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Polysaccharide-Based Nanocarriers for Oral Delivery of Proteins and Peptides: A Paradigm Shift in Biopharmaceutical Transport

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ABSTRACT

The oral administration of protein and peptide drugs (PPDs) remains a significant challenge due to the harsh physiological environment of the gastrointestinal (GI) tract. PPDs are susceptible to enzymatic degradation, denaturation from pH extremes, and poor absorption across the intestinal epithelium. To overcome these barriers, polysaccharide-based nanocarriers have emerged as a highly promising delivery platform. This manuscript provides a comprehensive overview of the design, fabrication, and application of these nanocarriers, using insulin as a model drug. The review highlights the unique properties of key polysaccharides like chitosan and alginate, which enable pH-responsive drug release and enhance intestinal permeability through mucoadhesion and tight junction modulation. The methodology section details fabrication techniques such as ionic gelation and polyelectrolyte complexation, alongside characterization methods and both in vitro and in vivo studies to evaluate efficacy. Results from such studies demonstrate that these nanocarriers successfully protect PPDs from degradation, leading to a significant increase in oral bioavailability. While challenges related to batch-to-batch reproducibility and clinical scalability remain, the use of biocompatible and biodegradable polysaccharides holds immense potential for developing patient-friendly oral formulations for PPDs.

KEYWORDS: Oral drug delivery, Protein and peptide drugs, Polysaccharide nanocarriers, Chitosan, Alginate, Insulin, Bioavailability, Nanoparticle.

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INTRODUCTION

The field of medicine has witnessed a paradigm shift with the advent of protein and peptide drugs (PPDs). These biologics, including hormones like insulin, therapeutic antibodies, and growth factors, offer unparalleled specificity and efficacy in treating chronic diseases such as diabetes, cancer, and autoimmune disorders [1]. Despite their clinical superiority, the primary mode of administration for PPDs remains parenteral (via injection), which is associated with significant drawbacks. These include patient discomfort, potential for injection site reactions, and, critically, poor patient compliance, particularly in long-term treatment regimens [2]. Consequently, the development of an oral delivery system for PPDs represents a major goal in pharmaceutical science, promising enhanced patient convenience, improved quality of life, and the potential for greater therapeutic adherence [3].The gastrointestinal (GI) tract, however, presents a formidable series of physiological barriers that severely limit the oral bioavailability of PPDs. The primary challenges can be systematically categorized into three key areas:

Enzymatic Degradation: A Gauntlet of Proteolytic Enzymes

PPDs are composed of amino acid chains linked by peptide bonds, which makes them highly susceptible to enzymatic cleavage. The GI tract is a rich environment of proteolytic enzymes, including pepsin in the stomach and trypsin and chymotrypsin in the small intestine, which are evolved to digest proteins from food [4]. This extensive enzymatic activity rapidly degrades PPDs into inactive fragments, rendering them therapeutically ineffective before they can be absorbed into the bloodstream.

pH Extremes: Navigating a Volatile Environment

The GI tract is characterized by a dramatic change in pH. The stomach's highly acidic environment (pH 1-3) is designed to denature dietary proteins and kill pathogens, but it also causes the denaturation and loss of tertiary structure of many PPDs, leading to irreversible loss of biological activity [5]. While the small intestine is more neutral (pH 5-7.5), this environment still poses stability challenges for some therapeutic proteins.

Poor Permeability: The Barrier of the Intestinal Mucosa

Beyond the challenges of degradation and denaturation, PPDs face the final hurdle of permeation across the intestinal epithelium. Due to their large molecular weight and hydrophilic nature, PPDs cannot readily pass through the lipophilic cell membranes via passive diffusion. Their passage is further hindered by the dense mucus layer and the tightly-packed tight junctions between epithelial cells, which form a highly selective barrier [6].

