5. Conclusion and future work

The present study evaluated the first pass metabolism of oral insulin-loaded nanoparticles formula with unimodal particle size (85 ± 2.53 nm) in normal and STZ-intoxicated rats. *In vivo* evaluation revealed significant sustained hypoglycemic effect in the glucose level of STZ-induced diabetic rat model.

However, the intestinal first pass metabolism was tested by absorption studies as *ex vivo* everted gut sac and *in situ* intestinal perfusion. The everted gut experiments showed that insulin in a solution form was absorbed more than insulin formulated in the tested nanoparticle oral delivery systems may due to the presence of free insulin particles available for absorption or enzymes elimination of everted model. On the other hand, the intestinal *in situ* perfusion study produced a significant hypoglycemic effect in both normal and diabetic rats.

In situ liver perfusion technique and cell culture model in both normal and STZ-diabetic rats studied insulin first pass metabolism in liver. The results indicated that hepatic insulin metabolism is decreased in STZ-diabetic rats compared to normal animals. Similarly, insulin degradation is reduced in STZ-diabetic isolated hepatocyte compared to normal hepatocytes. Moreover, 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 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. Bacitracin as insulin