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Emerging Zein-Based Nanocarrier Technologies for Efficient Oral Drug Delivery

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ABSTRACT

The preferred drug delivery technique is oral administration, although it is hampered by gastrointestinal obstacles such as poor absorption, solubility problems, and enzymatic degradation. Zein-based nanocarriers (ZBNs) from maize prolamin offer a solution to these issues, displaying structural stability across pH levels, self-assembly adaptability, and the capacity to be surface functionalized. This research emphasizes how tailored ZBNs overcome barriers through hydrophobic encapsulation for protection, increased penetration or adhesion via surface engineering, and improved transport with ligand conjugation. They are used to improve oral bioavailability, facilitate pH-responsive drug release, stabilize sensitive therapies, and increase the solubility of BCS Class II/IV medicines. ZBNs are a viable platform for administering BCS Class II–IV medications, but difficulties with scaling and predictive translation point to the necessity for continued study in multifunctional systems and continuous manufacturing.

Keywords: Zein, Drug Delivery, Nanocarriers, Bioavailability, Oral Administration

INTRODUCTION

Oral administration is the most frequent drug delivery technique, recommended for its non-invasiveness and high patient compliance, accounting for roughly 90% of formulations. However, attaining effective systemic distribution through the gastrointestinal (GI) tract is impeded by significant physiological hurdles, including severe pH fluctuations, enzymatic degradation, mucus trapping, intestinal epithelial tight junctions, and efflux pumps. Larger, hydrophilic molecules and biologics are difficult to absorb due to these obstacles, which can result in insufficient systemic concentrations, inconsistent bioavailability, and increased toxicity concerns. In order to overcome these obstacles, creative formulation techniques are required. [1-3]

Nanotechnology has become a crucial technique to reduce gastrointestinal (GI) barriers in medicine administration. Drug payloads are shielded against deterioration by engineered nanocarriers, which also improve contact with epithelial layers and increase absorption through mucus barriers. They can lengthen GI residence time and modulate medication release according to physiological parameters.[4] Lipid-based platforms, biopolymers, synthetic polymers, inorganic materials, and hybrid composites are examples of nanocarrier types; protein-based carriers stand out for their biocompatibility and usefulness. Because of their inherent binding sites, these protein nanocarriers allow for targeted distribution, controlled release through enzymatic reactions, and easy modification for improved stability and specificity in the GI tract. [5]

Animals (like collagen and gelatin), plants (like soy and pea), or microorganisms (like microalgae) can all provide proteins. Nevertheless, a lot of hydrophilic proteins have problems such quickly dissolving in the gastrointestinal (GI) tract, which causes early drug release. Additionally, animal proteins may cause contamination and immunogenicity problems. Zein, a hydrophobic protein derived from maize, has advantages as an oral nanocarrier because of its GRAS classification, affordability, and safety. It is

very hydrophobic, stable in acidic environments, and resistant to digestion in the stomach. Zein's self-assembly tendency makes it possible to create stable nanocarriers, and its surface chemistry permits functionalization to produce characteristics like mucoadhesion and pH-dependent release. [6, 7]

This review analyzes how the molecular structure of zein effects its self-assembly into functional nanocarriers. It emphasizes the potential of these carriers to overcome gastrointestinal barriers by providing enzyme protection by hydrophobic encapsulation, boosting mucus interaction via surface engineering, and enhancing epithelial transport through ligand conjugation. The applications emphasized include the stabilization of sensitive therapies, enhanced solubility for several drug classes, pH-responsive release, and considerable increases in oral bioavailability, alongside addressing difficulties and future possibilities for clinical application.

ZEIN-BASED NANOCARRIERS

Characteristics of Zein

Zein is a complex prolamin protein from maize, first characterized by John Gorham in 1821. It is a heterogeneous mix of polypeptides, defined by changes in molecular weight, solubility, and charge, which has led to classifications into discrete fractions such as α-zein, β-zein, and γ-zein based on solubility in different alcohol concentrations. Notably, α-zein makes for 75–85% of zein, while β-zein and γ-zein constitute lesser proportions. Zein's hydrophobic nature and distinctive solubility characteristics are attributed to its amino acid composition, which is rich in nonpolar residues. It dissolves in some solvents, especially alcohols, but stays insoluble in water. Zein's distinct molecular configurations, which are determined by its amino acid makeup, are reflected in a number of models proposed by structural research, including helical and ribbon-like forms. [8-10]

