum*. During the experiment water was also withdrawn.

Methods:

For the pharmacodynamic study, rats were divided into three groups of six each. They were fasted for 18 h before the experiment and both water and food were withdrawn during the experiment. Group I/II/III were administered with Gliclazide namely 3.6mg/200g bd.wt.(1/2TD), 7.2mg/200g bd.wt.(TD) and, 14.4mg/200g bd.wt.(2TD). The same groups were administered with Rosuvastatin weight respectively after a washout period of one week. Later group II was treated with the combination of Gliclazide ½ TD and Rosuvastatin 0.72mg/200g body weight with a washout period of one week. Diabetes was induced in rats by the administration of Alloxan monohydrate in two doses i.e., 100mg and 50mg/Kg bodyweight intraperitonially for two consecutive days. Six Alloxan induced diabetic rats were treated with a combination of Gliclazide. TD and Rosuvastatin with a washout period of one week between the treatments. The blood samples were collected in rats from retro orbital puncture at 0, 1, 2, 3, 4, 6, 8, 10, and 12h and were analyzed for blood glucose by GOD/POD method using commercial glucose kits.

To find out the influence of selected dose of Rosuvastatin on pharmacodynamics and pharmacokinetics of Gliclazide, a group of 6 normal healthy rabbits were used. The rabbits were fasted for 18 h before the experiment and both water and food were withdrawn during the experiment. They were administered with 5.6mg/ 1.5 kg body weight of Gliclazide (1/2 TD), orally. The blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 12, 16 and 24 h time intervals. The same group after a wash out period of one week was administered with the combination of Rosuvastatin and Gliclazide orally; 30 minutes prior to Gliclazide administration (2.8mg /1.5kg body weight). The blood samples were withdrawn at 0, 1, 2, 3, 4, 6, 8, 12, 16 and 24 h time intervals. They were analyzed

for blood glucose levels by GOD-POD method using UV spectroscopy at 520 nm. and blood gliclazide levels were estimated by HPLC.

RESULTS:

Study of Influence of Drugs on Normal Rats

a) With Gliclazide: The Gliclazide was used as prototype drug of sulphonylurea in the present study of herb-drug interactions .Gliclazide induced hypoglycaemia was studied by administering it in different doses namely 3.6mg/200g bd.wt.(1/2TD), 7.2mg/200g bd.wt.(TD) and, 14.4mg/200g bd.wt.(2TD) for the dose response effect in the actual laboratory conditions. Gliclazide ½ TD produced 35.21□0.74 % and 36.34□0.74% reduction in blood glucose at 2h and 8h respectively. Gliclazide TD produced 66.78□0.56% and 50.14□11.46 % reduction in blood glucose at 6h and 8h respectively. Gliclazide 2TD produced 23.17□5.7.% and .22.91□6.94% reduction in blood glucose at 1h and 12h respectively.

Gliclazide has shown dose dependent effect on blood glucose of rats. After establishing the dose response effect, a dose of 3.6mg/200g bd.wt.(1/2 TD) was selected for studying the interaction in other sets of experiments. The blood glucose levels observed with ½ TD, TD and 2TD of Gliclazide were shown in table 5.1a,5.2a, 5.3a and respectively. The results of dose effect relationship were given in the tables 5.1b,5.2b, 5.3band the graphical representation was done in figure 5.1. The dose of ½ TD of

Gliclazide was selected based on ideal blood glucose reduction which was about 30%.

Table 5.1a Blood glucose levels (mg/dl) with GLICAZIDE (1/2 TD) in normal rats (N=6)

	Blood glucose levels in rats (mg/dl)						
	R_1	**R_2**	**R_3**	**R_4**	**R_5**	**R_6**	
0	77	80	76	80	90	99	83.21±3.35
1	53	55	58	56	65	70	59.5±2.45
2	50	52	49	50	59	65	54.17±2.39
3	54	56	54	54	61	72	58.5±2.66
4	52	53	55	55	64	72	58.5±2.93
6	53	55	54	53	62	65	57±1.92
8	50	51	50	49	58	61	53.16±1.87
10	60	63	66	67	73	75	67.33±2.14
12	69	70	72	70	85	88	75.66±3.16

Table 5.1b Percent Blood glucose reduction with GLICAZIDE (1/2 TD) in normal rats (N=6)

Time(h)	Percent blood glucose reduction in rats						**Mean SEM**
	R_1 (180g)	**R_2 (204g)**	**R_3 (196g)**	**R_4 (190g)**	**R_5 (210g)**	**R_6 (212g)**	
0	-	-	-	-	-	-	-
1	31.16	31.25	23.6	30	27.7	29.2	28.81±1.17
2	35.06	35	35.05	37.5	34.4	34.3	35.21±0.47
3	29.8	30	28.9	32.5	32.2	27.2	30.1±0.81
4	32.46	33.7	27.6	31.2	28.8	30.3	30.67±0.92
6	31.16	31.25	28.9	33.7	31.1	34.3	31.74±0.80
8	35.05	36.25	34.2	38.7	35.5	38.3	36.34±0.74
10	22.07	21.2	13.1	16.2	18.8	24.2	19.26±1.67
12	10.3	12.5	5.2	12.5	6.2	11.1	9.6±1.29

Table 5.2a Blood glucose levels (mg/dl) with GLICAZIDE (TD) in normal rats (N=6)

Time(h)	**R_1**	**R_2**	**R_3**	**R_4**	**R_5**	**R_6**	**Mean SEM**
0	90	100	101	80	85	95	91.84± 3.42
1	95	95	59	76	54	61	73.34±7.4
2	80	66	85	69	70	75	74.17±2.9
3	70	59	47	70	63	50	59.84±3.99
4	53	48	55	42	60	53	51.83±2.5
6	50	22	19	35	26	26	29.67±4.6
8	81	17	17	50	48	53	44.34±9.93
10	75	28	34	74	84	23	53±11.21
12	83	33	25	65	79	30	52.5±10.69

Table 5.2b Percent Blood glucose reduction with GLICAZIDE TD in normal rats (N=6)

Time(h)	Percent blood glucose reduction in rats						Mean□SEM
	R1	R2	R3	R4	R5	R6	
0	-	-	-	--	-	-	-
1	6.2	4.9	40.7	5	35.4	34.8	21.17±7..12
2	11.7	34.3	15.5	13.7	17	20.7	18.81±3.34
3	22.4	41.3	53.3	12	25.5	46.6	33.58±6.45
4	41.7	51.8	45.6	47.2	29.4	43.6	43.21±3.12
6	44.8	77.6	81	56	69.4	71.8	66.78±5.6
8	10.8	83.2	82.5	37.2	43.7	43.4	50.14±11.46
10	17.3	72	66	6.7	11	75.5	41.41±13.43
12	7.9	67.1	75.1	18.7	7	68.3	40.68±13.33

Table 5.3a Blood glucose levels (mg/dl) with GLICAZIDE (2 TD) in normal rats (N=6)

Time(h)	Blood glucose levels in rats (mg/dl)						Mean□SEM
	R-1 (260g)	R-2 (220g)	R-3 (230g)	R-4 (250g)	R-5 (240g)	R-6 (220g)	
0	90	88	100	110	100	100	98□2.98
1	53.5	55	86	100	80	88	77.08□7.02
2	90	100	90	67	85	98	83.33□4.41
3	50	79	94	88	98	71	80□6.59
4	80	90	102	90	110	80	92□4.47
6	57	111	84	82	91	95	86.67□6.64
8	65	95	68	91	93	93	84.17□5.13
10	39	80	62	80	103	90	75.67□8.36
12	45	85	70	85	95	79	76.5□6.51

Table 5.3bPercent Blood glucose reduction with GLICAZIDE (2 TD) in normal rats (N=6)

Time(h)	Percent blood glucose reduction in rats						Mean□SEM
	R-1 (260g)	R-2 (220g)	R-3 (230g)	R-4 (250g)	R-5 (240g)	R-6 (220g)	
0	-	-	-	-	-	-	-
1	46.5	38.1	14.6	8.36	20	11.5	23.17□5.7
2	10	-13	10.6	38.5	14.8	7.9	11.47□6.13
3	49.3	10.3	6.3	19.8	2	28.8	19.41□6.53
4	19.8	-1.6	-2	17.9	-10.4	19.9	7.26□5.01
6	42.6	-26.4	16.6	25.1	8.5	5	21.07□8.63
8	35.2	-7.1	3.21	17.4	6.4	7.1	10.36□5.39
10	60.4	9.8	38.5	27	-3	9.8	23.75□8.62
12	54.5	4.17	30.4	22.7	4.8	20.9	22.91□6.94

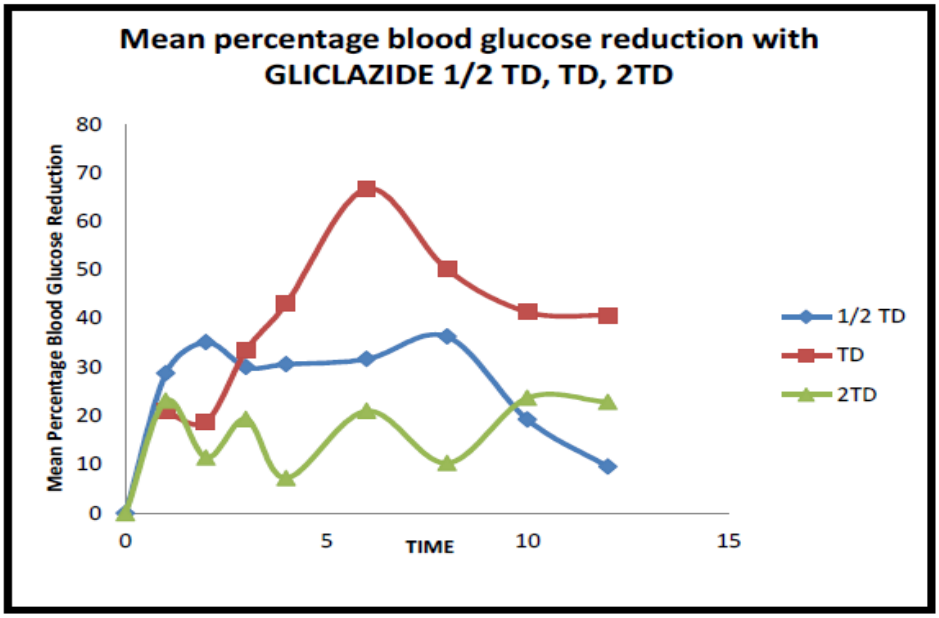


Fig: 5.1Mean percentage blood glucose reduction with GLICLAZIDE 1/2 TD, TD, 2TD

b) With Rosuvastatin The results of the blood glucose levels and the percent blood glucose reduction with½ TD 0.36mg/200g, TD 0.72mg/200g, 2TD 1.44mg/200g, of Rosuvastatin were tabulated in tables 5.4a-4b, 5.5a-5b, 5.6a-6b respectively. This treatment produced a minimum reduction of 0.54%, 3.01% and 6.58 %, and a maximum reduction of 4.52%, 13.54% and 26.63% respectively. Percent blood glucose reduction with different doses of Rosuvastatin in normal rats were presented graphically in figure 5.2.The dose of 2mg/200g bodyweight of Rosuvastatin was selected based on ideal blood glucose reduction which is about 10%.

