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Effect of *Allium Sativum* on the pharmacokinetic of Metformin in rat plasma: A herb-drug interaction study

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ABSTRACT

Allium sativum (Liliaceae) commonly known as garlic or lahsun is a medicinal plant, used in Ayurveda for treating various diseases, like hypertension, hyperlipidemia and diabetes mellitus. In this an effort has been made on the normal rats ; to study the pharmacokinetic interactions of Metformin (320mg/kg) with Allium sativum . The garlic extract (500mg/kg) was administered alone and along with allopathic drugs (MET) so that blood glucose lowering effect can be studied by administrating them orally to rats. Also alteration in absorption, metabolism, distribution and excretion of the drug are the causes of pharmacokinetic interactions; were studied. Plasma concentration of Metformin was analyzed by HPLC. Plasma concentration – time curve was plotted, and the peak plasma concentration (C_{max}) and time needed to reach the peak plasma concentration (T_{max}) were noted directly from the generated data. The area under the plasma level – time curve ($AUC_{0\text{-}12h}$) was calculated using Trapezoidal rule. The elimination rate constant (K_{el}) was calculated from the semi-log plot of the data using slope of the terminal elimination phase; and half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$ and results were analyzed using one-way ANOVA to determine the significant difference in the pharmacokinetic parameters of Metformin between control and test group on 0^{th} and 8^{th} day. Significant changes were noticed in blood glucose.

Key words : Metformin, pharmacokinetic interactions, RP – HPLC.

INTRODUCTION

These days people are preferring herbal and Ayurvedic medicines over the allopathic drugs due to lesser side effects of the formers or are using the combination of herbal drugs along with allopathic drugs for better relief and to reduce side effects. The popularity of herbal medicinal products (HMPs) makes it important to understand potential interactions between herbs and prescribed drugs. The likelihood of herb-drug interactions could be higher than drug-drug

interactions, its only because drugs usually contain single chemical entities, while almost all HMPs (even single herb products) contain mixtures of pharmacologically active constituents.

Also there are various traditions for the use of herbal medicines in different parts of the world and consequently in many countries the potential for clinically relevant interactions is much greater. Diabetes is one of the most common ailments for which Ayurvedic help is being sought these days. So in view of the growing complexity of choices in the treatment of type 2 diabetes, it is important to consider drug-drug and drug-herb interactions between various antihyperglycaemic agents. [1-3]

Diabetes is an important human ailment affecting many from various walks of life in different countries. Diabetes is many a times is also associated with hyperlipidemia. In India it is proving to be a major health problem, especially in the urban areas [4]. Though there are various approaches to reduce the ill effects of diabetes, hyperlipidemia, blood pressure and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost. *Allium sativum* is commonly used as an antidiabetic, antihyperlipidemic, and antihyperglycaemic agent in India as well as other Asian countries. Among various herbal drugs used garlic is selected for the present pharmacokinetic interaction study because it is the most popular herb that is used for the treatment of hypertension and hyperlipidemia that are in 90% cases associated with type 2 diabetes and Metformin hydrochloride is the first line drug for the treatment of diabetes. [5,6] The herbs used as the drugs for the treatment of disease may interact with the allopathic drugs used at the same period of time for the cure of other diseases. So it is very important to determine the interaction between herb and the drugs. Whether they have a positive or a negative effect on each other's pharmacokinetic profile

Literature review of garlic *(Allium sativum)* reveals that it has blood glucose lowering properties without causing hypoglycemia. The hypoglycaemic action of garlic could possibly be due to an increase in pancreatic secretion of insulin from β-cells, release of bound insulin or enhancement of insulin sensitivity. It has been previously suggested that garlic (allicin) can enhance serum insulin by effectively combining with compounds like cysteine, which would spare insulin from SH group reactions which are a common cause of insulin inactivation [7].