To circumvent these formidable obstacles, significant research has been directed toward developing advanced delivery vehicles. Polysaccharide-based nanocarriers have emerged as a highly promising solution. Polysaccharides, derived from natural sources, are celebrated for their inherent biocompatibility, biodegradability, and low immunogenicity [7]. Notably, they possess unique properties that can be exploited to address the specific challenges of oral PPD

delivery:

Muco-adhesiveness
Cationic polysaccharides like chitosan can adhere to the negatively charged mucus layer, increasing the residence time of the nanocarrier at the absorption site [8].

pH-Responsiveness
Polysaccharides such as alginate can be engineered to form stable hydrogels in the acidic stomach and then swell or dissolve in the neutral pH of the intestine, facilitating targeted drug release at the optimal site of absorption [9].

Permeation Enhancement
Some polysaccharides can transiently open tight junctions, allowing for paracellular transport of the encapsulated drug [10].

This manuscript provides a comprehensive overview of the design, fabrication, and application of these innovative polysaccharide-based nanocarriers, highlighting their potential to revolutionize the oral delivery of PPDs and transform patient care.

LITERATURE REVIEW

The design and fabrication of an effective oral delivery system for protein and peptide drugs (PPDs) must address the complex physiological barriers of the GI tract. Significant research has focused on utilizing polysaccharide-based nanocarriers due to their biocompatibility, biodegradability, and diverse physicochemical properties [11]. These nanocarriers are engineered in various forms, including nanoparticles, nanogels, and nanoemulsions, each offering unique advantages for drug encapsulation and controlled release [12] [Table 1].

Table 1: Key Polysaccharide Nanocarriers for Oral Delivery of Protein and Peptide Drugs

Polysaccharide	Properties	Mechanism in Oral Delivery	Advantages	Limitations	Example Application
Chitosan (cationic)	Biocompatible, biodegradable, positively charged in acidic pH	- Mucoadhesion via electrostatic interaction with mucus - Opens tight junctions for paracellular transport	- Prolonged GI residence time - Enhances permeability - Protects against enzymatic degradation	- Limited solubility at neutral/basic pH - Batch variability in deacetylation	Insulin-loaded chitosan nanoparticles improve oral bioavailability and reduce blood glucose
Alginate (anionic)	Forms hydrogels with divalent cations (Ca^{2+}), pH-responsive	- Protects drug in acidic stomach - Swells/dissolves in neutral intestine for release	- Excellent gastric protection - pH-triggered targeted release - Simple ionotropic gelation method	- Fragile structure in intestinal conditions - Low mechanical strength alone	Alginate-Ca^{2+} nanoparticles releasing insulin in intestine
Chitosan–Alginate Complex	Core–shell (alginate core, chitosan shell)	- Combines mucoadhesion (chitosan) + gastric protection (alginate)	- Synergistic protection + absorption - Controlled release	- More complex fabrication	Oral insulin nanoparticles with dual protection
Dextran	Neutral, modifiable	- Modified for amphiphilic nanocarriers & hydrogels	- Flexible chemical modification - Good drug encapsulation	- Needs derivatization for oral delivery efficacy	Dextran-based nanogels for peptides
Pectin	Plant-derived, colonic bacteria-degradable	- Hydrogel formation - Colon-targeted release	- Enables site-specific delivery to colon - Natural & safe	- Not suitable for drugs needing small-intestinal absorption	Pectin-based nanocarriers for colon-targeted peptides
Other Polysaccharides (cellulose, pullulan, etc.)	Structural diversity, film- and gel-forming	- Used as excipients or hybrid systems	- Biodegradable & safe - Tailorable	- Limited standalone stability	

Chitosan: A Cationic Polymer for Mucoadhesion and Permeation Enhancement
Chitosan, a linear polysaccharide derived from the deacetylation of chitin, is a cornerstone material in oral drug delivery. Its primary advantage stems from its cationic nature in acidic environments, which facilitates strong electrostatic interactions with the negatively charged sialic acid residues on the mucosal layer of the GI tract. This property, known as mucoadhesion, significantly prolongs the residence time of the nanocarrier at the intestinal absorption site, thereby increasing

the opportunity for drug uptake [13].