Table 5.4 a Blood glucose levels (mg/dl) with Rosuvastatin (1/2 TD) in normal rats (N=6)

Time(h)	Blood glucose levels in rats (mg/dl)						Mean SEM
	R-1 (182g)	R-2 (204g)	R-3 (190g)	R-4 (195g)	R-5 (210g)	R-6 (220g)	
0	80	82	80	70	86	76	79 ± 2.23
1	79	80	78	67	85	76	77.5 ± 2.43
2	78	81	77	66	85	75	77±2.62
3	78	81	76	65	84	70	75.66±2.88
4	78	79	75	64	82	71	74.83±2.65
6	79	81	76	65	84	74	76.5±2.71
8	80	80	78	66	85	76	77.5±2.604
10	75	80	70	65	80	75	74.16±2.38
12	79	81	76	67	85	75	77.16±2.50

Table 5.4 b Percent Blood glucose reduction with Rosuvastatin (1/2 TD) in normal rats (N=6)

Time(h)	Percent blood glucose reduction in rats						Mean SEM
	R-1 (182g)	R-2 (204g)	R-3 (190g)	R-4 (195g)	R-5 (210g)	R-6 (220g)	
0	-	-	-	-	-	-	-
1	1.25	0.22	0.25	1.47	1.16	0	0.73±0.25
2	1.25	1.22	1.28	2.94	1.17	1.32	1.53±0.28
3	2.5	1.22	1.28	2.94	1.17	1.82	1.82±0.30
4	2.5	3.66	3.85	5.88	4.65	6.58	4.52±0.31
6	1.25	1.22	2.56	4.41	2.32	2.63	2.39±0.47
8	0	2.44	0.25	2.94	1.16	0	1.29±0.52
10	1.25	2.44	1.58	4.41	2.44	1.32	1.18±0.48
12	0	1.22	2.56	1.47	1.16	1.32	0.54±0.22

Table 5.5 a Blood glucose levels (mg/dl) with Rosuvastatin (TD) in normal rats (N=6)

	Blood glucose levels in rats (mg/dl)						
	R_1	R_2	R_3	R_4	R_5	R_6	
0	70	74	72	78	72	68	72.33±1.54
1	68	72	70	76	70	65	70.17 ± 1.65
2	65	69	68	73	68	64	67.84±1.54
3	62	65	66	68	63	58	64.67±1.54
4	59	63	63	68	63	58	62.33±1.59
6	61	64	66	67	64	59	63.50±1.34
8	62	65	68	69	64	60	64.67±1.54
10	65	66	64	68	66	62	65.67±0.91
12	68	68	66	72	68	63	67.50±1.31

Table 5.5 b Percent Blood glucose reduction with Rosuvastatin TD in normal rats (N=6)

Time(h)	Percentage Blood glucose reduction in rats (mg/dl)						Mean SEM
	R_1 (195g)	R_2 (210g)	R_3 (200g)	R_4 (196g)	R_5 (185g)	R_6 (212g)	
0	-	-	-	--	-	-	-
1	2.86	2.70	2.78	2.56	2.78	4.41	3.01±0.30
2	7.14	6.76	5.56	6.41	5.56	5.88	6.21±0.29
3	11.43	12.16	8.33	10.26	9.72	11.76	10.61±0.64
4	15.72	14.86	12.50	12.82	12.50	14.70	13.85±0.63
6	12.86	13.51	8.34	14.10	11.11	13.23	12.19±0.95
8	11.43	12.16	5.56	11.54	11.11	11.76	10.59±1.11
10	7.14	10.82	11.12	12.84	8.33	8.82	9.84±0.93
12	2.86	8.11	8.34	7.69	5.56	7.36	6.65±0.94

Table 5.6 a Blood glucose levels (mg/dl) with Rosuvastatin (2 TD) in normal rats (N=6)

	Blood glucose levels in rats (mg/dl)						
	R-1	R-2	R-3	R-4	R-5	R-6	
0	76	80	78	82	92	94	83.67±3.34
1	73	76	72	75	85	88	78.17±2.98
2	70	72	66	70	83	80	73.50±2.93
3	68	68	63	67	80	77	70.50±2.92
4	60	63	55	58	68	65	61.50±2.13
6	65	65	60	60	70	69	64.83±1.90
8	66	64	58	65	73	70	66.0±2.31
10	65	63	62	66	71	72	66.50±1.84
12	63	60	63	69	73	75	67.17±2.71

Table 5.6 b Percent Blood glucose reduction with Rosuvastatin (2 TD) in normal rats (N=6)

	Percent blood glucose reduction in rats						
	R-1	R-2	R-3	R-4	R-5	R-6	
0	-	-	-	-	-	-	-
1	4.28	5	7.69	8.53	7.61	6.38	6.58±0.74
2	8.57	10	15.38	14.63	9.78	14.89	12.21±1.37
3	11.43	15	19.23	18.29	13.04	18.08	15.84±1.42
4	22.86	21.25	29.48	29.26	26.08	30.85	26.63±1.74
6	15.72	18.75	23.07	26.82	23.91	26.59	22.48±1.97
8	14.28	20	25.64	20.73	20.65	25.53	21.14±1.87
10	15.72	21.25	20.51	19.51	22.82	23.40	20.54±1.23
12	18.57	25	19.23	15.85	20.65	20.21	19.92±1.34

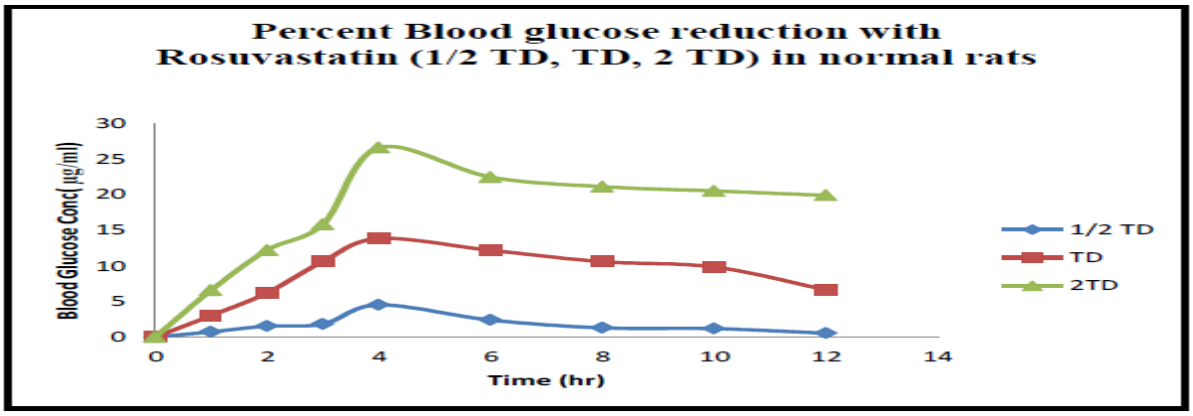


Fig: 5.2Mean percentage blood glucose reduction with ROSUVASTATIN1/2 TD, TD, 2TD

Effect of RosuvastatinandGliclazide combination on Normal Rats:

Table 5.7 (a) Blood glucose levels (mg/dl) with Rosuvastatin (TD) in normal rats (N=6)

	Blood glucose levels in rats (mg/dl)						
	R-1	R-2	R-3	R-4	R-5	R-6	
0	54	50	67	59	64	54	58±2.67
1	34	45	57	46	51	59	48.66±3.72
2	66	55	46	49	51	54	53.5±2.83
3	54	50	64	51	54	54	54.5±2.02
4	46	48	54	54	54	55	51.83±1.55
6	57	60	64	49	57	51	56.33±2.25
8	51	45	64	59	51	62	55.33±3.04
10	41	40	62	54	46	57	50±3.67
12	64	35	59	54	46	52.5	10.44±4.26

Table 5.7 (b) Percent Blood glucose reduction with Rosuvastatin (TD) in normal rats (N=6)

Time(h)	Percent blood glucose reduction in rats						Mean SEM
	R-1	R-2	R-3	R-4	R-5	R-6	
0	-	-	-	-	-	-	
1	37.03	14092	10	22.03	20.31	-9.25	15.84±6.24
2	-22.2	31.34	-10	16.94	20.31	0	6.065±8.2
3	0	4.47	0	13.55	15.62	0	5.60±2.93
4	14.81	19.40	4	8.47	15.62	-9	8.88±4.22
6	-5.55	31.34	-20	22.03	10.931	5.55	7.38±7.57
8	5.55	31.34	10	0	20.31	-14.81	8.73±6.55
10	24.07	7.4	20	8.47	28.12	-5.55	13.75±5.14
12	-18.51	11.94	30	8.47	28.12	-5.55	9.07±7.77

Table 5.8 (a) Blood glucose levels (mg/dl) with GLICAZIDE1/2(1/2TD) in normal rats (N=6)

Time(h)	blood glucose reduction in rats						Mean SEM
	R1	R2	R3	R4	R5	R6	
0	121	105	84	110	105	91	102±5.43
1	71	70	70	100	77	84	78.66±4.81
2	126	100	56	100	84	77	90.5±9.7
3	49	56	21	110	28	35	49.83±13.14
4	77	70	84	56	35	49	61.83±7.54
6	65	63	56	56	42	42	54±4.07
8	56	112	70	77	49	35	66.5±10.95
10	28	77	65	42	55	42	51.5±7.25
12	25	50	75	50	60	50	51.66±6.66

Table 5.8 (b) Percent Blood glucose reduction with GLICAZIDE 1/2TD in normal rats (N=6)

	Percent blood glucose reduction in rats						
	R1	R2	R3	R4	R5	R6	
0	-	-	-	-	-	-	-
1	40.85	33.3	16.6	9.09	26.6	7.6	22.34±5.49
2	-4.3	4.7	33.3	9.09	20	15.3	13.01±5.32
3	59.05	46.6	75	0	73.3	61.5	52.57±11.33
4	36	33.3	0	49	66.6	45.6	38.41±9.06
6	46.2	40	33.3	49.09	60	45.6	38.41±9.06
8	53.5	-6.6	16.6	30	53.3	61.5	34.71±10.75
10	76.8	26.6	22.6	61.8	47.6	53.8	48.2±8.4
12	79.3	52.3	10.7	54.5	42.8	45	47.33±9.06

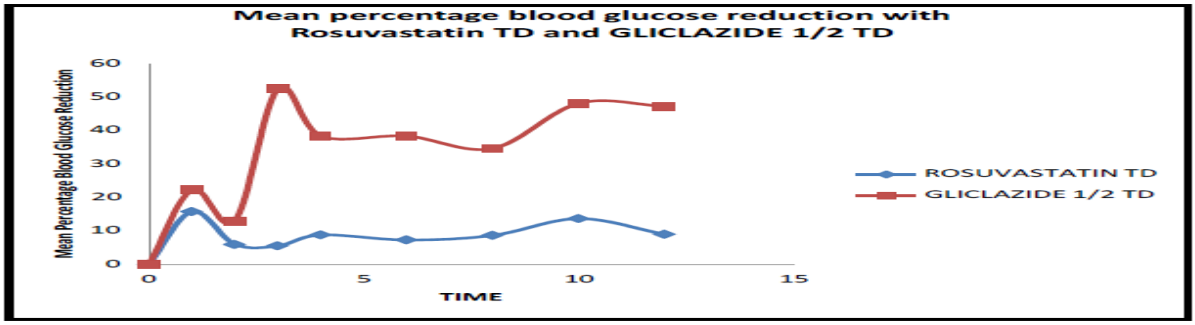


Fig: 5.3Mean percentage blood glucose reduction with GLICLAZIDE 1/2 TD, ROSUVASTAIN TD in Normal Rats

The blood glucose levels observed with ½ TD of Gliclazide and with Rosuvastatin TD were studied, the percent blood glucose reduction observed with ½ TD of Gliclazide and Rosuvastatin 0.72 mg/200g and were graphically represented in ***figure 5.3.***

Since the results are from normal rats show a increased mean percentage reduction in blood glucose reduction, to validate the existence of interaction in diabetic state, the work was carried out in diabetic rats