Preparation of Zein-based Nanocarriers

The structure of zein exhibits hydrophobic lateral surfaces and hydrophilic top/bottom surfaces, which are rich in glutamic acid, leading to spontaneous aggregation and self-assembly into diverse morphologies including micro/nanospheres and hollow nanoparticles. The efficacy of zein-based nanoparticles (ZBNs) is controlled by their structural properties such as particle size, shape, and surface potential. Optimizing preparation processes provides for fine control over these features. [11, 12]

Zein-based nanoparticles (ZBNs) can be manufactured using numerous procedures, with phase separation being the most frequent. This approach utilizes an ethanol-water system, where zein solubility varies (2-60% w/w) depends on ethanol concentration. Self-assembly of zein happens when ethanol concentration is below 40% or above 90% (v/v), resulting in coacervates that form into nanoparticles. Particle aggregation, which results in bigger particle sizes and broad polydispersity, is a problem for conventional phase separation techniques. To overcome these concerns, various methods have been devised, including liquid-liquid dispersion, flash nanoprecipitation, built-in ultrasonic dialysis, and atomizing/antisolvent precipitation. Additionally, spray drying enables a more efficient technique by creating dry powder directly, suited for microencapsulating thermosensitive medicines. Zein-based n Zein fibers can be generated using electrospinning and electrospraying. Supercritical fluid technology employing supercritical CO2 is a useful substitute for medicines with low solubility in ethanol-water systems. Furthermore, chemical conjugation of medicines onto zein side chains using crosslinking agents can assist prevent premature drug release and promote stimuli-responsive profiles. [13-15]

ZEIN-BASED NANOCARRIERS VS. GI BARRIERS

Orally given formulations face difficulties in the gastrointestinal (GI) environment because of mucus layer trapping, poor intestinal epithelial penetration, and quick chemical and enzymatic breakdown. Zwitterionic nanoparticles (ZBNs) leverage their hydrophobicity and enzymatic resistance to shield payloads from degradation. Innovations in surface modifications boost their efficacy by addressing difficulties including intestine aggregation sensitivity and enhancing mucus penetration and epithelial interface. The design concepts and efficiency of ZBNs in removing these GI obstacles are examined in this section.

Mucoadhesion/Mucus Penetration

The mucus layer, a viscoelastic hydrogel coating mucosal surfaces, limits oral medication absorption due to its physicochemical qualities and fast renewal. Its tight network, produced by crosslinked glycoprotein fibers, provides nanoscale holes that exclude larger particles and absorb oppositely charged or hydrophobic molecules, trapping them within the gel.[16] The mucus's shear-thinning characteristics trap particles under low shear, inhibiting diffusion towards epithelial cells. Continuous turnover and enzymatic degradation clear trapped drugs before absorption. Zein-based nanoparticles (ZBNs) show potential in overcoming this barrier, demonstrating strong mucoadhesion through hydrogen bonding, hydrophobic interactions, and electrostatic attraction,

significantly extending drug retention time. Thiolated zein improves mucoadhesion via covalent disulfide bonding with mucin's cysteine-rich regions, outperforming weaker connections.[17]

Stability in GI Tract

Zein-based nanoparticles (ZBNs) provide great protection against the gastrointestinal (GI) environment due to their hydrophobicity and resistance to enzyme degradation, promoting the delivery of sensitive medicines further into the GI tract. However, a significant downside is linked to their proteinaceous content, specifically the neutral isoelectric point (~6.2), which leads to aggregation in the alkaline environment of the small intestine. This aggregation diminishes their nanoscale size, severely reducing dispersion stability and cellular absorption.

Composite formulations and surface alterations are essential to solve aggregation problems.

Covalent coupling of charged moieties or hydrophilic polymers to the side-chain groups of zein creates steric/electrostatic barriers and decreases hydrophobicity. Sabra et al.,[18] for instance, created an amphiphilic zein–lactoferrin (Lf) co-polymer that enhanced colloidal stability via electrostatic repulsion and steric stabilization (+41.4 mV zeta potential). Ballegooie et al. examined polyethylene glycol (PEG) modification, which established a steric barrier on zein nanoparticles, limiting undesired interactions and efficiently resolving aggregation concerns. These PEGylated zein nanoparticles retained size and dispersity over 72 hours in DMEM at 37°C and for three months in water at 4°C. [19, 20]

