Review Article

Nanoparticle-based Drug Delivery in Celiac Disease

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ABSTRACT

Celiac disease is a chronic autoimmune enteropathy triggered by the ingestion of dietary gluten in genetically predisposed individuals, resulting in the progressive atrophy of the intestinal villi. At present, the only standard of care is a strict, lifelong gluten-free diet, a treatment often compromised by inadvertent cross-contamination and associated nutritional deficiencies. Conventional oral therapeutics are rapidly degraded by gastric acids, face large transport barriers across the dense intestinal mucus layer, or induce dose-limiting systemic toxicities. This review discusses the role of engineered nanomedicines to overcome these physiological barriers for targeted therapeutic delivery. We review oral delivery systems, including luminally active silica nanocomposites for enzymatic degradation of immunogenic gluten peptides in the duodenum and multi-layered polymeric networks for localized gene delivery to intestinal epithelium to suppress local inflammatory cascades. We also examine intravenous platforms utilizing biodegradable nanoparticles designed to evade the mononuclear phagocyte system (MPS). These systemic carriers transport gluten antigens directly to antigen-presenting cells in the liver and spleen to induce antigen-specific immune tolerance. Current data demonstrate high efficacy in preclinical murine models, and proof-of-concept human clinical trial data (limited to the TAK-101 platform) show a significant reduction in gluten-driven inflammation and preservation of villous architecture. Finally, the translational trajectory for these therapeutics is discussed, emphasizing the manufacturing scale-up, long-term biocompatibility profiling, and the need for tailored pharmacokinetic modeling.

Keywords: Celiac disease; Nanomedicine; Targeted drug delivery; Immune tolerance; Mucosal gene silencing.

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INTRODUCTION

Celiac disease (CD) is a chronic, systemic autoimmune illness characterized by severe inflammation of the small intestine mucosa in response to the consumption of dietary gluten. The etiology of CD is exclusively related to genetic predisposition, specifically the expression of human leukocyte antigen (HLA) class II molecules HLA-DQ2 and HLA-DQ8, which coordinate the pathogenic immune response in affected individuals. The global prevalence of CD is estimated to be 0.7% using biopsy-confirmed cases and 1.4% using serological screening, but comprehensive epidemiological data show a significant increase in the global incidence of CD over time due to the complex interplay of genetic susceptibility, environmental changes, and patterns of gluten exposure (1, 2).

The clinical signs and symptoms of CD include a wide spectrum of typical gastrointestinal symptoms, including chronic stomach pain, malabsorptive diarrhea, and gradual weight loss. Extra-intestinal systemic complications are also increasingly diagnosed (for instance, refractory anemia, accelerated osteoporosis, autoimmune liver damage, neurological deficits, and dermatitis herpetiformis), revealing the systemic burden of the disease (3, 4). At the macromolecular level, gluten consists of two protein fractions, prolamin (gliadin) and glutelin (glutenin), with the gliadin component being the main driver of toxicity. The unique fundamental structure of alpha-gliadin is extremely rich in proline and glutamine residues, which sterically hinders complete proteolysis by gastric, pancreatic, and brush-border endopeptidases within the intestinal lumen (3). As a result, large, intact immunogenic peptide fragments are resistant to digestion, particularly the cytotoxic p31–43 fragment and the highly immunogenic 33-mer peptide. These fragments pass through the damaged epithelial barrier to the lamina propria. The enzyme tissue transglutaminase 2 (TG2) deamidates neutral glutamine residues to negatively charged glutamic acid primarily upon entry into the subepithelial space. This modified charge enables the deamidated peptides to have extremely high affinity for the peptide-binding grooves of HLA-DQ2 and HLA-DQ8 molecules located on the surface of antigen-presenting cells (APCs). This initiates the activation and proliferation of antigen-specific CD4+ T helper cells, which then coordinate a cascade of inflammatory cytokines, including interferon-gamma (IFN-gamma), tumor necrosis factor-alpha (TNF-alpha), interleukin-2 (IL-2), interleukin-21 (IL-21), and interleukin-15 (IL-15). In the meantime, the overproduction of these cytokines promotes the recruitment and intraepithelial migration of cytotoxic CD8+ T cells, finally resulting in severe enterocyte death, crypt hyperplasia, and entire villous atrophy (3, 5, 6).

The only clinically recognized treatment for people with CD so far is a strict, lifelong gluten-free diet (GFD). Although a GFD can result in mucosal healing and symptomatic relief in some patients, it is being increasingly recognized as a suboptimal and burdensome intervention because of variable gluten sensitivity and unforeseen cross-contamination of foods (especially commercially packaged foods) (7, 8). In addition, people have different thresholds of sensitivity; for example, little amounts of gluten (< 1 mg) may trigger serious clinical and histological relapses. Besides being variable in therapeutic efficacy, lifelong GFD has significant negative impacts on patients' quality of life, including severe psychosocial restrictions, nutritional deficiencies, and a significant lifelong financial burden due to the high cost and limited accessibility of certified gluten-free foods (9). In reality, full management of daily gluten intake is still very challenging due to the presence of gluten in many products from the harvest phase up to the cooking phase, as well as high marketplace costs and limited access to safe dining options (3). Therefore, these restrictions have encouraged scientists to look for other treatment techniques, such as modifying gluten metabolism, inhibiting gluten-induced immune responses, or achieving sustained systemic immunological tolerance to gluten (10). The active pharmaceutical pipeline is focused on non-dietary therapeutic candidates designed to modulate luminal gluten processing, prevent the subsequent autoimmune cascade, or restore systemic immunological tolerance in a lasting manner to overcome the severe restrictions of a rigid dietary regime (10, 11). This clinical pathway includes oral enzymatic therapies such as TAK-062, engineered to proteolytically cleave immunogenic gluten fragments in the gastric cavity, tight-junction regulators such as Larazotide acetate to maintain epithelial barrier integrity, and targeted small-molecule inhibitors such as ZED1227 to block tissue transglutaminase 2 activity in the subepithelial space (12, 13). In addition, systemic biologicals have advanced through clinical assessment, notably the anti-interleukin-15 (anti-IL-15) monoclonal antibody AMG 714 (PRV-015), which showed attenuation of gluten-induced mucosal inflammation and symptom reduction in peer-reviewed Phase 2a human trials (14, 15). The unmodified pharmacological substances are therapeutically promising but confront significant physiological challenges in the human body (11, 13). Orally-administered enzymes and peptides are rapidly inactivated by proteolysis in the extremely acidic gastric fluids (pH 1.2-2.0), and small molecules and biologics cannot pass through the thick, negatively charged intestinal mucus layer to reach their cellular targets (13). Systemic delivery of bare immunomodulators or soluble antigens