Study of Influence of Drugs on Diabetic Rats:

With Gliclazide1/2TD alone maximum percentage reduction of blood glucose 42.04□0.5% and 40.17 ± 0.87 at 2h, 8h respectively, tables shown,5.10a, 5.10b. With Rosuvastatin in diabetic rats maximum percentage reduction 18.91±1.8, 19.14±1.71 table shown 5.9a, 5.9b at 3h,4h respectively. The mean percentage reduction were graphically represented in ***figure 5.4.***

Table 5.9a Blood glucose levels (mg/dl) with Rosuvastatin (TD) in diabetic rats (N=6)

Time(h)	blood glucose reduction in rats						Mean□SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0	250	270	242	280	310	320	278.66±11.70
1	235	250	225	270	300	310	265±12.90
2	215	233	198	240	290	290	244.33±14.26
3	210	192	200	242	255	260	226.5±10.97
4	200	198	210	235	245	262	225±9.7
6	214	196	230	240	246	270	232.66±9.61
8	230	220	252	230	250	288	245±9.12
10	232	221	250	262	280	285	255±9.55
12	235	224	255	265	282	290	258.5±9.63

Table 5.9b Percent Blood glucose levels (mg/dl) with Rosuvastatin (TD) in diabetic rats (N=6)

Time(h)	Percent blood glucose reduction in rats						Mean□SEM
	R_1	R_2	R_3	R_4	R_5	R_6	
0	-	-	-	-	-	-	-
1	6	7.4	7	3.5	3.2	6.2	5.55±0.66
2	14	13.7	18.1	14.2	6.4	9.3	12.61±1.53
3	16	28.8	17.3	15	17.7	18.7	18.91±1.86
4	20	26.6	13.2	16.07	20.9	18.1	19.14±1.71
6	14.4	27.4	4.9	14.2	21.2	15.6	16.28±2.8
8	8	18.5	-4.1	17.8	19.3	100	11.5±3.36
10	7.2	18.1	3.3	6.4	9.6	10.9	9.25±1.89
12	6	17	-4.6	5.3	9	9.3	7.0±2.62

Table 5.10a Blood glucose levels (mg/dl) with GLICAZIDE (1/2TD) in diabetic rats (N=6)

Time(h)	blood glucose reduction in rats						Mean SEM
	R1	R2	R3	R4	R5	R6	
0	320	300	340	335	295	310	316.66±6.8
1	300	180	300	240	204	195	236.5±19.75
2	187	171	190	195	177	180	183.33±3.32
3	230	212	257	255	222	221	232.83±7.02
4	220	202	247	235	210	230	224±6.19
6	190	180	230	218	190	195	200.5±7.16
8	195	170	210	210	173	180	189.66±6.69
10	240	213	250	270	240	236	241.50±6.93
12	270	220	270	280	245	260	257.83±8.30

Table 5.10b Percent Blood glucose levels (mg/dl) with GLICAZIDE (1/2TD) in diabetic rats (N=6)

	Percent blood glucose reduction in rats						
	R1	R2	R3	R4	R5	R6	
0	-	-	-	-	-	-	-
1	6.25	37.5	13.3	28.3	30.8	37.06	25.35±4.81
2	41.56	43	44.1	41.7	40	41.9	42.04±0.51
3	28.12	29.3	24.4	32.8	24.7	28.7	28.03±1.16
4	31.2	32.6	27.3	29.8	28.8	25.8	29.25±0.93
6	40.6	40	32.3	34.9	35.5	41.9	37.53±1.42
8	39.06	43.3	38.2	37.3	41.3	41.9	40.17±0.87
10	25	29	26.4	19.4	18.6	23.7	3.68±1.50
12	15.6	26.6	20.5	15.8	13.8	16.1	4.21±1.7

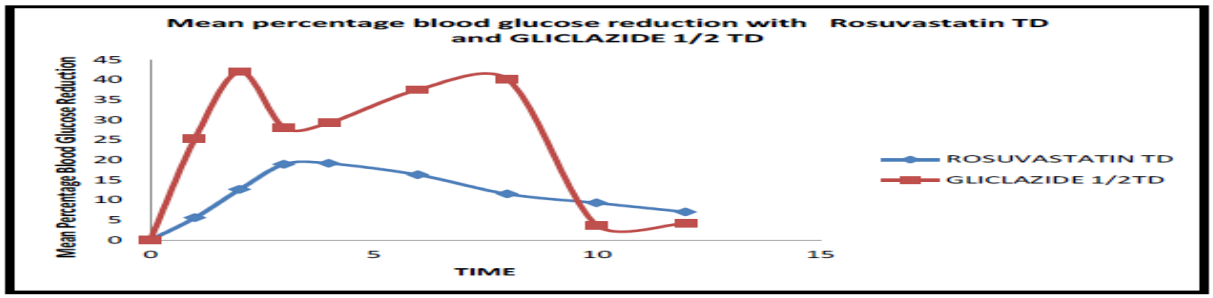


Fig: 5.4Mean percentage blood glucose reduction with GLICLAZIDE 1/2 TD, ROSUVASTAIN TD in Normal Rats

TREATMENT IN DRUG COMBINATION:

From the above studies we observed that TD dose of Rosuvastatin alone produced maximum blood glucose reduction around 10% and in normal rats it produced a maximum and around 19% in Diabetes rats. Gliclazide alone produce a 30% reduction in blood glucose levels in normal rats and it produced a reduction of blood levels up to 42% in diabetic rats.

It is well established that sulphonylurea produce insulin secretion and improve tissue utilization of glucose at cellular level [68] Gliclazide being a sulphonylurea might produce similar action which was responsible for its

hypoglycemic activity. The biphasic peak effect in rats with Gliclazide [69,70] might be due to its reabsorption during its entero hepatic circulation in its biliary excretion which is similar to human [71]. Rosuvastatin given alone produced the hypoglycemic effect about 10 %. It might be because of inhibiting the cyp2c9 and 3A4 which are metabolizing enzymes of Gliclazide so prolongs the effect of Gliclazide given when combination of both drugs, indicating that Rosuvastatin enhances the pharmacodynamic activity of Gliclazide either by improving insulin release or inhibit the metabolizing enzymes or by both. Hence from the previous results and the literature survey there is every possible for the rais of blood glucose levels when the drugs are used in combination, so the effect this combination is studied in Normal and Diabetic rats and the results were tabulated in Tables 5.11a,5.11b and 5.12a and 5.12b

When treated in combination the drugs produced a maximum reduction of 34.14 %and 45.73 % in 3rd and 6th hours in normal rats and a maximum reduction of 53.13% and 54.03% in diabetic rats. The results were represented graphically in ***figure 5.5.***

Table 5.11a Blood glucose levels (mg/dl) with Rosuvastatin and GLICAZIDE (1/2TD) in normal rats (N=6)

Time(h)	blood glucose reduction in rats						Mean SEM
	R1	R2	R3	R4	R5	R6	
0	80.1	76.4	70	64.7	94.1	102	81.21±5.32
1	72	64.7	57	70.5	52.9	64.7	63.33±2.78
2	70	64.7	55	70.5	52.9	64.7	62.96±2.77
3	65	52.9	43	52.9	41.1	58.8	52.28±3.40
4	50	47	47	64.7	35.2	47	48.48±3.52
6	47	29.4	38	47	29.4	52.9	40.61±3.68
8	37	35	29.5	41.1	52.9	49	40.75±3.28
10	60.1	52.9	55	70.5	41.1	52.9	55.41±3.60
12	65	58.8	60	70.5	30	64.7	58.16±5.37

Table 5.11b Percent Blood glucose levels (mg/dl) with Rosuvastatin andGLICAZIDE (1/2TD) in normal rats (N=6)

Time(h)	Percent blood glucose reduction in rats						Mean SEM
	R1 (210g)	R2 (200g)	R3 (195g)	R4 (200g)	R5 (220g)	R6 (240g)	
0	-	-	-	-	-	-	-
1	10.1	15.3	18.5	-7.5	62.5	0	16.48±9.14
2	14.2	15.3	24.2	-7.5	43.7	36.5	21.06±6.78
3	18.7	30.7	38.5	18.2	56.3	42.3	34.11±5.4
4	37.5	38.4	0	0	62.5	53.9	32.04±9.90
6	41.2	61.5	27.6	27.3	68.7	48.1	45.73±6.39
8	53.7	0	35.9	36.4	43.7	0	28.28±8.5
10	25	30.7	9.3	-8.9	56.3	48.1	26.75±9.01
12	18.7	23	9.2	-8.9	0	36.5	13.08±6.11

Table 5.12a Blood glucose levels (mg/dl) with Rosuvastatin and GLICAZIDE(1/2TD) in diabetic rats (N=6)

Time(h)	blood glucose reduction in rats						Mean SEM
	R1	R2	R3	R4	R5	R6	
0	119	330	204	342	155	211	226.83±37.17
1	70	401	98	64	105	98	139.33±52.77
2	100	107	92	98	77	85	93.16±4.43
3	88	328	85	70	85	93	124.83±40.75
4	78	292	100	64	86	100	120±34.85
6	85	314	70	63	77	70	113.16±40.28
8	85	278	70	60	64	56	102.16±35.40
10	75	457	68	55	50	77	130.33±65.48
12	70	400	60	53	50	70	117.16±56.68

Table 5.12b Percent Blood glucose levels (mg/dl) with Rosuvastatin and GLICAZIDE (1/2TD) in diabetic rats (N=6)

	Percent blood glucose reduction in rats						
	R1	R2	R3	R4	R5	R6	
0	-	-	-	-	-	-	-
1	41.3	-58.6	51.7	81.2	31.9	53.3	33.46±19.61
2	16.4	67.2	54.6	71.1	50	59.5	53.13±8.00
3	28.57	0.84	58.1	79.5	44.8	56.1	44.65±11.11
4	34.4	11.7	68.6	81.2	44.8	52.6	48.33±10.70
6	28.5	5	65.6	81.5	50	66.6	49.53±11.54
8	28.5	15.9	65.6	82.4	58.5	73.3	54.03±10.70
10	37.3	-38.14	66.6	83.9	67.2	63.3	46.69±18.03
12	41	-20.9	70.9	84.5	67.2	66.8	51.58±15.59

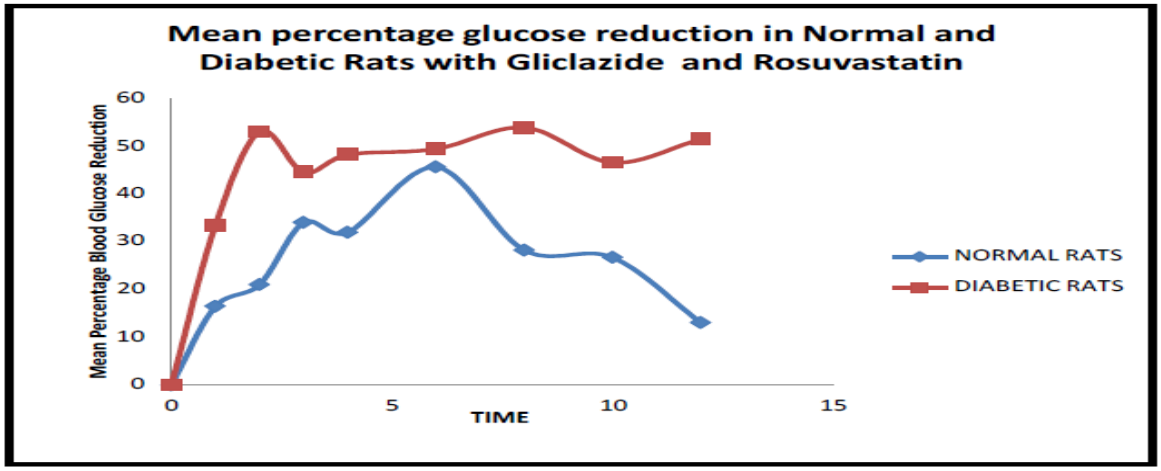


Fig: 5.5Mean percentage blood glucose reduction with treatment of a combination of GLICLAZIDE 1/2 TD and ROSUVASTAIN TD in Normal Rats and Diabetic Rats.

