membrane such as the Golgi apparatus or the endoplasmic reticulum being unable to pass across the cells intactly. Moreover, due to the presence of some limiting factors for the use of everted rat intestine studies, such as tissue viability, loss of protein and enzymes elimination.

On the other hand, Matsuzawa et al. in 1995 reported that significant hypoglycemic effect was obtained after *in situ* intestinal perfusion of W/O/W insulin emulsion, and determined the best region for insulin absorption by comparing the biologic effects of the emulsion after administration to various sites in the rat intestine. According to the effectiveness of *in situ* intestinal perfusion technique, *in situ* intestinal perfusion model was performed for testing nanoparticles permeation.

In the current study, results indicate that the single-pass intestinal perfusion *in situ* model, a significant hypoglycemic effect was obtained in both normal and diabetic rats post oral insulin preparation administration, while the administration of insulin solution did not decrease glucose level significantly **(Figure 3.19, 3.20)**. As expected, such results seems more representative than the *ex vivo* results since *in situ* approaches provide experimental conditions closer to what is encountering following oral administration (Hogerle & Winne, 1983). In addition, these techniques maintain an intact blood supply to the intestine, and can be used to estimate the impact of clearance pathways such as enzymes and transporters, that are present in the gut. Moreover, drug permeability, expression of drug metabolizing enzymes and transporters has been shown to vary along the intestinal tract (Ungell et al., 1998).

Evaluation the hepatic first pass metabolism of the current oral insulin preparation was conducted by using *in situ* liver perfusion and cell culture methods. Which the liver plays a major role in the first pass metabolism of insulin (Duckworth et al.,