AJPMHS
GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 4, Issue 9, 2026 ISSN (E): 2993-2149

The Role of Chitosan-Based Nanoparticles in Enhancing the Oral Bioavailability of Protein and Peptide Drugs

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Abstract: Insulin, calcitonin, growth hormone, and other peptide-based drugs are currently administered predominantly by injection, since, when taken orally, they lose almost all of their activity owing to the acidic environment of the gastrointestinal tract, proteolytic enzymes, and the epithelial barrier — the absolute oral bioavailability of such preparations is typically below 1%. Chitosan — a natural, biosensitive, and minimally toxic polysaccharide — is being extensively studied as a promising platform for the oral delivery of peptide drugs owing to its cationic nature, mucoadhesive properties, and its ability to transiently open the tight junctions between epithelial cells. This article analyzes the mechanisms by which chitosan nanoparticles protect peptide drugs from enzymatic degradation, adhere to the mucosal layer (mucoadhesion), and enhance absorption via paracellular transport, and it further examines the comparative efficacy of pH-sensitive and ligand-modified chitosan systems. Research on chitosan derivatives conducted at the Institute of Polymer Chemistry and Physics of the Academy of Sciences of the Republic of Uzbekistan is discussed within the national context.

Keywords: chitosan nanoparticles, peptide drugs, oral bioavailability, mucoadhesion, insulin, tight junctions, intestinal epithelial transport

Introduction

Protein and peptide-based drugs — insulin, calcitonin, glucagon-like peptide-1 (GLP-1) analogues, growth hormone, and others — constitute a rapidly developing area of modern pharmacotherapy. However, their large molecular weight, complex three-dimensional structure, and high susceptibility to proteolytic enzymes render oral administration of such preparations nearly impossible. As a result, patients require daily injections for many years, which reduces treatment compliance and adversely affects patients' quality of life [1].

The principal barriers to oral peptide drug delivery manifest in three stages: (1) rapid chemical degradation caused by the acidic environment and proteolytic enzymes (pepsin, trypsin, chymotrypsin) in the gastrointestinal lumen; (2) a diffusion barrier arising from the densely networked structure of the mucus layer, which limits the molecule's access to the epithelium; (3) near-complete blockage of the paracellular transport of hydrophilic macromolecules by the tight junctions of the intestinal epithelium. Nanotechnological approaches, in particular chitosan-based nanoparticles, have been actively investigated in recent decades as a means of overcoming this multilayered barrier system [2].

The advantage of chitosan in peptide drug delivery arises from a combination of several unique properties: strong mucoadhesion through electrostatic binding, via its positively charged amino groups, to the negatively charged mucin (the main component of mucus); the ability to transiently and reversibly open the tight junctions between epithelial cells; and a gel-forming property under low-pH conditions, which partially protects the drug from the acidic environment. In Uzbekistan, research in the field of chitosan chemistry is actively conducted at the Institute of Polymer Chemistry and Physics of the Academy of Sciences of the Republic of Uzbekistan under the leadership of Academician S.Sh. Rashidova, laying the scientific groundwork for the development of a national nanopharmaceutical field [3].

The aim of this article is to provide a systematic analysis of the mechanisms by which chitosan-

based nanoparticles enhance the oral bioavailability of peptide and protein drugs, as well as to address the practical challenges and prospects of their application [4].

Materials and Methods

This work was carried out as a literature review, analyzing scientific articles published between 2012 and 2026 on the ScienceDirect, PubMed/PMC, Springer Nature, and De Gruyter platforms. The search was conducted using the keywords "chitosan nanoparticles," "oral peptide delivery," "oral insulin," "bioavailability," "mucoadhesion," and "tight junction." Sources were selected on the basis of peer-review status, direct relevance to the topic, and experimental or theoretical validity. The selected works were analyzed by grouping them thematically according to mechanism (mucoadhesion, paracellular transport, enzymatic protection, ligand-directed delivery).

Results and Discussion

Results

Biological barriers to oral peptide drug delivery

After oral administration, a peptide drug must overcome several sequential biological barriers to reach the systemic circulation (Figure 1). In the first stage, the drug molecule undergoes rapid hydrolysis in the acidic and enzymatically active environment of the stomach and small intestine. Molecules that survive this stage encounter the mucus layer — which acts not only as a physical diffusion barrier but also as a selective filter with respect to molecular size, owing to the narrow pores between mucin fibers. Finally, molecules that pass through the mucus layer encounter the tight junctions between epithelial cells, which almost completely block the paracellular passage of hydrophilic, high-molecular-weight substances. As a result, the absolute oral bioavailability of a free peptide drug — for example, insulin — is typically below 1% [5].

Figure 1. Biological barriers along the pathway of orally administered peptide drugs and their circumvention by chitosan nanoparticles.