Study of effect of drugs In Rabbits: The results of the blood glucose levels and the percent blood glucose reduction with Gliclazide ½ TD, Rosuvastatin 2.8 mg/Kg body wt. and in with combination of Gliclazide ½ TD and Rosuvastatin 2.8 mg/Kg body. Wt. in rabbits were tabulated in tables 5.13a, 5.13b, 5.14a, 5.14b, 5.15a, 5.15b, 5.16a. 5.16b, Gliclazide 1/2TD, Rosuvastatin TD, Gliclazide and Rosuvastatin acute, chronic study respectively. The percent blood glucose reduction with Gliclazide ½ TD and with 2.8 mg/kg body.wt. of Rosuvastatin were presented graphically in ***figure 5.6.***

The acute study of Gliclazide and Rosuvastatin percentage reduction of blood glucose were graphically represented in ***figure 5.7***,the chronic study of Gliclazide and Rosuvastatin percentage reduction of blood glucose were represented in ***figure 5.8.***

The hypoglycemic effect and % blood glucose reduction with Gliclazide was found to be less in rabbits compared to rats. There was only a single peak in its response indicating that enter hepatic circulation (biliary excretion) may not be involved in its excretion pattern in rabbits. So this appears to be due to species difference between rabbits and rats in Gliclazide response and pharmacokinetics.

The maximum percentage fall in blood glucose reduction and peak serum Gliclazide concentration in Gliclazide treated matching control group were 33.11□1.155 and 326.79 ng/ml (table 5.17a) at 3^{rd} h respectively. Rosuvastatin altered blood glucose levels, when administered, orally. In combination with Rosuvastatin in acute study the % fall in blood glucose reduction was 35.45□1.04 at 3^{rd}h (table 5.15b) and peak serum concentration of Gliclazide in blood was 414.2 ± 8.33ng/ml at 3^{rd} h (table 5.17b). in chronic study the percent blood glucose reduction 37.44 at 3h (table 5.16b) and serum Gliclazide level 427 ng/ml.

The comparison of Gliclazide 1/2TD, acute study, chronic study serum Gliclazide levels were tabulated in tables 5.17a, 5.17b and 5.17c respectively and are graphically represented in ***figure 5.9.*** Rosuvastatin has been found to enhance the hypoglycemic effect of Gliclazide. The peak hypoglycemic effect of Gliclazide was correlated with the peak concentration of Gliclazide in serum. The study indicates that peak serum Gliclazide levels and hypoglycemic effect were at 3^{rd} hour.

Table 5.13a Blood glucose levels with Gliclazide ½ TD

TIME	R1	R2	R3	R4	R5	Mean± SEM
0	100	112	100	109	107	105.6±2.42
1	85	95	85	95	90	90±2.23
2	70	75	69	79	82	75±2.5
3	71	73	63	71	75	70.6±2.03
4	69	67	60	67	68	66.2±1.59
6	76	75	67	74	73	73±1.58
8	80	79	73	77	77	77.2±1.2
10	85	83	79	82	80	81.8±1.06
12	91	90	83	87	89	88±1.41
18	95	93	85	90	93	91.2±1.74
24	99	97	85	96	100	95.4±2.69

TIME	Table 5.13b Mean percentage reduction Blood glucose levels with Gliclazide ¼ TD					Mean± SEM
	R1	R2	R3	R4	R5	
0	-	-	-	-	-	-
1	15	15.17	15	12.84	15.88	14.77±0.51
2	30	33.03	31	27.52	23.36	28.98±1.66
3	29	34.82	37	34.86	29.90	33.11±1.55
4	31	40.17	40	38.53	36.44	37.22±1.69
6	24	33.03	33	32.11	31.77	30.78±1.71
8	20	29.46	27	29.35	28.03	26.76±1.75
10	15	25.89	21	24.77	25.23	22.37±2.03
12	9	19.64	17	20.18	16.82	16.52±2.00
18	5	16.96	15	17.43	13.08	13.48±2.25
24	1	13.39	15	11.92	6.54	9.57±2.57

TIME	Table 5.14a Blood glucose levels with Rosuvastatin TD					Mean± SEM
	R1	R2	R3	R4	R5	
0	95	100	105	111	105	103.2±2.69
1	94	98	102	107	102	100.6±2.18
2	90	91	97	104	98	96.0±2.54
3	92	93	92	100	94	94.2±1.49
4	91	92	90	96	91	92.0±1.04
6	91	93	92	98	92	93.2±1..24
8	92	94	93	99	94	94.4±1.20
10	92	95	94	98	96	95.0±1
12	92	95	96	99	97	95.8±1.15
18	93	94	97	101	99	96.8±1.49
24	94	96	99	103	102	98.8±1.71

	Table 5.14b Percentage of blood glucose inhibition with Rosuvastatin TD					Mean± SEM
	R1	**R2**	**R3**	**R4**	**R5**	
0	-	-	-	-	-	-
1	1.05	2	2.86	3.60	2.86	2.47±0.43
2	5.26	9	7.62	6.30	6.67	6.97±0.63
3	3.16	7	12.38	9.90	10.47	8.58±1.60
4	4.21	8	14.28	13.51	13.33	10.67±1.96
6	4.21	7	12.38	11.71	12.38	9.54±1.66
8	3.16	6	11.43	10.81	10.48	8.38±1.62
10	3.16	5	10.48	11.71	8.57	7.78±1.61
12	3.16	5	8.57	10.81	7.62	7.03±1.34
18	2.11	6	7.62	9.01	5.72	6.09±1.15
24	1.05	4	5.71	7.20	2.86	4.16±1.07

	Table 5.15a Blood glucose levels Gliclazide ½ TD and Rosuvastatin TD in rabbit (acute)					Mean± SEM
	R1	**R2**	**R3**	**R4**	**R5**	
0	102	107	103	105	102	103.8±0.96
1	92	101	97	101	98	97.8±1.65
2	82	96	95	95	95	92.6±2.65
3	65	75	77	78	74	73.8±2.31
4	70	78	73	82	80	76.6±2.22
6	73	82	86	85	83	81.8±2.31
8	80	86	90	91	88	87.0±1.94
10	84	88	95	96	94	91.4±2.31
12	89	92	100	99	98	95.6±2.15
18	90	96	100	101	100	97.4±2.03

24	92	96	101	103	101	98.6±2.01

	Table 5.15b Mean Percentage Blood glucose levels Gliclazide ½ TD and Rosuvastatin TD in rabbit (acute studies)					**Mean± SEM**
	R1	**R2**	**R3**	**R4**	**R5**	
0	0	0	0	0	0	0
1	10.53	5.60	5.83	3.81	3.92	5.93±1.22
2	21.05	10.28	7.77	9.52	6.86	11.09±2.56
3	38.96	29.90	25.24	25.71	27.45	29.45±2.51
4	33.68	27.10	29.13	21.90	21.57	26.68±2.28
6	30.53	23.36	16.50	19.04	18.63	21.61±2.49
8	23.16	19.63	12.62	13.33	13.73	16.49±2.08
10	18.95	17.76	7.77	8.57	7.84	12.18±2.53
12	13.68	14.02	2.91	5.71	3.92	8.05±2.41
18	12.63	10.28	2.91	3.81	1.96	6.32±2.14
24	10.53	10.28	1.94	1.90	0.98	5.13±2.16

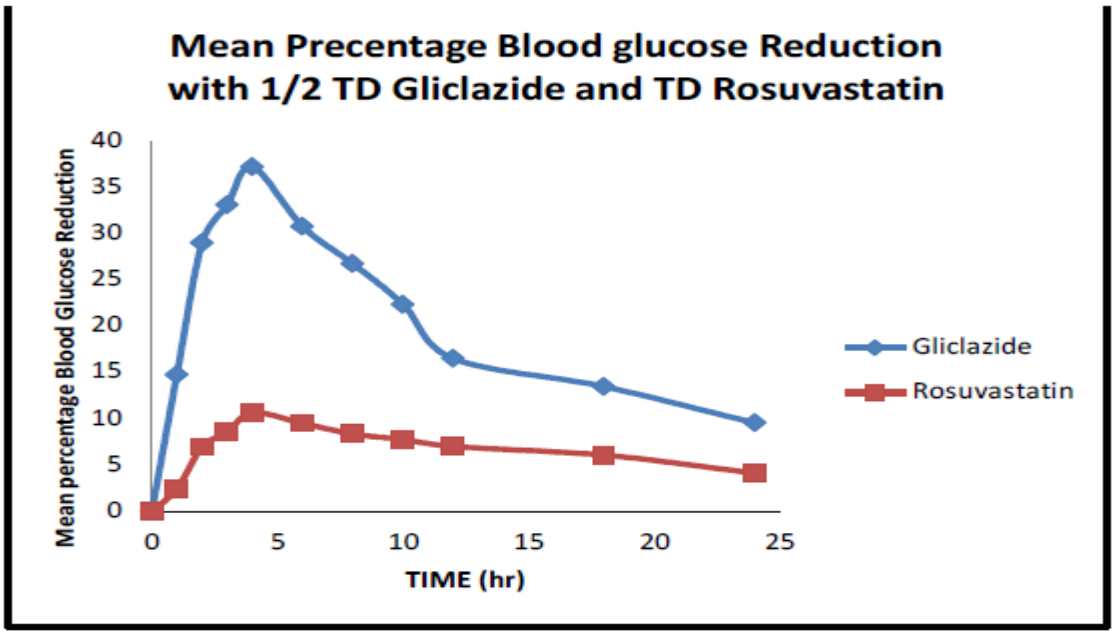


Figure 5.6Mean Percentage blood glucose Reduction in Normal Rabbits with Gliclazide ½ TD and Rosuvastatin TD

	Table 5.16a Blood glucose levels Gliclazide 1/2TD and Rosuvastatin TD in rabbit (Chronic)					Mean± SEM
	R1	R2	R3	R4	R5	
0	112	109	107	104	110	108.4±1.36
1	88	96	90	87	92	90.6±1.60
2	79	85	82	80	83	81.8±1.06
3	69	66	67	66	71	67.8±0.96
4	73	70	73	72	75	72.6±0.81
6	78	75	77	75	76	76.2±0.58
8	82	81	82	85	83	82.6±0.67
10	86	85	97	91	88	89.4±2.15
12	90	93	101	97	94	95±1.87
18	90	99	102	102	101	98.8±2.26
24	97	99	103	105	102	101.2±1.42

	Table 5.16b Percentage Blood glucose levels Gliclazide 1/2TD and Rosuvastatin TD in rabbit (Chronic studies)					Mean± SEM
	R1	R2	R3	R4	R5	
0	0	0	0	0	0	0
1	21.43	11.92	15.88	16.34	16.36	16.39±1.51
2	29.46	22.02	23.36	23.07	24.54	24.49±1.30
3	38.39	39.45	37.38	36.53	35.45	37.44±0.69
4	34.82	35.77	31.77	30.76	31.81	32.99±0.97
6	30.36	31.19	28.03	27.88	30.9	29.67±0.71
8	26.78	25.68	23.36	18.27	24.54	23.73±1.47
10	23.21	22.02	9.34	12.5	20	17.41±2.74
12	19.64	14.67	5.6	6.73	14.54	12.24±2.64
18	19.64	9.17	4.67	1.92	8.18	8.72±3.01