Beyond mucoadhesion, chitosan possesses the remarkable ability to transiently open tight junctions between intestinal epithelial cells. This is thought to occur through the rearrangement of cellular junctional proteins like zonula occludens (ZO-1) and occludin, allowing for paracellular transport of the encapsulated PPDs [14]. Numerous studies have demonstrated the efficacy of chitosan nanoparticles in protecting model PPDs, such as insulin, from enzymatic degradation. For instance, in animal models, oral administration of insulin-loaded chitosan nanoparticles has resulted in a notable increase in the drug's oral bioavailability and a significant reduction in blood glucose levels, comparable to subcutaneous injection [15].

Alginate

An Anionic Polymer for pH-Responsive Protection

Alginate, an anionic polysaccharide extracted from brown algae, is widely employed for its ability to form stable hydrogels. This property is particularly useful for protecting PPDs from the harsh gastric environment. The process of ionotropic gelation, where alginate chains cross-link in the presence of divalent cations (most commonly Ca^{2+}), results in the formation of a gel matrix that effectively encapsulates and shields the drug payload [16]. This protective mechanism prevents the drug from being exposed to the low pH and proteolytic enzymes of the stomach.

Alginate's utility is further enhanced by its pH-responsive nature. While the hydrogel remains intact in the acidic stomach, it undergoes swelling and partial dissolution as it moves into the more neutral environment of the small intestine (pH ~6.8). This pH-triggered change facilitates the controlled and sustained release of the encapsulated PPDs at the site of absorption [17]. A highly effective strategy involves creating polyelectrolyte complexes or core-shell nanostructures, such as an alginate core protected by a chitosan shell. This combination leverages the protective capabilities of alginate in the stomach and the mucoadhesive and permeation-enhancing properties of chitosan in the intestine, creating a synergistic delivery system [18].

Other Polysaccharides and Hybrid Systems

The versatility of polysaccharides extends beyond chitosan and alginate. Dextran, a glucose-based polymer, has been chemically modified to create various amphiphilic nanocarriers and hydrogels for PPD encapsulation. Other natural polysaccharides, including cellulose, pectin, and pullulan, have also been investigated as core materials or excipients in hybrid nanocarrier systems [19]. For example, pectin, a component of plant cell walls, can form hydrogels that are selectively degraded by colonic bacteria, offering a pathway for targeted delivery to the large intestine [20].

The current literature underscores a multifaceted approach to oral PPD delivery using polysaccharide nanocarriers. These systems employ a combination of strategies, including enzymatic protection, pH-responsive release, mucoadhesion, and enhancement of intestinal permeability. While significant progress has been made, challenges such as achieving high drug loading efficiency, ensuring batch-to-batch reproducibility, and establishing scalable manufacturing processes remain critical hurdles to overcome before these nanocarriers can be successfully translated into clinical practice [21].

Methodology

This section provides a detailed and systematic methodology for the development and assessment of polysaccharide-based nanocarriers for the oral delivery of protein and peptide drugs (PPDs). The process is divided into key stages, from materials selection and fabrication to comprehensive in vitro and in vivo characterization.

Materials and Reagents

The foundational materials for nanocarrier synthesis include a selection of biocompatible polysaccharides such as chitosan (low to medium molecular weight) and alginate (e.g., sodium alginate). Cross-linking agents like sodium tripolyphosphate (TPP) and calcium chloride ($CaCl_2$) are essential for nanoparticle formation via ionic gelation [22]. The therapeutic payload, such as recombinant human insulin, is used as a model PPD. For in-depth in vitro analysis, a range of reagents are necessary, including simulated gastric fluid (SGF) (pH 1.2) and simulated intestinal fluid (SIF) (pH 6.8), both prepared according to pharmacopeial standards [23]. Enzymes like pepsin and trypsin are incorporated into these fluids to simulate the enzymatic degradation environment of the GI tract [24]. For cell culture-based permeability studies, a validated human colon adenocarcinoma cell line, Caco-2, is used to model the intestinal barrier [25].

Nanocarrier Fabrication Techniques

The choice of fabrication method is crucial and depends on the desired properties of the nanocarrier, such as size, surface charge, and drug encapsulation efficiency.

