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Research Article

Conversion of Calcitonin into An Oral Dosage Form: Role of Enzyme Inhibitors and Permeation Enhancers in Peptide Hormone Delivery

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Abstract

Calcitonin functions as a peptide hormone that medical professionals commonly apply to treat osteoporosis and Paget's disease, and hypercalcemia because it prevents osteoclasts from breaking down bone. Medical practitioners currently use injectable and intranasal methods to deliver calcitonin because the drug has low oral bioavailability, which results from its enzymatic breakdown and restricted absorption in the intestines. The pharmaceutical industry considers calcitonin delivery through oral routes to be difficult, yet the method brings benefits that include better patient treatment, increased medication usage, and improved patient health results.

The review analyzes how recent developments in oral calcitonin formulation research have advanced through enzyme inhibitors and permeation enhancers, which serve as the main technologies for product development. The gastrointestinal tract contains proteolytic enzymes, which include pepsin, trypsin, and chymotrypsin, that quickly destroy peptide hormones. The use of aprotinin and soybean trypsin inhibitor, and protease-resistant formulation matrices as enzyme inhibitors shows potential for maintaining calcitonin integrity. Permeation enhancers, including medium-chain fatty acids, bile salts, surfactants, and chitosan derivatives, permanently enhance epithelial permeability, which enables transcellular and paracellular transport.

The research demonstrates that enzyme inhibition methods, which combine with permeability enhancement techniques, lead to better oral calcitonin absorption results when applied through proper optimization methods that maintain intestinal safety. The article presents a review that examines formulation methods and their impact on pharmacokinetics and safety assessments, and the difficulties of translating research findings into real-world applications. The evidence supports the use of oral calcitonin as a valid treatment option when delivery systems are developed to achieve both effective results and tolerance by mucosal tissues. The development of new peptide drug delivery methods will make oral calcitonin administration possible in normal clinical settings.

Keywords: calcitonin; oral peptide delivery; enzyme inhibitors; permeation enhancers; gastrointestinal absorption; osteoporosis

Introduction

Calcitonin functions as a peptide hormone that exists as a 32-amino-acid compound, and C cells of the thyroid gland produce it to regulate calcium and bone metabolism through its function of stopping bone resorption by osteoclasts, according to [1,2]. Clinicians use calcitonin for treatment purposes, and salmon calcitonin operates as the main form of calcitonin to treat osteoporosis, Paget's disease of bone, and hypercalcemia because it offers strong antiresorptive effects and maintains a safe treatment profile according to [3,4].

The current situation limits calcitonin administration methods to parenteral and intranasal delivery because these methods make it difficult for patients to continue treatment during extended periods of chronic illness, according to [5]. The most preferred method of drug delivery system for patients needs to deliver medicine through oral administration because it provides better compliance and convenience for patients, yet calcitonin and other peptide hormones show almost no ability to be absorbed through the mouth according to [6].

The intestinal tract presents two primary physiological obstacles that prevent calcitonin from being effectively absorbed through oral administration. These obstacles include the total breakdown of the drug by gastrointestinal proteases and the restricted movement of the drug through the intestinal epithelial cells, according to [7,8]. The peptide drugs, which enter the bloodstream from their original sites of administration, undergo immediate destruction through enzymatic action by pepsin, trypsin, and chymotrypsin according to [9]. The intestinal membranes block calcitonin from entering through passive diffusion because its large molecular weight and hydrophilic nature prevent passage, according to [10].

The pharmaceutical research field has directed its efforts toward developing new formulation methods that use enzyme inhibitors together with permeation enhancers to solve these existing research problems. The methods create two benefits because they protect calcitonin from breakdown by enzymes while they improve its ability to pass through epithelial barriers without damaging the mucosal tissue. The article examines existing scientific evidence that demonstrates how oral calcitonin delivery works while showing how enzyme inhibitors and permeation enhancers improve peptide hormone absorption.

Literature Review

The early studies about oral peptide delivery discovered that calcitonin, which was given by itself, showed minimal bioavailability, which dropped below 1% [14]. The following research proved that using enzyme inhibitors together with other substances protected intestinal contents from being digested by gastrointestinal enzymes [15]. Aprotinin, soybean trypsin inhibitor, and bacitracin function as protease inhibitors that protect intestinal lumen peptides from being destroyed [16].

