ABSTRACT

Pharmacokinetic studies are performed to examine the absorption, distribution, metabolism and excretion of a drug under investigation in healthy volunteers and/or patients. Data obtained from such studies are useful for the design and conduct of subsequent clinical trials. Such studies also provide useful information for the appropriate and safe conduct of clinical trials and for the evaluation of the mechanism of action in human subjects. They are also necessary for appropriate analysis and evaluation of the efficacy and safety data obtained in clinical trials for new drug development and in post-marketing clinical trials. Outcomes of clinical pharmacokinetic studies are useful for determining the appropriate use of medicines according to patient characteristics, such as disease and genotype of drug-metabolizing enzymes, and for predicting the influence of pharmacokinetic drug interactions. The results can also provide information for therapeutic drug monitoring. Development of a new medicine may be achieved, thereby avoiding unnecessary studies.

Recently, a growing body of information obtained from different studies conducted around the globe showed a striking rise in healthcare expenditures and the developing countries are not exception. Previous studies conducted in Pakistan showed that a considerable portion of the healthcare costs goes to medicine price. The present dissertation was the first detailed investigation in the relationship between the patient's socioeconomic status and physician's choice on multisource solid oral drugs. Such association had not been fully investigated in developing countries, particularly in Pakistan.

My dissertation work will provide the information about important aspect and parameters involved in Pharmacokinetic studies.The purpose of this research was to evaluate Pharmacokinetic parameters of a combination formulation of Vildaglipton and metformin hydrochloride50/1000 mg tablet of an established branded formulation.One set of parallel study design was employed in healthy normal rabbits as well as in *Alloxan* induced diabetic rabbits.The other set of parallel study design was employed in healthy male human subjects as well as in diabetic patients.The concentrations of Vildagliptonand metformin hydrochloride in blood plasma were analyzed using High

Performance Liquid Chromatographic (HPLC) technique. The plasma concentration-time curves were used to obtain the different pharmacokinetic parameters.

Six healthy rabbits, six diabetic rabbits, twelve diabetic Pakistani patients and twelve healthy Pakistani subjects were selected to participate in this study. A single dose, open label parallel study design was employed in all study subjects. In this study, a once-daily dose of metformin HCl 1000 mg and vildagliptin 50 mg was used in human subjects, as this allowed assessment of the full pharmacokinetic profile of metformin HCl and vildagliptin over 24 hours at the maximum individual dose. All the rabbits, weighing between 1.25 to 1.5 kg, were given combined dose of drugs metformin HCl 70 mg per 1.5 kg and vildagliptin 15 mg per 1.5 kg orally. Blood samples were withdrawn at predetermined intervals of 0, 0.25, 0.50, 1, 2, 3, 4, 5, 6, 8, 10 and 12 hours from a marginal ear vein puncture. The concentrations of vildagliptin and metformin HCl in blood plasma were analyzed using High Performance Liquid Chromatographic (HPLC) technique and using developed and validated method. The concentration of drugs in blood plasma were determined using standard calibration curves of metformin HCl and vildagliptin having concentrations 50, 100, 200, 500 and 750 ng/mL for vildagliptin and 250, 500, 1000, 2500 and 3750 ng/mL for metformin HCl. The pharmacokinetic parameters were calculated by using different pharmacokinetic formulae. Data is shown as arithmetic mean±SD.

The aim of this work was to develop and validate a simple, rapid, more sensitive, more accurate and precise method for simultaneous determination of metformin HCl and vildagliptin in formulations and blood serum. Furthermore, its applications for studying and comparison of pharmacokinetic parameter in Pakistani population among healthy and diabetic individuals along with healthy and diabetic rabbits were analyzed. No significant difference was observed in pharmacokinetic parameters for healthy and diabetic individuals among the humans and the rabbits. There was no statistically significant difference for the treatment values. In both of groups healthy and diabetic pharmacokinetic parameters were equal in terms of rate and extent of absorption. There was no significant difference of drugs absorption and clearance in healthy and diabetic Pakistani subjects.