

Since liver is the major organ involved in the metabolism of insulin, *in situ* liver perfusion technique was performed and isolated hepatocytes were cultured from both normal and STZ-diabetic rats in order to investigate insulin's metabolism in liver. The results indicated that hepatic insulin metabolism was decreased in STZ-diabetic rats compared to normal rats. Similarly, insulin degradation was reduced in STZ-diabetic isolated hepatocyte compared to normal hepatocytes. When the *in situ* "liver passed" insulin was re-injected *in vivo* in both normal and diabetic rats, it was found that the insulin collected from diabetic livers was more active than the collected from non-diabetic livers. Such effect can be attributed to the decrease in insulin degradation in diabetic liver and diabetic isolated hepatocytes due to the toxic action of STZ. In addition, the result also confirms the effect of bacitracin on inhibiting insulin metabolism when incubated with hepatic cells *in vitro*.

In conclusion, the current study confirms the ability of the current investigated nanoparticle system with its modifications to enhance the pharmacological response of insulin when administered orally. The first pass metabolism of the absorbed oral insulin was seen variable between normal and STZ-intoxicated rats where the effect of insulin was more enhanced in diabetic animals. This enhancement in activity is mainly due to the reduction of insulin's first pass metabolism in these animals. The toxic effects of STZ on the liver and intestinal function is expected to be responsible of such reduction in metabolism.