24	13.39	9.17	3.74	-0.96	8.18	6.70±2.45

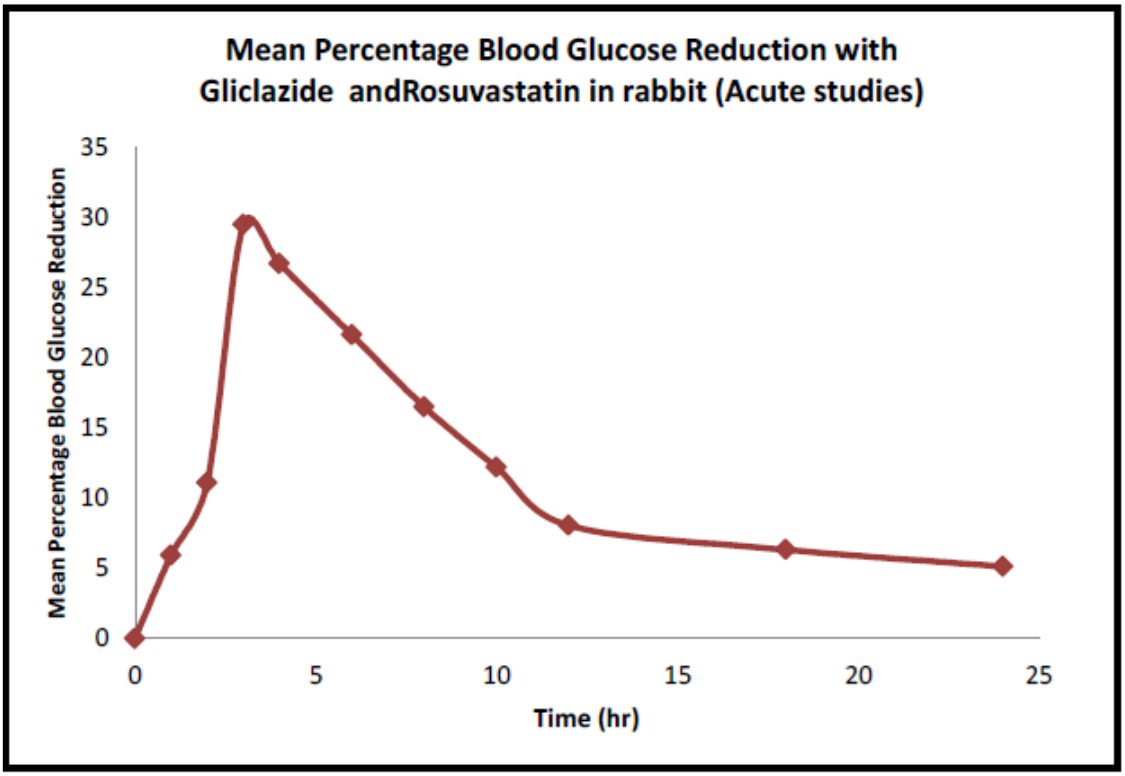


Figure 5.7 Mean Percentage Blood Glucose level Reduction in rabbits – Acute Studies

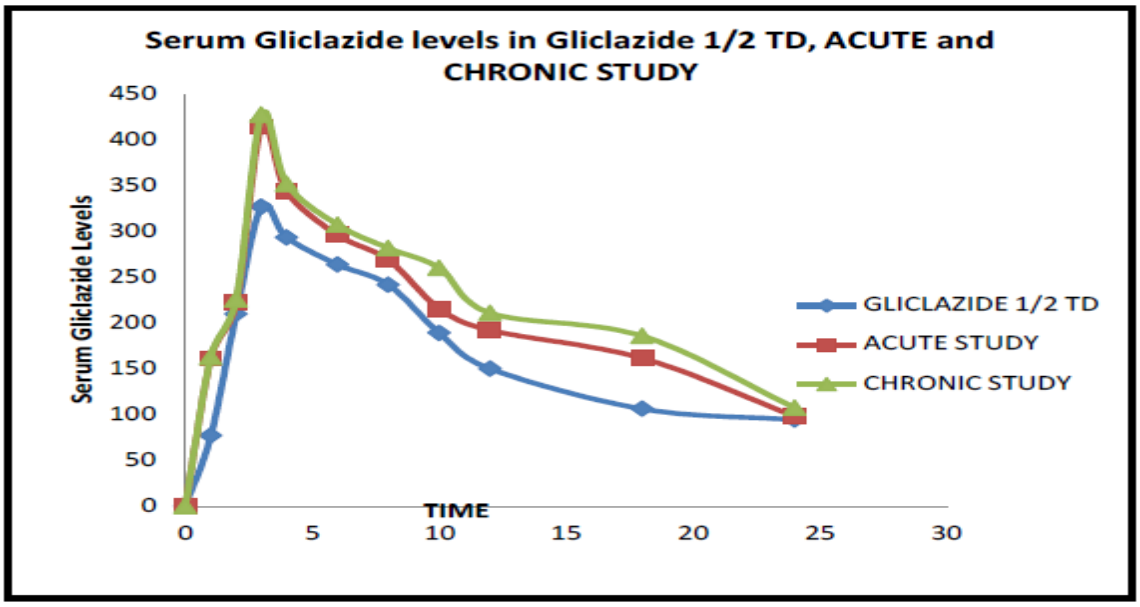
	Table 5.17a Serum Gliclazide levels in rabbits with ½ TD HPLC					**Mean± SEM**
	R1	**R2**	**R3**	**R4**	**R5**	
0	0	0	0	0	0	0
1	72.56	76.45	80.1	70.45	85.1	76.93±2.62
2	227.16	236.13	175.54	230.13	180.54	209.90±10.11
3	312.14	326	345.41	320	330.41	326.79±5.57
4	279.11	297.01	290.62	290.01	310.62	293.47±5.16
6	267.12	254	267.45	260	270.45	263.80±2.99
8	251.14	228	240.62	238	250.85	241.72±4.33
10	192.92	182.82	200.15	179.82	189.15	188.97±3.62
12	148.11	133.12	168.65	143.12	157.65	150.13±6.09
18	107.76	102.11	109.23	100.11	112.23	106.29±2.25

24	92.32	94.13	99.11	90.13	96.11	94.36±1.54

	Table 5.17b Serum Gliclazide levels with Gliclazide (1/2 TD) and Rosuvastatin (TD) – Acute Study					**Mean± SEM**
	R1	**R2**	**R3**	**R4**	**R5**	
0	0	0	0	0	0	0
1	170.56	150.11	130.12	155.17	200	161.19±7.65
2	210.11	200.1	180	230.18	290.13	222.10±12.32
3	440.06	420.09	390	421.08	400.15	414.28±8.75
4	356.02	347.09	330.08	343	340	343.24±4.25
6	310	320.15	290.1	290	270	296.05±8.73
8	285.36	292.15	256.1	263	247.32	268.79±8.59
10	230.79	220.56	208.66	212.36	205.45	215.55±4.56
12	220.01	170.05	190.03	190.1	190.04	192.05±7.99
18	176.09	152.02	157.01	160.05	162.03	161.44±4.03
24	103	96	97	99	96	98.20±1.31

	Table 5.17c Serum Gliclazide levels with Gliclazide (1/2 TD) and Rosuvastatin (TD) – Chronic Study					**Mean± SEM**
	R1	**R2**	**R3**	**R4**	**R5**	
0	0	0	0	0	0	0
1	166.1	153.16	157	169.9	167.01	162.63±3.20
2	217.16	220.11	252.12	206.01	233.16	225.71±7.89
3	427.13	428.16	440.09	396.03	446.13	427.51±8.65
4	343.01	353.11	361.16	327.19	375.2	351.93±8.12
6	309.11	301.16	336.03	288.2	302.12	307.32±7.93
8	276.13	284.12	308.14	252.12	288.13	281.73±9.08
10	248.79	257.36	289.76	233.97	270.36	260.04±9.49
12	201.11	212.09	222.13	203.16	216.21	210.94±3.94
18	179.13	184.2	196.16	180.13	189.31	185.79±3.15

24	103.16	112.13	115.03	98.11	109.03	107.49±3.06



5.9 Serum Gliclazide levels in Rabbits with Gliclazide ½ TD, ACUTE Study and in Chronic Study

PHARMACOKINETIC DATA ANALYSIS:

USING PK SOLVER 2.0, EXTRAVASCULAR DATA

Table 5.18a Pharmacokinetic data for Serum Gliclazide levels in rabbits with ½ TD HPLC

PARAMETER	***R1***	***R2***	***R3***	***R4***	***R5***	***MEAN±SEM***
AUC_{0-24} (ng/ml/h)	3968.84	3841.26	4080.73	3854.62	4075.19	3964.13±57.74
$AUMC_{0-24}$ (ng/ml/h*h)	39614.44	37856.17	41301.41	37926.17	40951.09	39529.86±725.86
Kel (h^{-1})	0.062	0.063	0.061	0.065	0.063	0.063±0.0006
$AUC_{0-\alpha}$ (ng/ml/h)	5448.43	5317.17	5688.23	5236.04	5598.13	5457.6±84.21
$AUMC_{0-\alpha}$ (ng/ml/h*h)	98837.13	96414.14	105954.55	92245.03	101633.67	99016.9±2319.95
T1/2 (h)	11.10	10.86	11.24	10.62	10.98	10.96±0.11

$K_a(h^{-1})$	0.0411	0.0454	0.0435	0.0412	0.044	0.0434±0.0008
Clearance (ml/h)	1027.82	701.51	655.74	740.76	666.29	758.42±68.97
Clearance (ml/h/kg)	684.66	467.43	437.16	411.53	380.73	476.30±54.02
Vdarea (ml)	16472.52	10998.43	10635.72	11352.96	10557.94	12003.51±1126.19
Vdarea (ml/kg)	10981.68	7332.28	7090.48	6307.02	6033.11	7548.91±891.09
MRT $_{0-24}$(h)	9.98	9.85	10.12	9.84	10.04	9.97±0.054
MRT $_{0-\alpha}$(h)	18.14	18.13	18.62	17.62	18.15	18.13±0.15
C_{max} (ng/ml)	312.14	326.0	345.41	320	330.41	326.79±5.57
T_{max} (h)	3	3	3	3	3	3±0.0