Concurrent administration of garlic with Metformin may influence the pharmacokinetics of latter drugs. Therefore, the aim of the present investigation was to study the effect of garlic on the pharmacokinetics of Metformin. Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion. It provides a mathematical basis to assess the time course of drugs and their effects in the body. It enables the following processes to be quantified: Absorption, Distribution, Metabolism, and Excretion. These pharmacokinetic processes often referred to as ADME.[8-10]

The LC system consists of pump (Shimadzu LC-10AT*VP*) with universal loop injector (Rheodyne) of injection capacity 20 µL. Detector consists of photodiode array detector (PDA) SPD-10 AT*VP* UV-Visible detector. Column used was Chromatopak C_{18} is usually a stainless steel tube packed with octa-decylsilane or octa-acylsilane coated silica gel (5µm×25cm×4.6mm i.d). The equipment was controlled by a PC work station equipped with software CLASS M 10-

VP software (Shimadzu, Kyoto, Japan). Male Wistar rats (150–200 g) were used and were housed in individual cages under natural light and dark cycles at a temperature of 28 ± 4ºC, feeded with a standard pellet diet supplied by Godrej Agrowet Ltd., Sanwer Road, Indore, M.P. Pure sample of Metformin was obtained from Modern Laboratories, 45/D-2 Sanwer road, Indore (M.P.) India and garlic ayurvedic extract used in the study was obtained from Amsar Pvt Ltd.,Indore (M.P.).All the chemical and reagents used were of HPLC grade and purchased from Spectrochem, Mumbai, India.

MATERIALS AND METHODS

The interaction of Metformin with garlic was studied in rats. Twelve rats weighing between 150-200 g were divided into two groups of six each. Animals of Group I (control) were treated with Metformin (320 mg/kg p.o.) and Group II (Test) were treated with Metformin (320 mg/kg p.o.) and garlic (500 mg/kg p.o.) for a period of 8 days. For the analysis of the drug in plasma, blood samples (approximately 0.1ml) were collected in heparinized Eppendorf tubes (1.5ml) from the lateral tail veins after overnight fasting on day 0 and day 8 of treatment at 1, 2, 4, 6, 8 and 12 h of Metformin administration. Plasma concentration of Metformin was analyzed by HPLC. The HPLC system consisted of Shimadzu model LC-10 ATVP with diode array detector and attached with C_{18} column. Metformin was eluted by Phosphate buffer pH 5.5: {ACN: MeOH (130: 70)}(90:10) at the flow rate of 1ml/min at 234 nm (Fig 1). The retention time was found to be 2.89 min. [11-14]

Pharmacokinetic analysis(Table1) was done . Plasma concentration – time curve was plotted, and the peak plasma concentration (C_{max}) and time needed to reach the peak plasma concentration (T_{max}) were noted directly from the generated data. The area under the plasma level – time curve (AUC_{0-12h}) was calculated using Trapezoidal rule (the method involves dividing the curve by a series of vertical lines in to a number of trapezoids, calculating separately the area of each trapezoid and adding them together). The elimination rate constant (K_{el}) was calculated from the semi-log plot of the data using slope of the terminal elimination phase; and half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$.[15]