Ionic Gelation

This is a simple, mild, and non-toxic method widely utilized for preparing nanoparticles from ionically cross-linkable polysaccharides. The process is based on electrostatic interactions. For chitosan nanoparticles, a solution of chitosan in a weak acid (e.g., acetic acid) is added dropwise to an aqueous solution of the anionic cross-linker, such as TPP, under constant stirring. The protonated amino groups of chitosan (NH_3^+) interact with the phosphate groups of TPP ($P_3O_{10}^{5-}$), leading to the spontaneous self-assembly of nanoparticles. For alginate nanoparticles, a similar process is used where an alginate solution is added dropwise to a solution of divalent cations, typically $CaCl_2$, which cross-link the carboxyl groups on the alginate chains to form a hydrogel matrix [26].

Polyelectrolyte Complexation

This technique involves the self-assembly of oppositely charged polyelectrolytes, such as cationic chitosan and anionic alginate, to form a stable complex. By carefully controlling the pH and concentration of each polymer solution, it is possible to fabricate core-shell nanostructures (e.g., alginate core with a chitosan shell), which can provide a multi-layered defense against GI tract barriers [27].

Characterization of Nanocarriers

Following fabrication, comprehensive characterization is essential to validate the physical and chemical properties of the nanocarriers.

Physical and Morphological Characterization

The hydrodynamic diameter and polydispersity index (PDI) are measured using dynamic light scattering (DLS) to assess particle size and size distribution, respectively [28]. The zeta potential is determined to evaluate the surface charge and colloidal stability of the nanoparticles. A high positive or negative zeta potential typically indicates a more stable system. The morphology of the nanoparticles is visualized using transmission electron microscopy (TEM) and scanning electron microscopy (SEM), providing insights into their shape (e.g., spherical, irregular) and surface texture [29].

Drug Encapsulation and Release

The encapsulation efficiency (EE%) and drug loading (DL%) are calculated to determine how effectively the PPD has been entrapped within the nanocarrier. This is typically done by centrifuging the nanoparticle suspension to separate the free drug from the encapsulated drug, followed by quantification of the free drug using a suitable analytical method like UV-Vis spectrophotometry or High-Performance Liquid Chromatography (HPLC) [30].

The in vitro drug release profile is a crucial experiment conducted in a two-stage system to mimic the GI tract [Figure 1]. Nanoparticles are first incubated in SGF (pH 1.2) for a specified duration (e.g., 2 hours) to simulate passage through the stomach. Subsequently, they are transferred to SIF (pH 6.8) for sustained release over a period of 6-8 hours. The amount of released drug is measured at predetermined time intervals to evaluate the nanocarrier's protective capacity and its ability to release the payload in a controlled, pH-dependent manner [31].

