

1988). Approximately 70% of portal insulin is removed by hepatocytes during first-pass effect before entering the systemic circulation. Bonora et al 1983 reported that hepatic insulin metabolism and clearance rates are decreased in diabetes mellitus. Also our results were in line with this assumption. After *in situ* liver perfusion technique was conducted on normal and STZ induced diabetic rats, more insulin was degraded by normal rat liver than diabetic liver (**Figure 3.21**). Similarly, insulin degradation is reduced in STZ-diabetic isolated hepatocyte compared to normal hepatocytes. Indeed, STZ causes liver function altering and destruct liver enzymes (Zafar et al., 2009) which are responsible for decreased insulin degradation in diabetic liver and diabetic isolated hepatocytes.

Concerning the factors that affect the insulin metabolism, *in situ* liver perfusion of insulin at different flow rate (1 ml/min and 5 ml/min) was performed. After insulin perfusion at different flow rates and drying the effluent, the dried effluent dissolved in distilled water and subcutaneously injected into normal rats to evaluate the effect of flow rate on insulin degradation and reveal the change on insulin efficacy and composition. According to our knowledge, this is the first *in situ* liver perfusion of insulin at different flow rate was conducted. The current study shows the high flow rate (5ml/min) of perfused insulin into the liver degraded the insulin less than the low flow rate (1 ml/min), while streptozotocin-treated livers at high flow rate were resulted the less degraded insulin. These results can be explained that the high flow rate, amount of insulin enters the liver rapidly for short time, liver enzymes metabolized so small amount of insulin while the rest of insulin will not be affected so when reinjected into normal rats should give hypoglycemic effect. On the other hand, insulin perfusion at low flow rate resulted in delaying of insulin in the liver, so the liver enzymes take enough time to degrade insulin then did not reduce glucose level