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DEVELOPMENT OF NANOPARTICLE-BASED MICROBEADS SYSTEM AND ITS EVALUATION IN INTESTINAL MODELS

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ABSTRACT

This study focuses on the development and evaluation of a nanoparticle-based microbeads system as an advanced oral drug delivery platform. Polymer-based microbeads were prepared using ionotropic gelation with sodium alginate as the matrix, incorporating nanoparticles (SNEDDS-based and PLGA-based) to form a hybrid "nano-in-micro" system. The obtained microbeads were evaluated under different ionic strength conditions (0, 50, and 200 mM NaCl) to assess their structural stability and biological performance.

The results demonstrated that ionic strength significantly affects the integrity of the microbeads. At low ionic strength (0 mM NaCl), the system exhibited optimal morphology, structural stability, and uniformity. Moderate ionic conditions (50 mM NaCl) led to partial swelling while maintaining overall integrity. In contrast, high ionic strength (200 mM NaCl) caused structural deformation and partial disintegration due to disruption of ionic crosslinking.

Biological evaluation using Caco-2 intestinal epithelial cells showed that microbeads prepared under low and moderate ionic conditions had acceptable biocompatibility, with cell viability ranging from 70–85%. However, samples exposed to high ionic strength demonstrated increased cytotoxicity, with viability decreasing to 40–50%. Additionally, the nanoparticle-loaded microbeads exhibited more controlled and sustained release profiles compared to nanoparticle systems alone, confirming the advantages of the "nano-in-micro" approach.

In conclusion, the developed system demonstrates strong potential as an oral drug delivery platform, providing enhanced stability, protection, and controlled release of bioactive compounds. Optimization of ionic conditions is critical for maintaining both structural integrity and biological compatibility.

Introduction. Polymer-based microbeads have attracted significant attention as versatile drug delivery systems due to their ability to protect sensitive bioactive compounds and provide controlled release. This is particularly relevant for peptide therapeutics such as insulin, which are highly susceptible to enzymatic degradation and physicochemical instability under physiological conditions (Lee & Mooney, 2012). Ionotropic gelation is a widely used method for microbeads preparation, especially with biopolymers like alginate. In this process, interactions between polymer chains and divalent cations (e.g., Ca^{2+}) result in the formation of a three-dimensional hydrogel network with tunable mechanical and diffusion properties (George & Abraham, 2006). Recent studies indicate that combining nanoparticles with micro-scale carriers ("nano-in-micro" systems) can further improve drug stability and enable more controlled release kinetics (Danhier et al., 2012). Such hybrid systems are particularly promising when integrating lipid-based systems such as SNEDDS or polymeric nanoparticles into hydrogel matrices.

In this study, nanoparticle-loaded microbeads were developed and evaluated, with a focus on the effect of ionic strength on structural stability and biological performance using Caco-2 intestinal epithelial cells.

Materials and methods. Microbeads were prepared using ionotropic gelation with sodium alginate as the polymer matrix. Nanoparticles (SNEDDS-based or PLGA-based) were incorporated into the alginate solution under continuous stirring to ensure homogeneous dispersion. The mixture was then extruded dropwise into a calcium chloride ($CaCl_2$) solution, resulting in the immediate formation of spherical microbeads via ionic crosslinking. The beads were collected, washed, and incubated in media containing different NaCl concentrations (0, 50, and 200 mM) to evaluate the effect of ionic strength on stability. For biological assessment, Caco-2 cells were cultured under standard conditions and exposed to the microbeads. Cell viability was determined using the MTT assay, and results were expressed as a percentage relative to untreated controls.

Results and Discussion. The obtained results clearly demonstrated that ionic strength plays a critical role in determining the structural stability of the developed microbeads system. Under salt-free conditions (0 mM NaCl), the microbeads exhibited well-defined spherical morphology, uniform size distribution, and high structural integrity. These observations indicate effective crosslinking between alginate chains and calcium ions, resulting in a stable hydrogel network.

At moderate ionic strength (50 mM NaCl), partial swelling and softening of the microbeads were observed. However, the overall structure remained intact, suggesting that although electrostatic interactions within the polymer network were partially screened, the system retained sufficient crosslinking to maintain integrity.

In contrast, exposure to high ionic strength (200 mM NaCl) resulted in significant structural deformation and partial disintegration of the microbeads. This behavior can be explained by the disruption of ionic crosslinks due to competition between Na^+ ions and Ca^{2+} ions, weakening the gel network and leading to structural instability. Similar observations have been reported in previous studies on alginate-based hydrogels (Draget et al., 1994).

Cytotoxicity results obtained from the Caco-2 model further supported these findings. Microbeads prepared under 0 mM and 50 mM NaCl conditions demonstrated acceptable biocompatibility, with cell viability values in the range of approximately 70–85%. These values are generally considered indicative of low cytotoxicity and suggest that the developed system is suitable for intestinal applications.

However, microbeads exposed to 200 mM NaCl showed significantly reduced cell viability (approximately 40–50%), indicating increased cytotoxic effects. This decrease may be associated with structural breakdown of the microbeads, leading to uncontrolled release of encapsulated components and increased local concentrations affecting cellular metabolism. An important observation of this study was that nanoparticle-loaded microbeads exhibited more controlled and sustained release behavior compared to nanoparticle systems alone. This confirms the advantage of the “nano-in-micro” approach, where the microbeads matrix provides an initial diffusion barrier, followed by a secondary release phase from embedded nanoparticles. Such dual-release systems are known to improve pharmacokinetic profiles and enhance therapeutic efficacy (Danhier et al., 2012).

Overall, the results demonstrate that optimizing ionic conditions is essential for maintaining both structural integrity and biological compatibility of microbeads systems intended for oral drug delivery.

Conclusion. In this study, a nanoparticle-based microbeads system was successfully developed using ionotropic gelation and evaluated under varying ionic conditions. The results demonstrated that microbeads stability is highly dependent on environmental ionic strength, with optimal performance observed under low to moderate NaCl concentrations.

The system exhibited good biocompatibility in Caco-2 intestinal models and provided controlled release characteristics, supporting its potential as an advanced oral drug delivery platform. The integration of nanoparticles into microbeads structures represents a promising strategy for improving drug protection, stability, and delivery efficiency.

Future work should focus on further optimization of formulation parameters and in vivo evaluation to confirm the applicability of the system in clinical settings.

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