Paracellular/Transcellular Transport

Zein-based nanoparticles (ZBNs) facilitate effective transcellular transport by improving contacts with intestinal epithelium due to their hydrophobic characteristics. Surface modifications with ligands, such as folic acid, increase receptor-mediated endocytosis, leading to greater absorption and transcytosis of encapsulated medicines. Studies demonstrate that PEGylated zein nanoparticles showed greater mucosal penetration and longer gastrointestinal retention, greatly boosting the bioavailability of medicines like paclitaxel and docetaxel. Modifications, such as glucose conjugation, further increase bioavailability and tumor targeting by utilizing glucose transport pathways. Additionally, modified zein nanoparticles provide direct systemic circulation access via microfold (M)-cell targeting, skipping first-pass metabolism and efficiently overcoming the intestinal absorption barriers. [21, 22]

APPLICATIONS OF ZEIN-BASED NANOCARRIERS

Enhancing Drug Solubility

Since more than 40% of marketed medications and 70% of pipeline candidates fall into BCS Class II or IV, which limits oral bioavailability, the poor water solubility of bioactive chemicals impedes drug development. Zein-based nanoparticles (ZBNs) present a potential solution by improving the solubility of poorly soluble medicines through strong interactions, resulting in particles with enhanced surface area that improve dissolution kinetics.[23] ZBNs stabilize pharmaceuticals in a high-energy amorphous state, which offers better solubility than crystalline versions. For instance, quercetin attained an 89.41% encapsulation rate within a zein core, resulting in a 30.16-fold increase in water solubility and a 3.21-fold increase in bioavailability compared to its free form. Similar gains in solubility were reported for lutein, curcumin, and 7,8-dihydroxyflavone utilizing ZBNs.[24]

Enhancing Drug Absorption

Oral medication absorption has substantial obstacles, such as GI mucus entrapment and an epithelial barrier that prevents drug uptake. This is especially problematic for peptides and medicines with low permeability. Zein-based nanoparticles (ZBNs) improve oral bioavailability by increasing mucus penetration and epithelial transport. For example, zein/rhamnolipid nanoparticles complexed with cholic acid significantly increased liraglutide absorption while protecting the peptide and reducing self-aggregation. This approach improved mucus penetration and transcellular transport, yielding 9.6% oral bioavailability in diabetic mice, comparable to subcutaneous injection. Furthermore, zein nanoparticles coated with PEG improved insulin absorption in diabetic rats, resulting in lower blood glucose levels and higher oral bioavailability compared to uncoated particles. [25, 26]

Improving Drug Stability

Labile medicines such as peptides, proteins, nucleic acids, and tiny compounds are extensively destroyed in the gastrointestinal (GI) environment, lowering their bioavailability and therapeutic efficacy. Zein-based nanoparticles (ZBNs) offer a solution by offering stability and encapsulation. For example, Fu et al.[27] used lecithin/zein nanoparticles to increase the stability of Panax notoginseng saponins (PNSs), which led to increased residual drug levels in intestinal and gastric fluids. Similarly, Zhang et al. produced zein

nanoparticles with hydroxypropyl-β-cyclodextrin that protected curcumin during digestion, retaining gastric integrity and permitting extended intestinal release while increasing drug stability through the creation of a "protein corona." This encapsulation approach successfully mitigates deterioration in the GI tract.[28]

Controlling Drug Release

Oral controlled medication release overcomes issues including rapid gastric degradation and poor bioavailability by employing zein-based nanocarriers (ZBNs). These methods use GI stability, pH-triggered release, and sustained mechanisms to enhance medication effectiveness. Functionalization enhances pH responsiveness and mucoadhesion for targeted administration. For example, ZBNs showed pH-responsive activity when functionalized with tannic and glycyrrhizic acids, releasing contents in the intestines while retaining integrity in the stomach. Studies demonstrate zein shields drug payloads from stomach conditions while providing considerable release rates in the gut, allowing for multiple therapeutic effects, such as those shown with heparin for treating inflammatory bowel disease. [29, 30]

CONCLUSION

Because of their hydrophobicity, pH stability, and protease resistance, which safeguard therapeutic payloads, ZBNs provide a versatile platform for oral drug administration. They can overcome gastrointestinal obstacles through tailored construction and functionalization procedures. Therapeutic chemicals are protected by hydrophobic encapsulation, and mucus interactions are improved by surface changes. Transport across epithelial tissues is enhanced by processes such as receptor-mediated transcytosis. ZBNs are efficient in stabilizing labile chemicals, boosting solubility of BCS Class II/IV medicines, permitting controlled release, and promoting oral bioavailability. However, to fully realize their clinical potential, important issues including batch variability and manufacturing scalability must be resolved. Future studies should concentrate on improving predictive modeling and microfluidic manufacturing methods, as well as creating responsive systems linked to illness biomarkers.

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