Mechanism of action of chitosan nanoparticles

Chitosan nanoparticles act through several parallel mechanisms, each directed at overcoming one of the barriers described above (Figure 2). First, the polycationic nature of chitosan enables strong electrostatic binding — mucoadhesion — with mucin glycoproteins, the main component of the mucus layer; this prolongs the residence time of the nanoparticle near the intestinal wall and thereby increases the local drug concentration. Second, chitosan molecules transiently reorganize the tight-junction proteins between epithelial cells (such as occludin and claudins), opening the paracellular pathway; this effect is reversible, with the junctions typically restoring within a few hours, thereby minimizing the risk of long-term membrane damage. Third, the polymer matrix physically isolates the peptide drug from proteolytic enzymes, significantly increasing its chemical stability within the gastrointestinal tract [6].

Figure 2. Mechanism by which chitosan nanoparticles enhance peptide drug absorption through mucoadhesion and the transient opening of tight junctions.

Unmodified chitosan generally shows limited efficacy when used alone, since its solubility and positive charge decrease at neutral pH (in the distal regions of the intestine). For this reason, current research frequently modifies chitosan with pH-sensitive polymers (for example, poly(methacrylic acid)) or targeting ligands (for example, cell-penetrating peptides, PAMAM dendrimers), enabling the nanoparticle to become selectively activated in the desired region of the intestine and further increasing absorption efficiency [7].

Schematic indicators of the effect on bioavailability

A conceptual model summarizing the research findings reported in the literature shows that, in the case of insulin, a free orally administered preparation produces almost no measurable effect on blood glucose levels, whereas insulin encapsulated in chitosan nanoparticles produces a moderate but prolonged hypoglycemic effect — an effect that, unlike the rapid and pronounced action of injected insulin, has a slower onset and a longer duration (Figure 3). This difference is explained by the gradual dissolution and absorption of the chitosan-NP system within the intestine [8, 9].

Figure 3. Schematic comparison (a conceptual model summarized from the literature) of the effect

on blood glucose levels for injected insulin, free oral insulin, and chitosan-NP-based oral insulin.

Chitosan modification strategies

Various modification strategies have been developed to further enhance the efficacy of chitosan nanoparticles, summarized in Table 1 below. Systems functionalized with PAMAM dendrimers or cell-penetrating peptides enhance absorption through receptor-targeted or active transport, while pH-sensitive coatings ensure selective drug release in the desired segment of the intestine. Systems forming complexes with hyaluronic acid serve to overcome several absorption barriers simultaneously [10], [11].

Table 1. Chitosan nanoparticle modification strategies and their outcomes

Modification type	Mechanism	Result achieved	Model peptide/protein
Chitosan–PEG–poly(methacrylic acid) nanoparticles	pH-sensitive coating, selective dissolution in the intestine	High encapsulation efficiency (~99%), intestine-targeted release	Insulin
PAMAM–chitosan core–shell system	Targeted absorption via ligand–receptor interaction	Significant increase in relative bioavailability, low systemic toxicity	Insulin (diabetic model)
Functionalization with a cell-penetrating peptide (CPP)	Active transport across the epithelial membrane	~20-fold higher absorption compared with free insulin	Insulin
Chitosan–hyaluronic acid complex nanoparticles	Multilayer protection: mucoadhesion + enzymatic protection	Simultaneous overcoming of several absorption barriers	Insulin

Discussion

Several challenges remain in translating chitosan-based peptide delivery systems into clinical practice. First, the high bioavailability observed in vitro and in animal studies may not always be reproduced in humans, since the physiological parameters of the human gastrointestinal tract (pH gradient, enzyme activity, transit time) differ from those of laboratory animals [12], [13]. Second, the long-term safety of the tight-junction-opening mechanism, particularly with chronic use, requires further investigation — in principle, this mechanism could facilitate the passage not only of drug molecules but also of undesirable substances (allergens, pathogens). Third, ensuring consistent day-to-day dosing accuracy of the formulation remains a technologically complex issue. At the same time, the development of ligand-directed and stimuli-responsive chitosan systems, as well as the use of artificial intelligence for formulation optimization, are regarded as promising future directions [14], [15].

Conclusions

The analysis conducted shows that chitosan-based nanoparticles are capable of substantially enhancing the oral bioavailability of peptide and protein drugs. This effect arises from the combined action of three mechanisms of chitosan — retention at the intestinal wall through mucoadhesion, enhanced paracellular absorption through the transient opening of tight junctions, and protection from enzymatic degradation via the polymer matrix. The efficacy of these systems can be further enhanced through additional modification with pH-sensitive coatings and targeting ligands. At the same time, broader clinical translation requires further research into safety and dosing accuracy in the human body. The existing scientific potential in the field of chitosan chemistry in Uzbekistan (the Institute of Polymer Chemistry and Physics of the Uzbekistan Academy of Sciences) can serve as a promising foundation for the national development of this field.

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