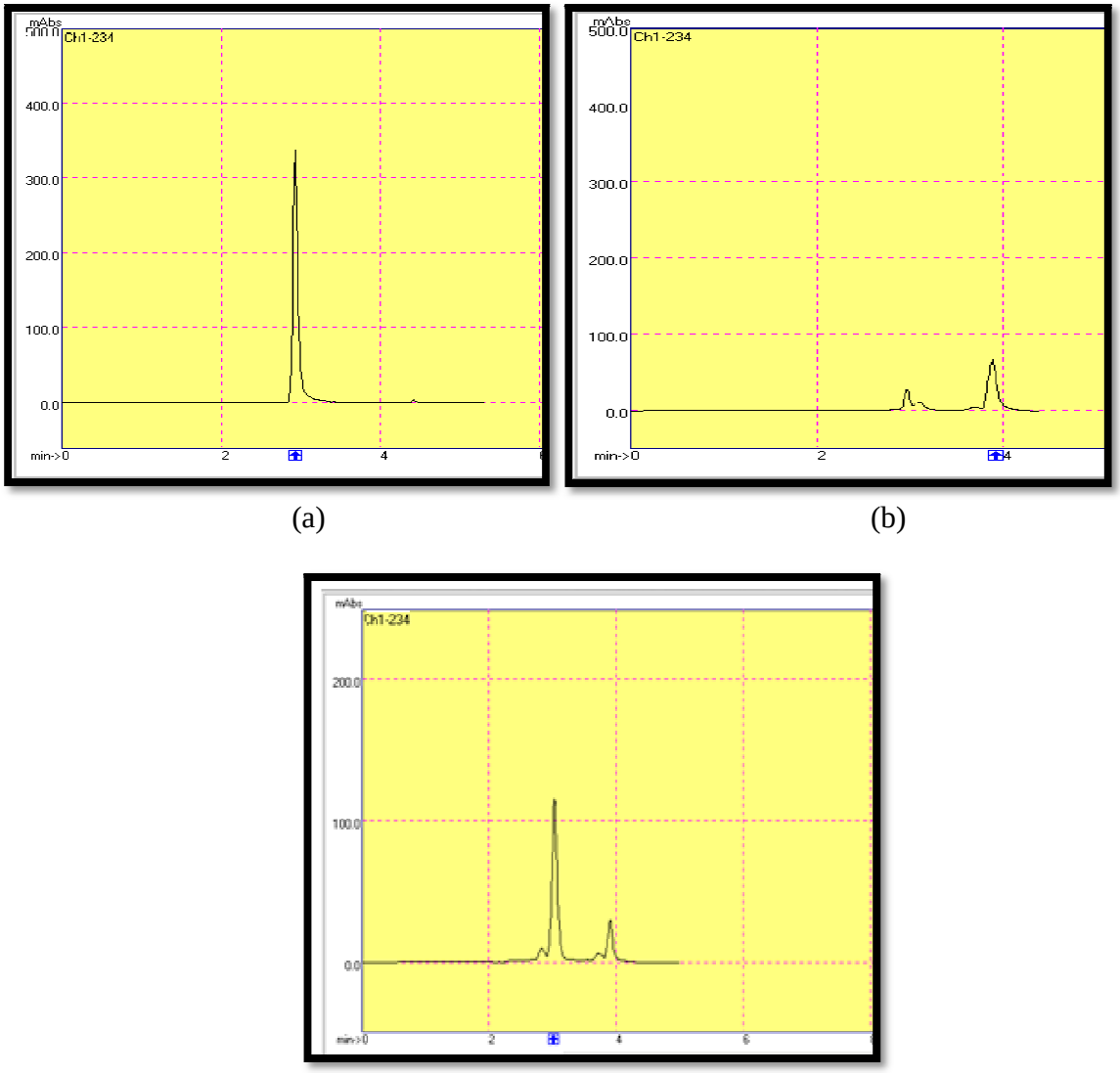
All the means are presented with their standard deviation (mean ± S.D.) and one-way ANOVA is used to determine the significant difference in the pharmacokinetic parameters of Metformin between control and test group.

Table 1: Mean value of pharmacokinetic parameters of Metformin in control and test group on day 0 and day 8

Parameters	On 0^{th} day		On 8^{th} day	
	Control	Test	Control	Test
C_{max} (µg/ml)	13.32±0.9473	14.31±0.1.49	19.54±0.68	31.49±0.1.46
T_{max} (h)	2	2	2	2
AUC_{0-24h} (µg h/ml)	44.04±2.04	43.5316±3.012	79.33±1.844	117.87±11.36
K_{el} (h^{-1})	0.33±0.0067	0.279±0.0147	0.35±0.054	0.3197±0.011
$t_{1/2}$ (h)	2.10±0.043	2.486±0.136	2.011±0.262	2.378±0.354

Blood Glucose Estimation: The blood glucose was estimated by glucose monitor strips.

S.No.	Blood glucose level on 0^{th} day (mg/100ml)	Blood glucose level on 8^{th} day (mg/100ml)
Control	134	103
Test	124	88



(a) (b)

(c)

Fig 1: Chromatogram of (a) standard drug Metformin , (b) blank rat plasma, (c) Metformin in rat plasma

RESULT AND DISCUSSION

Allium sativum is altering the pharmacokinetics of Metformin in rats by significantly increasing its C_{max} and $AUC_{0\text{-}12h}$. With repeated dose administration, a prominent effect is seen by a significant increase in $C_{max,}$, $AUC_{0\text{-}12h,}$ and a slight increase in $t_{1/2.}$ Hence doses require special

attention if used along with *Allium sativum* to avoid complications due to increased bioavailability of Metformin. However, extensive clinical pharmacokinetic studies are necessary to establish such drug-drug interactions in higher animals.

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