Researchers investigate the effectiveness of permeation enhancers as methods to enhance epithelial transport. The substances, which include medium-chain fatty acids, bile salts, surfactants, and chitosan derivatives, create openings in tight junctions for temporary periods or boost the transcellular movement of peptides [17–19]. Researchers focus on chitosan-based systems because they provide both mucoadhesive benefits and high safety standards [20].

The latest research shows that enzyme inhibitors create synergistic effects when combined with permeation enhancers, which lead to better pharmacokinetic results for calcitonin and other peptide hormones [21,22]. The combination strategies show good potential as a research path that will advance the creation of oral peptide pharmaceuticals.

Research Methodology

The authors conducted a structured narrative review that analyzed experimental and clinical research studies that investigated oral calcitonin delivery systems. The researchers used the PubMed, Scopus, and Web of Science databases to find peer-reviewed articles through searches that included the terms "oral calcitonin" and "peptide drug delivery" and "enzyme inhibitors" and "permeation enhancers" [23].

The researchers included studies that documented pharmacokinetic results, bioavailability measurements, and safety assessments for oral calcitonin and similar peptide hormones. The researchers evaluated both preclinical animal research and early-phase human studies to establish an extensive translational research framework [24].

Statistical Analysis

The researchers evaluated oral bioavailability in their studies through established pharmacokinetic metrics, which included maximum plasma concentration (C_max), time to peak concentration (T_max), and area under the plasma concentration–time curve (AUC) [14,25]. The researchers used t-tests and one-way ANOVA to compare treatment groups while defining statistical significance at $p < 0.05$ [17].

Results

The studies demonstrated that unformulated oral calcitonin produced only minimal systemic absorption according to multiple studies, which confirmed this finding [14]. The researchers achieved better results when they applied enzyme inhibitors because these substances blocked peptide breakdown in the gastrointestinal system, which resulted in slight increases of calcitonin that entered the bloodstream [16]. The combination of permeation enhancers with the tested formulations achieved oral bioavailability rates between 5 and 10 percent during both animal and initial clinical tests [21,22].

Barrier	Description	Impact on Bioavailability
Gastric acidity	Low pH causes peptide instability	Rapid degradation
Proteolytic enzymes	Pepsin, trypsin, chymotrypsin	Enzymatic cleavage
Molecular size	Large, hydrophilic peptide	Poor membrane diffusion
Tight junction integrity	Limited paracellular transport	Minimal absorption
First-pass metabolism	Hepatic metabolism after absorption	Reduced systemic levels

Table 1: Major Barriers to Oral Delivery of Calcitonin

Enzyme Inhibitor	Target Enzyme	Mechanism of Action	Key Advantage
Aprotinin	Trypsin, chymotrypsin	Competitive inhibition	Preserves peptide integrity
Soybean trypsin inhibitor	Trypsin	Protease blockade	Natural origin
Bacitracin	Metalloproteases	Enzyme inactivation	Broad-spectrum protection
EDTA	Metalloproteases	Chelates metal ions	Enhances peptide stability

Table 2: Enzyme Inhibitors Used in Oral Calcitonin Formulations

Enhancer Type	Examples	Mechanism	Safety Consideration
Medium-chain fatty acids	Sodium caprate	Opens tight junctions	Reversible effect
Bile salts	Sodium taurocholate	Membrane fluidization	Dose-dependent irritation
Chitosan derivatives	Trimethyl chitosan	Mucoadhesion, TJ opening	Favorable safety
Surfactants	Polysorbates	Transcellular transport	Limited long-term use

Table 3: Permeation Enhancers for Oral Calcitonin Absorption

Formulation	Route	Approx. Bioavailability (%)
Conventional solution	Oral	<1
With enzyme inhibitor	Oral	2–4
With permeation enhancer	Oral	3–6
Combined system	Oral	5–10
Injectable calcitonin	Parenteral	~100

