rat models, while the hypoglycemic effect of insulin preparation in normal rats was weak **(Figure 3.5)**. The increase of hypoglycemia in STZ-induced diabetic rats might be attributed to the deleterious and toxic actions of STZ on organs, other than pancreas, involved in maintaining normal glucose homeostasis in the body (Qinna & Badwan, 2015). Moreover, hypoglycemic effect of insulin-loaded nanoparticles administered orally was sustained for a longer period than the subcutaneous injection.

Streptozotocin is the most used diabetogenic agent for inducing diabetes in experimental animal models. Further studies with STZ revealed that it produced irreversible damage to pancreatic β cells, triggered intermittent hypoglycemia (Ohno et al., 2000). Streptozotocin is able to pass through any cell membrane that contains glucose transporter (GLUT-2). Once STZ passes the cell membrane, it causes alkylation of DNA. This damage leads to the depletion of cellular NAD+ and ATP and the formation of superoxide radicals. STZ can also liberate nitric oxide inside the cells that inhibits aconitase activity resulting in further DNA damage. Indeed this toxic activity is more pronounced in β cells in pancreas. In addition, STZ-induced diabetes complication in liver is as destruction of hepatocytes, alteration in liver enzyme levels and morphological changes (Zafar et al., 2009).

Comparing the effect of insulin in diabetic with normal rats, the current results are in line with a recent study, which reported that STZ reduces the endogenous insulin secretions due to pancreatic destruction while the exogenous insulin accumulates more in the blood of the diabetic animals. This might be caused by decreasing in kidney and liver functions. Such combination of inefficient metabolism and excretion caused the accumulation of the injected insulin in the blood circulation (Qinna & Badwan, 2015). In other words, STZ is responsible for the loss of normal glucose