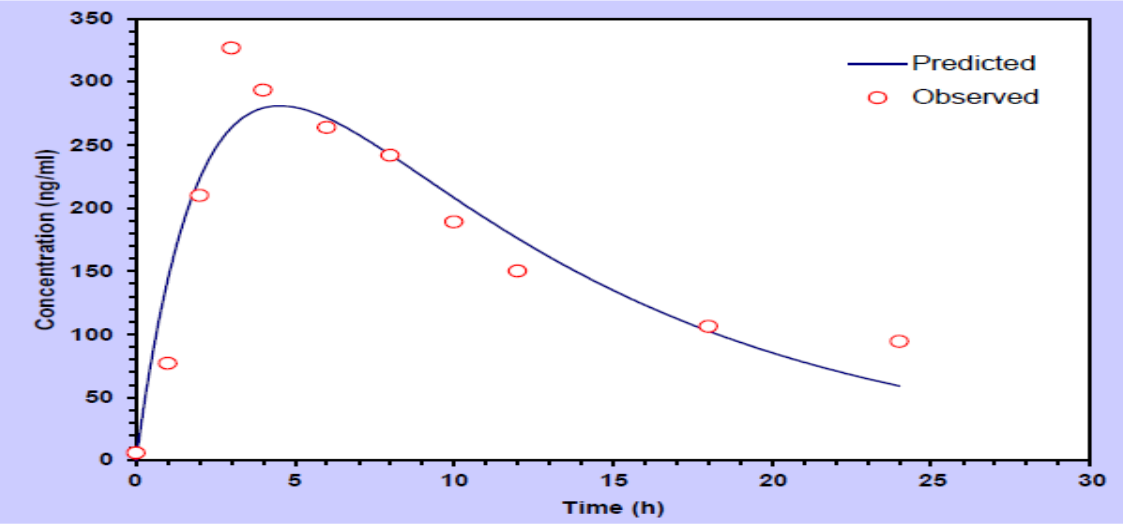


Fig 5.10 a. Predicted Plot for AUC Gliclazide ½ TD

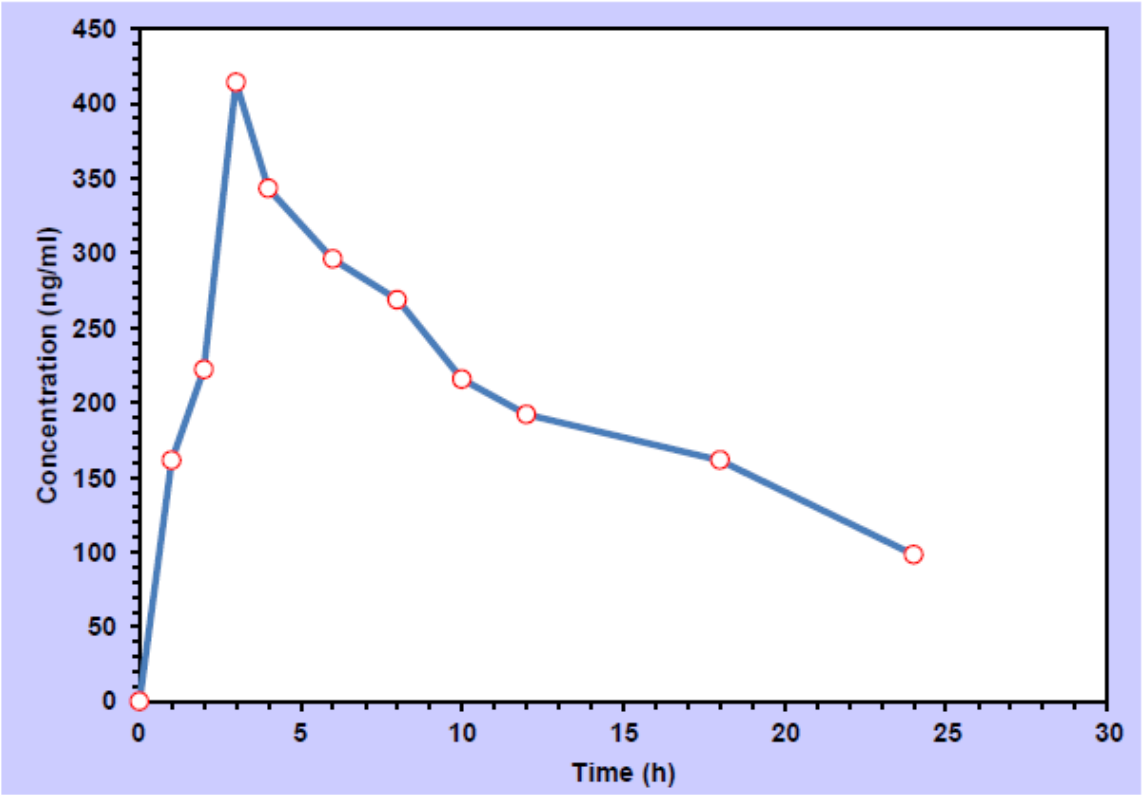


Fig 5.10 b. Plot for AUC Gliclazide ½ TD

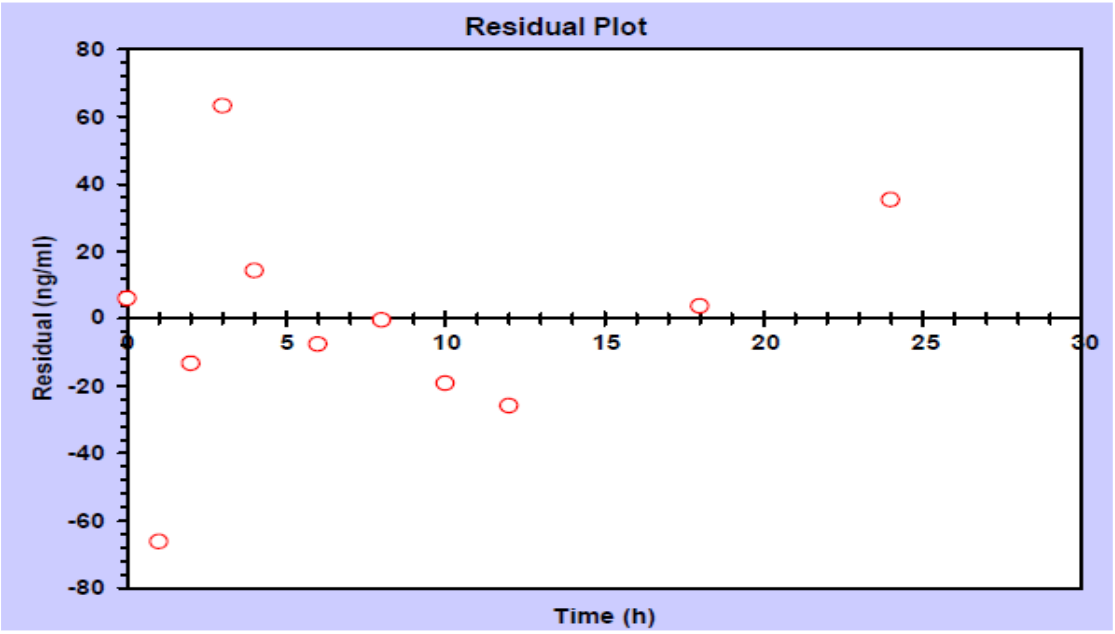


Fig 5.10 c. Residual Plot for Gliclazide ½ TD

Table 5.18b Pharmacokinetic data for Serum Gliclazide levels with Gliclazide(1/2 TD) and Rosuvastatin (TD) – Acute Study

PARAMETER	***R1***	***R2***	***R3***	***R4***	***R5***	***MEAN±SEM***
AUC_{0-24} (ng/ml/h)	5252.64	4836.97	4698.14	4869.35	4866.16	4904.652±92.48
$AUMC_{0-24}$ (ng/ml/h*h)	53942.84	48313.08	48455.12	49410.17	48859.99	49796.24±1053.99
Kel (h^{-1})	0.063	0.048	0.056	0.054	0.056	0.0554±0.0024
$AUC_{0-\alpha}$ (ng/ml/h)	6881.21	6851.86	6429.06	6690.23	6553.18	6681.12±86.36
$AUMC_{0-\alpha}$ (ng/ml/h*h)	118778.94	138959.61	120885.24	126602.47	118990.96	124843.40±3801.69
T1/2 (h)	10.95	14.55	12.36	12.74	12.18	12.56±0.58
$K_a(h^{-1})$	0.574	0.462	0.489	0.582	0.806	0.582±0.06
Clearance (ml/h)	810.07	816.55	870.27	836.28	853.78	837.39±11.25
Clearance (ml/h/kg)	540.05	544.37	580.177	557.52	569.19	558.26±7.49
Vdarea (ml)	12856.02	17138.42	15529.57	18458.01	15003.22	15795.05±954.76
Vdarea (ml/kg)	8570.67	11425.61	10353.05	10254.45	10002.15	10121.19±457.78
MRT_{0-24} (h)	10.26	9.98	10.31	10.14	10.04	10.15±0.06
$MRT_{0-\alpha}$ (h)	17.26	20.28	18.08	18.92	18.15	18.54±0.50
C_{max} (ng/ml)	440.06	420.09	390	421.08	400.15	414.28±8.75
T_{max} (h)	3	3	3	3	3	3±0.00

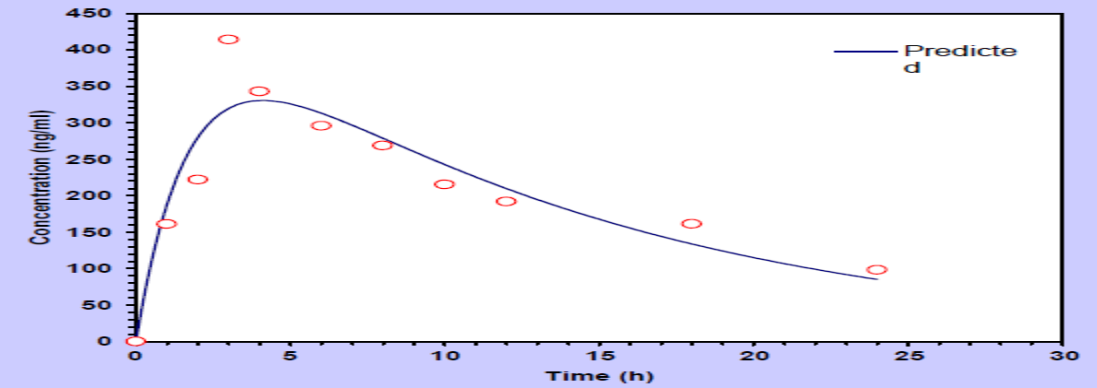


Fig 5.11 a. Predicted Plot for AUC Gliclazide- Acute Studies

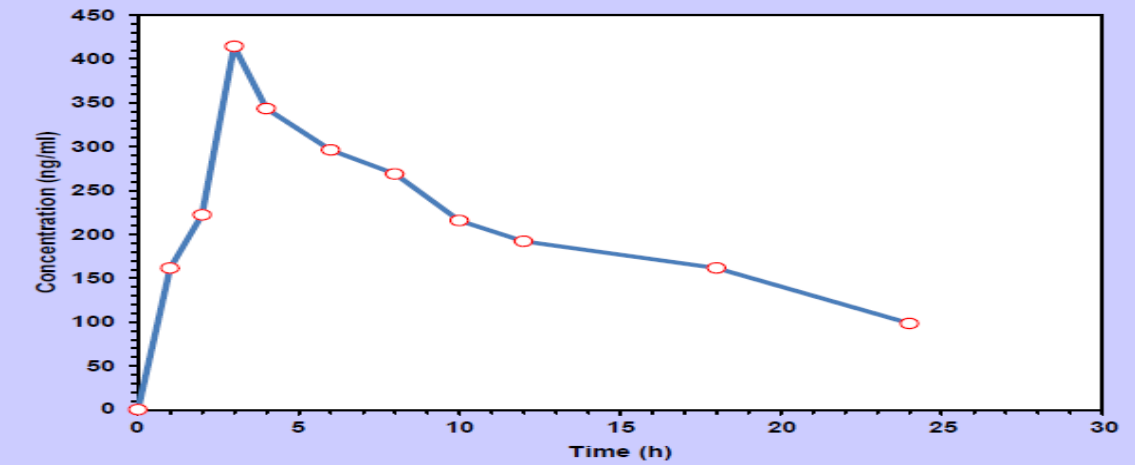


Fig 5.11 b. Plot for AUC Gliclazide- Acute Studies

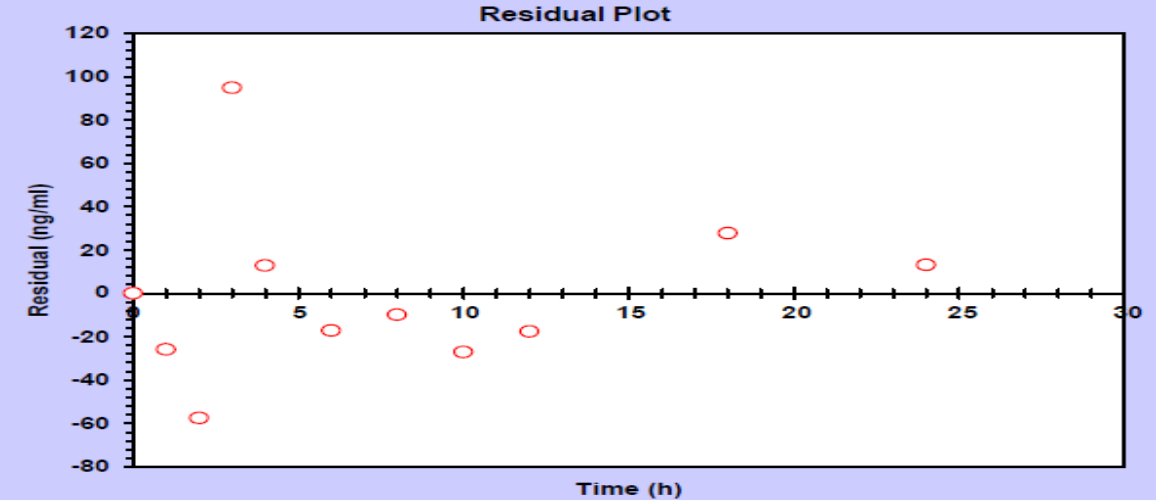


Fig 5.11 C. Residual Plot for AUC Gliclazide- Acute Studies

Table 5.18c PHARMACOKINETICS DATA for Serum Gliclazide levels with Gliclazide(1/2 TD) andRosuvastatin (TD) – Chronic Study

