

enough. Moreover, due to STZ effect on destroying liver enzymes. When insulin enters the liver at high flow rate, almost insulin will not be affected and then give the most potent hypoglycemic effect.

The first pass metabolism of insulin in liver mainly depends on the enzymatic mechanisms for metabolism, but these mechanisms have not been established. Three systems have been implicated for enzymatic mechanisms: insulin protease, glutathione-insulin transhydrogenase (GITE), and lysosomal enzymes (Duckworth & Kitabchi, 1981)

Further evidence provides that the GITE activity is the primary determination of the rate of hepatic insulin metabolism. It must be assumed, however, that insulin protease and lysosomal enzymes are involved in the process of insulin degradation.

Varandani, 1972 have shown that GITE is major enzyme responsible for hepatic insulin degradation by splitting the hormone at the disulfide bonds into A and B chains. Data of the current study in normal isolated hepatocytes model confirm their findings. While STZ caused alteration on enzymes levels the degradation (Zafar et al., 2009), the effect of GITE in STZ-induced diabetic hepatocytes was weak.

To avoid first pass metabolism, inhibition of this enzyme has been suggested to block internalization and, therefore, to result in an increase in surface-bound hormone. Bacitracin is commonly used in studies on insulin action, is widely used as an antibiotic and as an inhibitor to inhibit the degradation of insulin in studies on hormone-receptor binding and action (Juul & Jones, 1982). It was used to inhibit the ability of purified GITE to split insulin into its constituent A and B chains. Kinetic studies indicated that this inhibition was by a complex mechanism that decreased both the  $V_{max}$  and affinity of the enzyme for insulin (Roth, 1981). So that, the present