A novel investigational topolateral (≤ 150 μm in diameter) insulin delivery system, hepatic-directed vesicles insulin (HDV-I), that contains 1% encapsulated insulin and a specific proprietary hepatoctic targeting molecule (HTM) in its bilipid layer, has been developed. The HTM selectively targets the delivery of the encapsulated insulin to the hepatocytes in the liver in a manner similar to normal insulin physiology, in contrast to conventional SC insulin or untargeted insulin that readily distributes to peripheral tissues, fat, and muscle. HDV-I is formulated for oral gel capsule and SC administration in types 1 and 2 diabetes. The results of early evaluation studies in animal models have revealed that: (1) in streptozotocin/alloxan insulin deficient dogs, administration of regular insulin (RI) at varying doses via the jugular vein resulted in conversion of glucose output to mean change in blood glucose (Δ FBG) with elevated portal vein insulin levels (~ 40 mU/kg/min) that converted hepatic glucose output to hepatic glucose uptake at all doses tested from 0.4 to 2.0 μU/kg/min; (2) in streptozotocin/alloxan insulin deficient rats given oral glucose load containing 14C-glucose as a tracer, HDV-I markedly decreased peripheral blood glucose by ~35% and increased fold hepatic glucose uptake in the liver by 200%; (3) in portal-cannulated dogs given an OGTT, HDV-I had a more pronounced effect than that RI in reducing the PPGL excursion after administration of the glucose meal and it prevented secondary hypoglycemia that is believed to be due to the effect of RI on peripheral tissues (see Figure).

In conclusion, results of these animal studies show that HDV-I can elicit hepatic activity at a low dose superior to that of the other insulin preparations for liver administration, suggest that the enhanced antihyperglycemic effect of HDV-I is due to hepatic glucose uptake, and show that HDV-I was superior to RI in reducing postprandial glycaemia and was not associated with secondary hypoglycemia. HDV-I holds significant promise in the treatment of diabetes.

**Abstract**


**References**


**Conclusions**

HDV-I is superior to RI in controlling postprandial glycaemia and was not associated with secondary hypoglycemia. In contrast, the insulin-deficient dogs, with portal vein insulin deficiency, the animals remained in hepatic glucose output (Figure 14a) with a no change in portal vein insulin levels (Figure 15b).

HDV-I can stimulate hepatic activity at a dose of <1% of the dose of RI required for liver stimulation. HDV-I holds significant promise in the treatment of diabetes.