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Preparation and optimization of lipid-polymer hybrid nanoparticles for oral protein delivery

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Oral delivery of peptide/protein drugs is hindered by poor bioavailability due to their instability and limited systemic absorption. Multiple approaches have been proposed to overcome these challenges. Amongst them, lipid-polymer hybrid nanoparticles (LPHNs) may provide a promising solution by combining the structural stability of polymers with the biocompatibility of lipids to enhance peptide protection and absorption through biological barriers. The aim of this work is to design a cost-effective LPHN formulation and systematically optimize the factors affecting their physicochemical characteristics.

LPHN formulations were prepared by a combination of two simple methods: ionic gelation for preparation of polymeric cores, and ethanol injection method for lipid shell formation. Experimental design approach was implemented to study and optimize the factors affecting nanoparticle properties such as particle size, polydispersity index (PDI), zeta potential, and protein encapsulation efficiency (EE).

Polymer core optimization revealed that pH and temperature were the most significant factors, with the optimal core exhibiting a particle size of 235.1 nm, PDI of 0.061, zeta potential of –19.74 mV, and EE of 61.55%. On the other hand, Lipid shell optimization indicated that Aqueous/Organic volume ratio (A/O ratio) had the most significant effect on particle size, PDI, and EE, followed by the Lipid/Polymer mass ratio (L/P ratio). The final optimized LPHN formulation had a particle size of 258.16 nm, PDI of 0.277, zeta potential of -39.02 mV, and EE of 70.41%. These findings suggest that LPHNs prepared via simple, protein-friendly methods may offer a promising platform for oral protein delivery.

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