PARAMETER	***R1***	***R2***	***R3***	***R4***	***R5***	***MEAN±SEM***
AUC_{0-24} (ng/ml/h)	5181.66	5306.32	5669.38	4999.05	5458.11	5322.90±114.77
$AUMC_{0-24}$ (ng/ml/h*h)	53469.91	55450.84	59035.95	52174.51	56539.36	55334.11±1196.42
Kel (h^{-1})	0.056	0.053	0.054	0.060	0.056	0.056±0.0012
$AUC_{0-\alpha}$ (ng/ml/h)	7036.02	7417.49	7766.96	6616.46	7394.44	7246.27±195.35
$AUMC_{0-\alpha}$ (ng/ml/h*h)	131308.03	145867.96	147627.92	117656.44	137399.89	135972±5445.37
T1/2 (h)	12.45	13.05	12.63	11.42	12.31	12.372±0.26
$K_a(h^{-1})$	0.555	0.545	0.520	0.602	0.565	0.56±0.013
Clearance (ml/h)	795	753	720.48	1014.73	882.75	833.19±52.91
Clearance (ml/h/kg)	530.12	502.36	480.32	563.74	504.43	516.19±14.26
Vdarea (ml)	14294.89	14201.83	13135.84	16728.68	15677.45	14807.74±627.36
Vdarea (ml/kg)	9529.93	9467.89	8757.23	9293.71	8958.54	9201.46±148.95
MRT_{0-24} (h)	10.31	10.44	10.413	10.43	10.35	10.39±0.025
$MRT_{0-\alpha}$ (h)	18.66	19.66	19.01	17.78	18.58	18.74±0.31
C_{max} (ng/ml)	427.13	428.16	440.09	396.03	446.13	427.51±8.65
T_{max} (h)	3	3	3	3	3	3±0.00

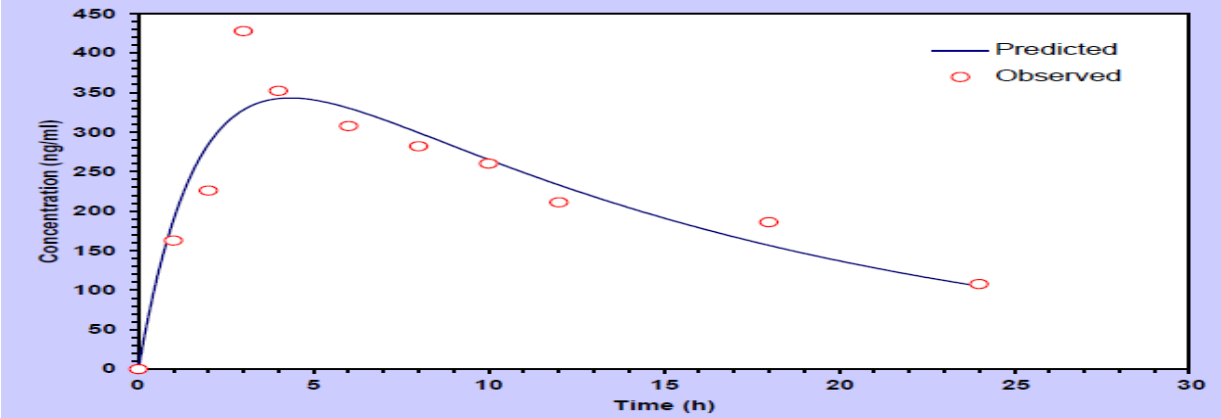


Fig 5.12 a. Predicted Plot for AUC Gliclazide- Chronic Studies

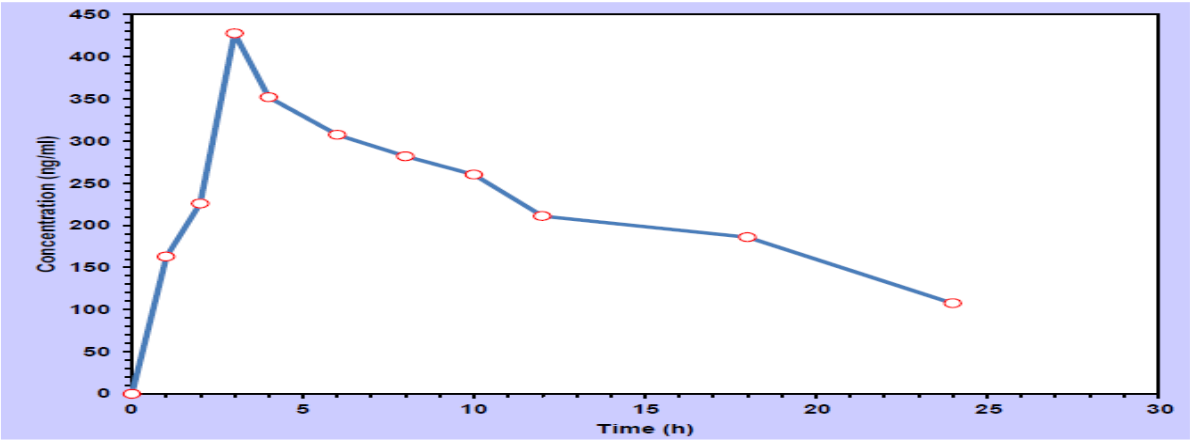


Fig 5.12b. Plot for AUC Gliclazide- Chronic Studies

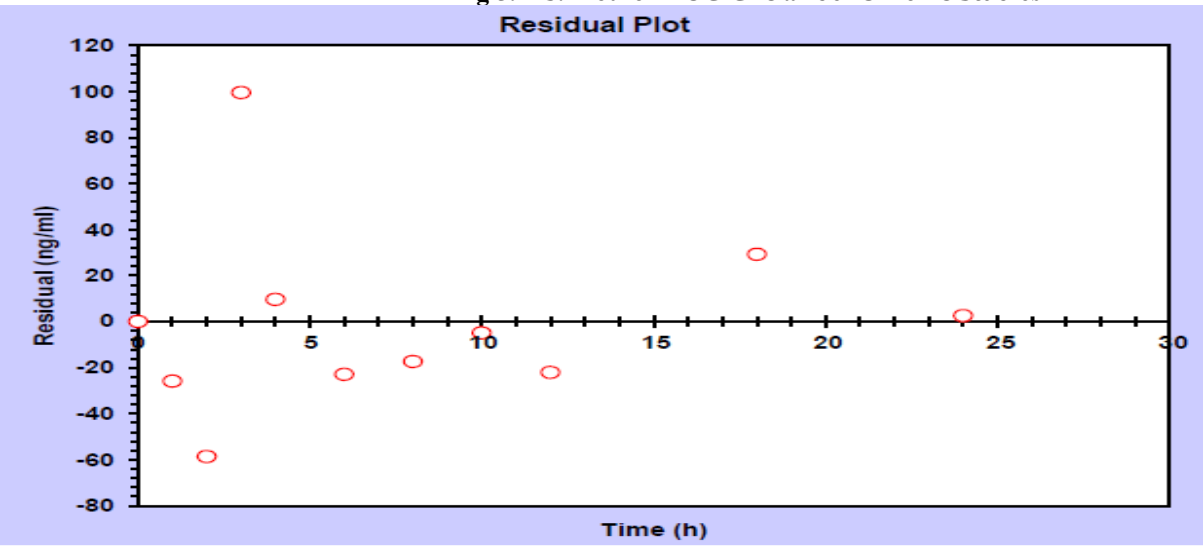


Fig 5.12 . Residual Plot for AUC Gliclazide- Chronic Studies

Rosuvastatin is an anti-hyperlipidemic agent

belonging to the class of satins and it has no significant hypoglycemic effect on blood glucose levels in rabbits when administered alone and has enhanced hypoglycemic effect administered along with Gliclazide. From the Acute and Chronic study in rabbits it was found that the serum Gliclazide levels were enhanced and the results of Data Analysis showed that the pharmacokinetic parameters such as AUC, AUMC, T½, clearance, Vdss, Vdarea, Cmax were enhanced significantly with single and multiple dose treatments. There was no significant difference in the pharmacokinetic parameters of between acute and chronic treatments with Rosuvastatin (TD) and Gliclazide (1/2 TD). The elimination half-life (T ½ K_{el}), elimination rate constant and the absorption rate constant and clearance were not altered in the presence of Rosuvastatin indicating that the enhanced serum Gliclazide levels might be due to either inhibition of metabolism or alteration in the distribution of Gliclazide in the presence of Rosuvastatin. The study indicates that, the interaction observed was a pharmacokinetic interaction. In the presence of Rosuvastatin, peak serum Gliclazide levels were observed at 3 hours and the peak activity was at the same interval.