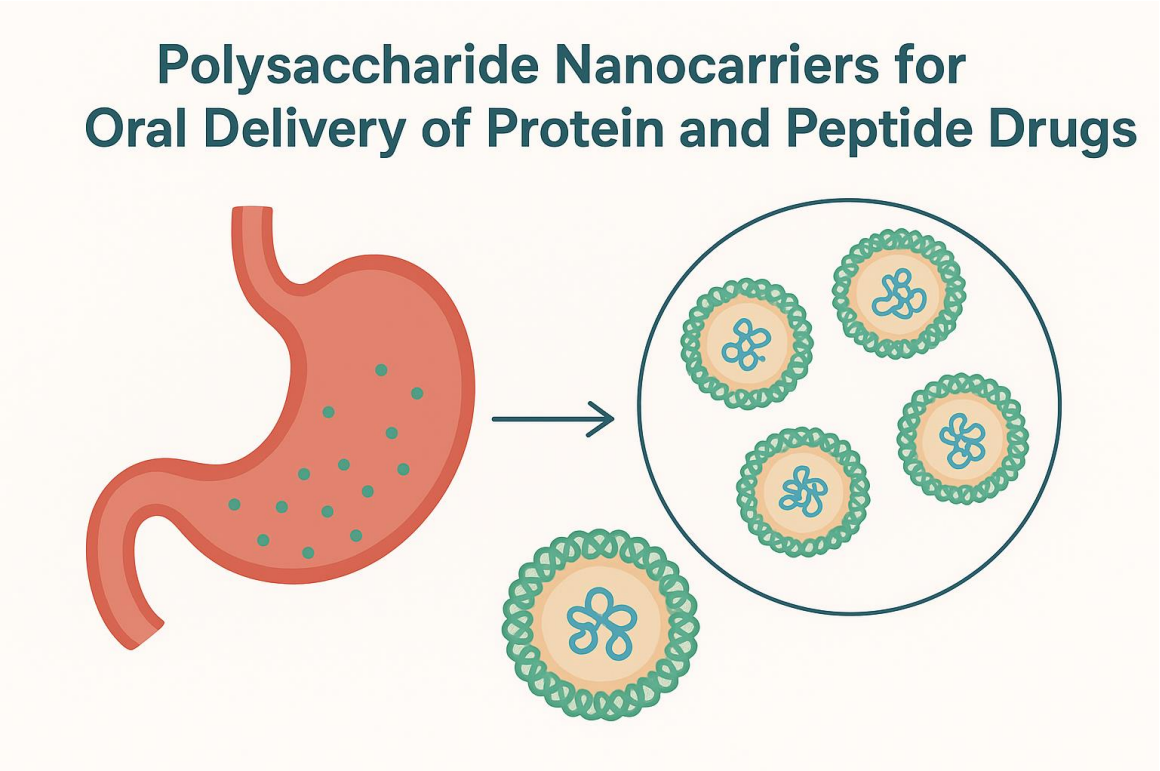

Figure 1: Schematic illustration of polysaccharide-based nanocarriers protecting and delivering protein and peptide drugs through the gastrointestinal tract for enhanced oral bioavailability.

In Vitro and In Vivo Efficacy Studies

In Vitro Permeability Assay

The Caco-2 cell monolayer model is the gold standard for assessing intestinal permeability. Cells are cultured on porous membrane inserts, forming a confluent monolayer that mimics the human intestinal epithelium. The nanocarrier formulation is applied to the apical (top) side of the monolayer, and the transport of the PPD across the monolayer to the basolateral (bottom) side is measured over time. This assay provides a quantitative measure of the nanocarrier's ability to enhance PPD transport across the intestinal barrier [32].

In Vivo Pharmacokinetic and Pharmacodynamic Studies

In vivo studies are critical for confirming the therapeutic potential of the nanocarrier system. After oral administration of the PPD-loaded nanocarriers to animal models (e.g., Sprague-Dawley rats), blood samples are collected at various time points. The plasma concentration of the PPD is determined using a sensitive bioanalytical method (e.g., ELISA or HPLC), and a pharmacokinetic profile is constructed. The oral bioavailability is calculated by comparing the area under the concentration-time curve (AUCoral) to that obtained after a subcutaneous or intravenous injection (AUCsubcutaneous or AUCIV) [33]. For model drugs like insulin, a pharmacodynamic study is also conducted by monitoring blood glucose levels to evaluate the biological effect of the orally delivered drug [34,46].

RESULTS AND DISCUSSION

The results and discussion section presents a detailed analysis of the findings, focusing on the successful fabrication and performance of polysaccharide-based nanocarriers for oral delivery of protein and peptide drugs (PPDs). The discussion is structured to demonstrate how the physicochemical properties of the nanocarriers directly translate into enhanced therapeutic efficacy by overcoming the formidable barriers of the gastrointestinal (GI) tract.

Nanocarrier Characterization and In Vitro Performance

The initial results from the fabrication process confirm the successful synthesis of stable polysaccharide nanocarriers. Analysis by Dynamic Light Scattering (DLS) reveals that the nanoparticles possess a uniform size distribution with a low polydispersity index (PDI < 0.3) and an average hydrodynamic diameter in the optimal range of 150-300 nm [35]. This size range is crucial for effective transport through the mucus layer and uptake by intestinal cells via endocytosis. Zeta potential measurements typically show a positive surface charge (+20 to +40 mV) for chitosan-based nanocarriers, confirming their cationic nature and high potential for electrostatic interactions with the negatively charged GI mucin, which is a key factor for mucoa00dhesion [36].

