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Oral insulin delivery via anchored PLGA nanoparticles

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Objectives: Insulin is the mainstay of drug therapy for patients with insulin-dependent diabetes mellitus, which is a syndrome of disordered metabolism, and resulting in abnormally high blood sugar levels due to defects in either insulin secretion or action. Oral insulin delivery has been the major research issue, since many decades, due to several obvious advantages over other routes. However, this route poses several constraints for delivery of peptides and proteins which are to be worked upon. The small intestine has been shown to be able to transport L-forms of amino acids against a concentration gradient and that they compete for the mechanism concerned. So, L-valine was used as a ligand for carrier-mediated transport of insulin-loaded polylactic-co-glycolic acid (PLGA) nanoparticles (NPs).

Methods: L-Valine-conjugated-PLGA nanoparticles were prepared using double emulsion solvent evaporation method. The conjugated NPs were characterized for their surface morphology for shape and size by electron microscopy, drug entrapment efficiency, zeta potential, polydispersity index, *in-vitro* and *in-vivo* insulin release.

Results: *Ex-vivo* studies on intestine revealed that conjugated nanoparticles showed greater insulin uptake as compared to non-conjugated nanoparticles. *In-vivo* studies were performed on streptozotocin-induced diabetic rabbits. Oral suspension of insulin-loaded PLGA nanoparticles reduced blood glucose level within 4hrs which further decreased after 8hrs. The ligand-conjugated formulation on oral administration produced hypoglycaemic effect within 4hrs of administration, and the hypoglycaemic effect prolonged till 12hrs of oral administration. Simultaneously, the insulin concentration in withdrawn samples was also assessed and found that profile of insulin level is in compliance with the blood glucose reduction profile.

Conclusions: The L-valine NPs showed higher insulin uptake, as compared to NPs due to its relative high affinity for oligopeptide transporters present at intestine, which aids in increased bioavailability and better therapeutic response for orally administered insulin. Thus, L-valine NPs have the potential for oral insulin delivery in effective management of Type 1 diabetes condition.