STASTICAL DATAANALYSIS:

Table 5.19a: Mean Percentage blood glucose reduction in Normal Rats (n=6)

TIME	Gliclazide	Rosuvastatin	Gli+ rosuva
0		-	
1	28.81±1.17	3.01±0.30***	16.48±4.14*
2	35.21±0.47	6.21±0.29***	21.06±3.78**
	30.1±0.81	10.61±0.64***	34.11±5.4
	30.67±0.92	13.85±0.63***	32.04±9.90
6	31.74±0.80	12.19±0.95***	45.73±3.39**
8	36.34±0.74	10.59±1.11***	28.28±8.5
10	19.26±1.67	9.84±0.93***	26.75±3.05*
12	9.6±1.29	6.65±0.94**	13.08±6.11

***** significant at P<0.001, Significant at P<0.01; *Significant at P<0.05 compared to Gliclazide Control**

Table 5.19b Mean Percentage blood glucose reduction in Diabetic rats (n=6)

TIME	Gliclazide	Rosuvastatin	Gli+ rosuva
0	-	-	-
1	25.35±4.81	5.57±0.79*	33.46±19.61
2	42.04±0.51	8.35±0.57*	53.13±3.05*
3	28.03±1.16	12.49±0.58***	44.65±6.11*
4	29.25±0.93	14.73±0.57***	48.33±7.70*
6	37.53±1.42	12.78±1.24	49.53±11.54
8	40.17±0.87	10.40±0.43	54.03±4.70*
1	3.68±1.50	8.17±1.39	46.69±18.03*
1	4.21±1.7	7.51±1.04	51.58±15.59*

***** significant at P<0.001, Significant at P<0.01; *Significant at P<0.05 compared to Gliclazide Control**

Table 5.19c. Mean Percentage blood glucose reduction in Normal Rabbits (n=6)

TIME	Gliclazide	Rosuvastatin	Gli+ rosuva(ACUTE)	Gli+ rosuva(Chronic)
0	-	-	-	-
1	14.77±0.51	2.47±0.43***	5.93±1.22***	16.39±1.51
2	28.98±1.66	6.97±0.63***	11.09±2.56***	24.49±1.30
3	33.11±1.55	8.58±1.60***	29.45±2.51	37.44±0.69*
4	37.22±1.69	10.67±1.96***	26.68±2.28**	32.99±0.97
6	30.78±1.71	9.54±1.66***	21.61±2.49*	29.67±0.71
8	26.76±1.75	8.38±1.62***	16.49±2.08*	23.73±1.47*
10	22.37±2.03	7.78±1.61***	12.18±2.53*	17.41±2.74*
12	16.52±2.00	7.03±1.34**	8.05±2.41*	12.24±2.64
18	13.49±2.25	6.09±1.15*	6.32±2.14*	8.72±3.01*
24	9.57±2.57	4.16±1.07	5.13±2.16	6.70±2.45

***** Significant at P<0.001, Significant at P<0.01; *Significant at P<0.05 compared to Gliclazide Control.**

Table 5.20 a. Serum Gliclazide levels in Normal Rabbits

TIME	GLICLAZIDE ½ TD	Gli+ rosuva (ACUTE)	Gli+ rosuva (Chronic)
0	0	0	0
1	76.93±2.62	161.19±7.65***	162.63±3.20***
2	209.90±10.11	222.10±12.32	225.71±7.89
3	326.79±5.57	414.28±8.75***	427.51±8.65***
4	293.47±5.16	343.24±4.25***	351.93±8.12***
6	263.80±2.99	296.05±8.73**	307.32±7.93***
8	241.72±4.33	268.79±8.59*	281.73±9.08**
10	188.97±3.62	215.55±4.56**	260.04±9.49***
12	150.13±6.09	192.05±7.99**	210.94±3.94
18	106.29±2.25	161.44±4.03***	185.79±3.15***
24	94.36±1.54	98.20±1.31	107.49±3.06**

***** Significant at P<0.001, Significant at P<0.01; *Significant at P<0.05 compared to Gliclazide Control**

Table 5.20b PHARMACOKINETIC DATA for Serum Gliclazide levels:

PARAMETER	GLICLAZIDE ½ TD	ACUTE STUDY	CHRONIC STUDY
AUC_{0-24} (ng/ml/h)	3964.13±57.74	4904.652±92.48	5322.90±114.77
$AUMC_{0-24}$ (ng/ml/h*h)	39529.86±725.86	49796.24±1053.99***	55334.11±1196.42***
Kel (h^{-1})	0.063±0.0006	0.0554±0.0024*	0.056±0.0012***
$AUC_{0-\alpha}$ (ng/ml/h)	5457.6±84.21	6681.12±86.36***	7246.27±195.35**
$AUMC_{0-\alpha}$ (ng/ml/h*h)	99016.9±2319.95	124843.40±3801.69**	135972±5445.37***
T1/2 (h)	10.96±0.11	12.56±0.58*	12.37±0.26**
$K_a(h^{-1})$	0.043±0.0008	0.58±0.06***	0.56±0.013***
Clearance (ml/h)	758.42±68.97	837.39±11.25	833.19±52.91
Clearance (ml/h/kg)	476.30±54.02	558.26±7.49	516.19±14.26
Vdarea (ml)	12003.51±1126.19	15795.05±954.76*	14807.74±627.36
Vdarea (ml/kg)	7548.91±891.09	10121.19±457.78*	9201.46±148.95
MRT_{0-24} (h)	9.97±0.054	10.15±0.06**	10.39±0.025***
$MRT_{0-\alpha}$ (h)	18.13±0.15	18.54±0.50*	18.74±0.31
C_{max} (ng/ml)	326.79±5.57	414.28±8.75**	427.51±8.65***
T_{max} (h)	3±0.0	3±0.00	3±0.00

***** Significant at P<0.001, Significant at P<0.01; *Significant at P<0.05 compared to Gliclazide Control**

The results of student's paired t-test shown that the results obtained are statistically significant for all the data of Blood glucose levels, Serum Gliclazide levels, pharmacokinetic parameters of Gliclazide ,acute ,chronic study with Rosuvastatin.

There was quantitative change in the interaction in normal and diabetic rats, hence studies on the interaction was conducted in rabbits. The results indicated that Rosuvastatin interfere with absorption, distribution, metabolism and excretion (ADME) of Gliclazide. The enhanced response of Gliclazide in the presence of Rosuvastatin might be because of pharmacodynamic mechanisms involving pancreatic or extra pancreatic or both. Since the interaction was found

to be similar in two dissimilar species namely rat (rodent) and rabbit (non-rodent), the probability of its occurrence in humans is also more. However severe hypoglycaemia leading to convulsions was not observed either in rat or rabbit. Hence the improved activity of Gliclazide by Rosuvastatin may be taken interactions produced these interactions are wanted or unwanted.

DISCUSSION:

Drug interactions are usually seen in clinical practice and are generally due to under medication or over medication. Drug interactions may be pharmacokinetic or pharmacodynamic . We studied the influence of Rosuvastatin on the pharmacodynamics and pharmacokinetics of Gliclazide in animal models rats and in rabbits. The normal rat model served to quickly identify the interaction and diabetic rat model served to validate the same response in the actually used condition of the drug. The rabbit model is another dissimilar species to validate the occurrence of the interaction.

Gliclazide produced biphasic response in the rat model when administered alone, which may due to its biliary excretion and enterohepatic cycling72 such effect was not seen in rabbit model. Gliclazide is known to produce hypoglycemic activity by pancreatic73(stimulating insulin secretion by blocking K+ channels in the pancreatic â cells) and extra pancreatic74 (increasing tissue uptake of glucose) mechanisms.

Rosuvastatin produced a slight anti-hyperglycemic action when administered alone in normal rats and this may be due to its activity on the insulin secretion and it also enhanced hypoglycemic effects produced by Gliclazide when administered in combination. Since Rosuvastatin is known to be metabolized to a major extent by CYP 450 2C9 by which Gliclazide is also metabolized primarily, the interaction might be at the level of their metabolism. Rosuvastatin may compete with Gliclazide for metabolism by CYP 450 2C9 and delay the metabolism of Gliclazide leading to its enhanced effect. The metabolites of Gliclazide namely hydroxy and carboxy Gliclazide are pharmacologically inactive. Hence inhibition of Gliclazide metabolism improves its unchanged level and pharmacological action, which is seen in the present study.

Further Gliclazide is eliminated through renal (80%) and biliary (20%) routes. Rosuvastatin and its major metabolites are eliminated primarily through bile 92±10% being excreted in the feces and 4.9±1.6% 76. Hence there was possibility for interaction between Rosuvastatin and Gliclazide at biliary excretion also. However the drug Rosuvastatin did not change the pattern of biphasic response of Gliclazide indicating that it did not interfere with the reabsorption of Gliclazide in its enterohepatic circulation in rats. In the presence of above drugs sustained hypoglycemic activity of Gliclazide was observed compared to Gliclazide control.

In rabbits, Rosuvastatin has shown less pronounced hypoglycemic effect on blood glucose levels when administered alone in normal rabbits. It enhanced the hypoglycemic effect of Gliclazide when administered in combination. The serum Gliclazide levels were found to be unaltered with single and multiple dose treatments of Rosuvastatin. There was no significant rise in pharmacokinetic parameters like AUC, AUMC, T½, clearance, Vdss, Vdarea, Cmax and Tmax of Gliclazide with single and multiple treatments of Rosuvastatin. In the presence of Rosuvastatin, the peak serum Gliclazide levels were observed at 3 h. The study indicates that, the improved activity of Gliclazide by Rosuvastatin was pharmacodynamic in nature. Rosuvastatin is known to be metabolized to a major extent by CYP 450 2C9 by which Gliclazide also is metabolized primarily, the interaction might be at the level of their metabolism. Rosuvastatin may compete with Gliclazide for metabolism by CYP 450 2C9 and delay the metabolism of Gliclazide leading to its enhanced effect. In presence of these two drugs sustained hypoglycemic activity of Gliclazide was observed compared to Gliclazide control.

There might not be interaction at absorption level since oral absorption of Rosuvastatin is poor. Gliclazide is a highly protein bound drug (85-99%) whereas Rosuvastatin is bound to the extent of 85-96%. Therefore the possibility of displacing Gliclazide from protein bound sites by Rosuvastatin was low. For this reason the rise of Gliclazide blood levels in the presence of Rosuvastatin might be other than improved absorption and altered distribution. Hence, there is possibility for interaction at hepatic metabolism of drugs with reduced Gliclazide metabolism leading to raised serum levels in the presence of Rosuvastatin.

The metabolism of Gliclazide appears to be different in rabbits and does not seem to involve biliary excretion. Mostly it is eliminated as metabolites in the urine and certain percentage as

unchanged drug. The elimination of Rosuvastatin in rabbits is not clear. Perhaps more amount of Rosuvastatin is eliminated through urine and hence interferes with Gliclazide elimination thereby raising its blood levels.

CONCLUSON:

- Dose related hypoglycemic effect was observed for Gliclazide with ½ TD, TD and 2TD/200g dose in normal rats.
- Rosuvastatin produced dose dependent hypoglycemia at the doses 0.36mg, 0.72mg, 1.44mg/200g bodyweight in normal rats.
- Biphasic peak effect was observed with Gliclazide in rats which might be due to its reabsorption during its enterohepatic circulation in its excretion which is similar to human.
- Rosuvastatin produced the hypoglycemic effect, and when given in combination with Gliclazide, enhanced the hypoglycemic effect of Gliclazide in normal rats.
- The similar results were observed in Alloxan induced diabetic rats with Gliclazide before and after Rosuvastatin 0.72mg/200mg. Rosuvastatin produced anti-hyperglycemic effect with peak effect at 3 h. The results indicated the presence of diabetic condition alter the effect of above drugs on blood glucose.
- Gliclazide alone produced hypoglycemia in normal rabbits with peak effect at 3h.
- Biphasic peak effect was not observed in rabbits indicating that it might not involve biliary excretion of Gliclazide.
- The hypoglycemic effect of Gliclazide was also less in rabbits compared to rats.
- Rosuvastatin alone produced hypoglycemia with peak effect at 4 h. However the intensity of its hypoglycemic effect was less in rabbits compared to its effect in normal/diabetic rats.
- It indicated that the pancreatic
- cells of rats might be more sensitive to Rosuvastatin than rabbit's pancreatic □cells or it may be due to difference in food habit the forming being carnivorous and the latter being herbivorous.
- Significant difference was observed in blood levels and pharmacokinetic parameters of Gliclazide when administered in the presence of Rosuvastatin compared to matching control in acute, chronic study of Gliclazide.

Finally it is concluded that Rosuvastatin produced anti-hyperglycemic and enhanced the pharmacodynamic activity of Gliclazide with altering pharmacokinetics. The interaction was observed in two dissimilar species. it is likely to occur in human also. Hence the combination of Gliclazide (1/2TD), Rosuvastatin (TD) should be contraindicated / used with caution in clinical situation.

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