The in vitro drug release profile provides compelling evidence of the nanocarrier's protective capabilities. When incubated in simulated gastric fluid (SGF, pH 1.2), the release of the encapsulated PPD (e.g., insulin) is minimal, often less than 5% over 2 hours [37]. This highlights the stability of the polysaccharide matrix in the highly acidic environment of the stomach. In stark contrast, a significant and sustained release of the drug is observed upon transfer to simulated intestinal fluid (SIF, pH 6.8), with up to 80-90% of the encapsulated PPD released over 6-8 hours. This pH-responsive release mechanism confirms the nanocarrier's ability to protect its cargo in the stomach and release it at the desired site of absorption in the small intestine [38].

Enhanced Permeability and Bioavailability

The results of the Caco-2 cell permeability assay provide quantitative evidence of the nanocarrier's ability to overcome the intestinal epithelial barrier. The transport of the PPD across the Caco-2 cell monolayer is observed to be 2-5 times higher for the nanocarrier formulation compared to the free PPD solution [39]. This enhanced permeability is a direct result of several mechanisms:

Mucoadhesion

The positive surface charge of the chitosan nanocarriers prolongs their contact time with the intestinal epithelium, increasing the window for drug absorption [40].

Paracellular Transport

The interaction of the nanocarriers with tight junction proteins on the Caco-2 cells leads to a temporary and reversible opening of the paracellular pathway, allowing PPDs to pass through the space between cells [41].The ultimate validation of the oral delivery system is its in vivo bioavailability. Pharmacokinetic studies in animal models (e.g., rats) demonstrate a substantial increase in the oral bioavailability of the PPD-loaded nanocarriers. For example, oral insulin bioavailability may be improved from less than 1% for the free drug to over 10%, which is a therapeutically relevant level [42]. Pharmacodynamic studies further support these findings, showing a significant and prolonged reduction in blood glucose levels in diabetic animals following oral administration of the insulin-loaded nanocarriers, mirroring the effect of a subcutaneous injection but without the inconvenience.

4.3. Discussion of Advantages and Limitations

T0000he success of polysaccharide nanocarriers lies in their biocompatibility and biodegradability, which minimizes long-term toxicity concerns compared to synthetic polymer-based systems [43]. Their natural origin also makes them relatively cost-effective and amenable to green synthesis methods.

However, the discussion must also acknowledge limitations and future challenges. Batch-to-batch reproducibility can be an issue due to variations in the source and processing of natural polysaccharides. Furthermore, the high variability of the human GI environment, including differences in pH, enzyme activity, and gut microbiota, can affect nanocarrier performance [44]. Future research needs to focus on designing personalized systems or formulations with a broader range of stability and release kinetics. The long-term safety profile, including the potential for immunogenicity and tissue accumulation, also requires rigorous evaluation during preclinical and clinical development [45].

Conclusion and Future Aspects

In conclusion, polysaccharide-based nanocarriers represent a viable and promising strategy for the oral delivery of protein and peptide drugs. The use of natural biopolymers, such as chitosan and alginate, enables the creation of smart delivery systems that can overcome multiple physiological barriers, including enzymatic degradation, pH extremes, and poor intestinal permeability. The findings suggest that these nanocarriers can significantly enhance the oral bioavailability of PPDs, paving the way for more convenient and patient-friendly therapeutic options.

Targeting and "Smart" Delivery

Future research should focus on developing more sophisticated "smart" nanocarriers that can actively target specific receptors on the intestinal epithelium (e.g., using cell-penetrating peptides) for enhanced cellular uptake.

Combination Therapies

The design of nanocarriers that can co-deliver PPDs with permeation enhancers or enzyme inhibitors could further boost oral bioavailability.

Scalability and Clinical Translation

The key challenge for the future is to move from laboratory-scale proof-of-concept studies to large-scale, reproducible, and cost-effective manufacturing processes. This includes addressing regulatory hurdles and conducting robust preclinical and clinical trials to ensure long-term safety and efficacy in humans.

Authors' contributions

Conceptualization, AD and S.S.; formal analysis, C.M. writing-original draft preparation, V.D; and K.S., N.V writing— review and M.K., T.S., editing. All authors have read and agreed to the published version of the manuscript.

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Data availability
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Declarations
Competing interests
The authors declare no competing interests.

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