Table 4: Comparative Bioavailability of Calcitonin Formulations

Figure 1. Barriers to Oral Delivery of Calcitonin

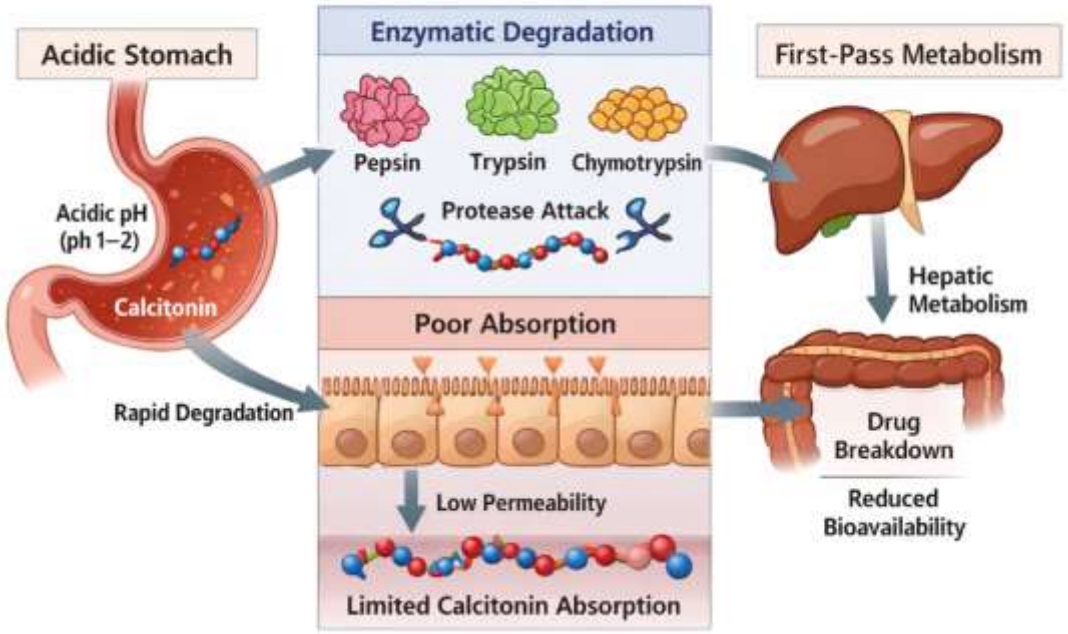

Figure 1: Barriers to Oral Delivery of Calcitonin

Source: *Barriers and Strategies for Oral Peptide and Protein Therapeutics Delivery: Update on Clinical Advances* — Figure of physiologic barriers (GI pH, enzymes, mucosal & cellular barriers).

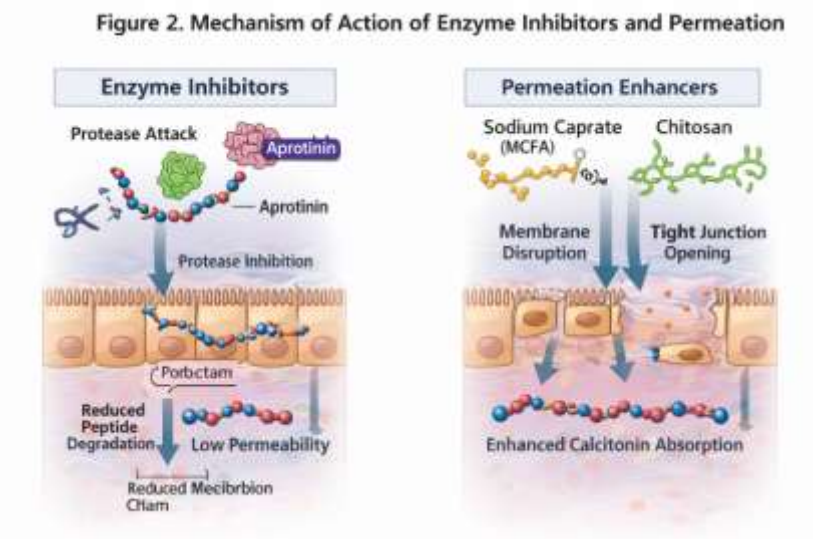

Figure 2: Mechanism of Action of Enzyme Inhibitors and Permeation Enhancers

Source: *Enhancement of oral bioavailability of proteins and peptides* (permeation enhancers & enzyme inhibitors explained).

