**Title:** Development of Bi-Polymer Lipid Hybrid Nanocarrier (BLN) to Improve the Entrapment and Stability of Insulin for Efficient Oral Delivery

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Solid lipid nanoparticles (SLN) have demonstrated favorable properties for oral protein delivery. However, their protein entrapment efficiency (EE%) values remain limited due to their hydrophobic nature. In this study, we reported a new strategy in which two polymeric excipients were incorporated into the double-emulsion based SLN to address this entrapment inefficiency issue. Using insulin as the model protein drug, the resulting hybrid nanocarriers known as bi-polymer lipid nanocarriers (BLN) were evaluated for physicochemical properties, drug and particle stability, in vitro biological behaviors and in vivo hypoglycemic effect. It was found that BLN containing PEG 6000 in internal aqueous phase and PLGA in lipid phase showed favorable size (around 240 nm) and reasonably narrow particle size distribution. The bi-polymer strategy improved insulin EE% over standard w/o/w SLN by 2.5-fold (~50% versus 20%) while preserving the insulin chemical stability and biological activity. BLN demonstrated good dispersion.
stability under gastrointestinal conditions, protected the entrapped insulin against enzymatic degradation well, and were well internalized into Caco-2 cells with minimal cytotoxicity. Pharmacological availability of oral insulin delivered by BLN (6.1%) was comparable to lectin-modified SLN. To conclude, BLN is a promising hybrid nanocarrier design to achieve efficient oral insulin delivery.

Keywords: Oral protein delivery, Insulin, Solid lipid nanoparticles, Hybrid nanoparticles