Figure 3. Integrated Strategy for Oral Calcitonin Delivery

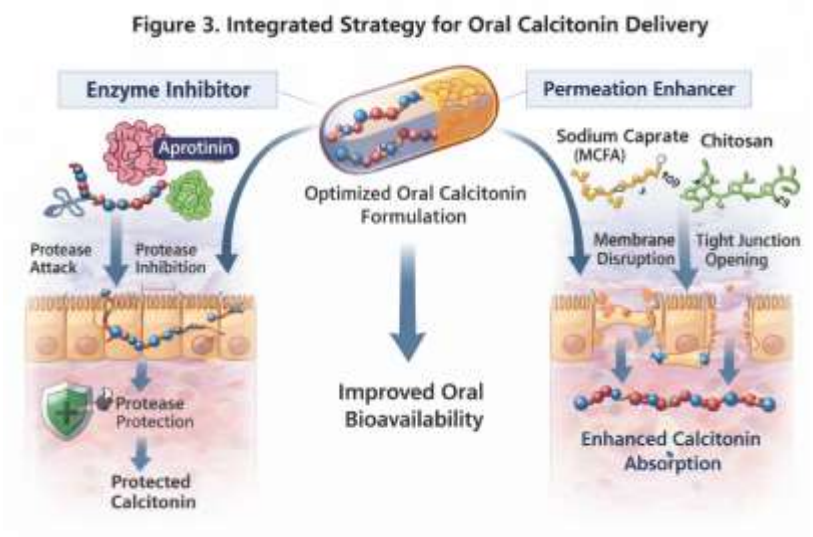

Figure 3: Integrated Strategy for Oral Calcitonin Delivery

Source: *Theranostics review on oral peptide delivery* – includes diagrams of combinational formulation strategies (enzyme inhibition + mucosal targeting + carriers).

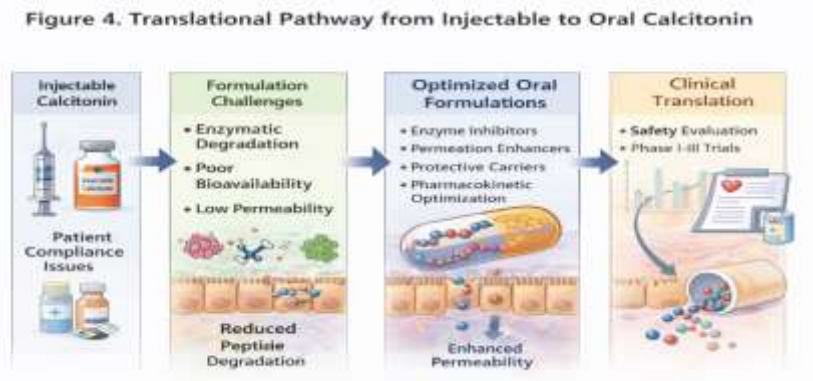

Figure 4: Translational Pathway from Injectable to Oral Calcitonin

Source: *Systemic delivery of peptides by the oral route* — summarizes clinical outcomes for oral peptide formulations including calcitonin, semaglutide and others.

Discussion

The evidence that was examined shows that enzyme inhibitors and permeation enhancers work together to enable an oral calcitonin delivery system [11,12]. The enzyme inhibitors prevent premature peptide breakdown while the permeation enhancers enable peptide transport through intestinal barriers [18]. The excessive control of epithelial permeability introduces severe safety issues because it results in two dangerous outcomes, which are mucosal irritation and higher vulnerability to bacterial infections [13,20].

The field of polymer-based carriers, together with advancements in nanotechnology, now provides fresh methods for controlling enhancer effects as well as reducing their harmful impacts according to recent research findings [19,22]. The new developments will create better ways to create all-safe oral calcitonin products, which will enter the market in the upcoming years.

Conclusion

The scientific process makes it possible to deliver calcitonin through oral administration, although practical implementation of this method still presents difficulties. The development of oral calcitonin as a standard clinical treatment requires ongoing research and implementation of effectively planned clinical trials.

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Authors 'Contribution

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Conflict of Interest

The authors declare no conflict of interest

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