also suffers from high off-target toxicities, rapid clearance from the bloodstream, or severe systemic immune responses, such as the massive interleukin-2 spikes that halted bare gluten-peptide trials (16). In light of these failures, engineered nanomaterials have emerged as a fundamental paradigm shift that can protect and actively target these new medicines (11). In fact, nanoparticles are designed to be active, targeted defenses rather than passive medication carriers. Nanoparticles can be made in different sizes, have a high surface-to-volume ratio, and their surface charges can be engineered. In oral delivery applications, advanced polymer and silica matrices protect delicate enzymes, small molecules, or nucleic acids from harsh gastric conditions, using localized physiological triggers such as pancreatic lipases or electrostatic mucosal attraction to release their payloads directly against the duodenal wall (14, 16, 17). Systemically administered polymeric nanoparticles can deliver immunogenic antigens directly to specific scavenger receptors in the liver and spleen when given intravenously, thereby evading circulating white blood cells and safety resetting antigen-specific immune tolerance without triggering a widespread immune alert (16,18). Nanomedicine addresses the crucial pharmacokinetics, stability, and transport obstacles that confound raw medicines, bridging the significant gap between theoretical molecular targets and safe, clinically feasible celiac therapy (11, 13).

Pathophysiological cascade of CD and molecular targets of novel pharmacological approaches are summarized in Figure 1 (19).

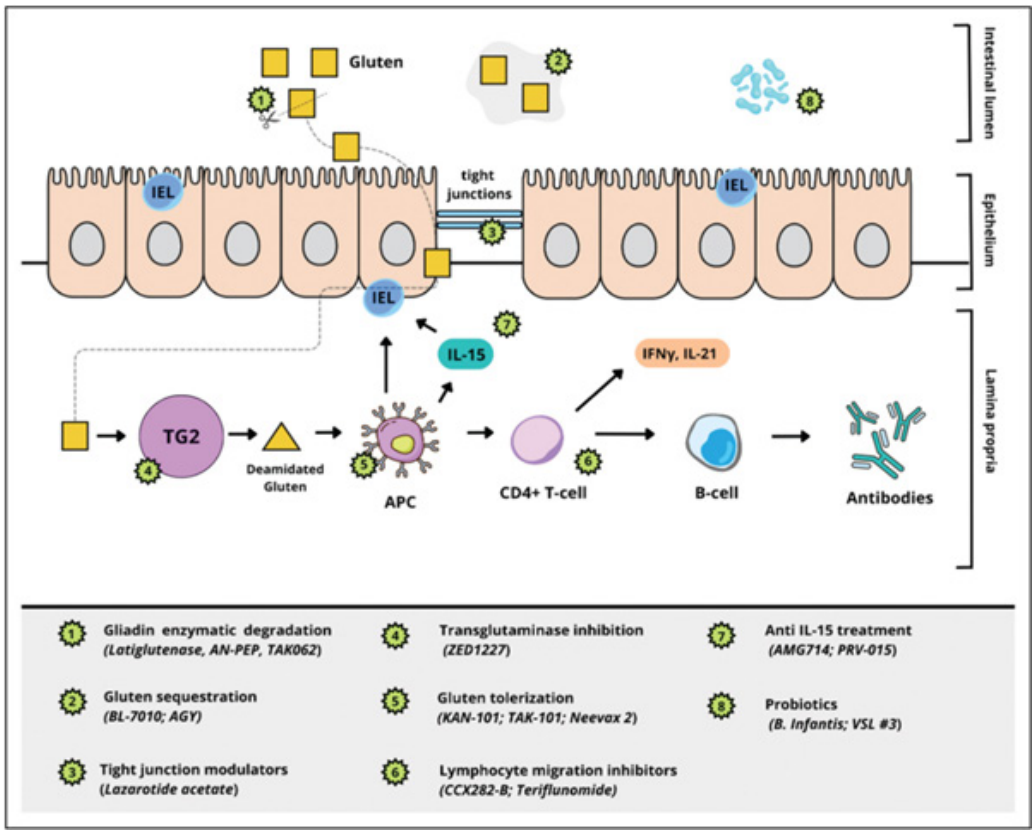

Figure 1. Pathophysiological cascade of celiac disease and molecular targets of novel pharmacological approaches. Gluten in the diet is resistant to human digestion and releases immunogenic gliadin fragments that cross the epithelial barrier to the lamina propria. These fragments are deamidated by tissue transglutaminase 2, allowing for tight binding to HLA-DQ2/8 receptors on antigen-presenting cells and activation of gluten-specific CD4+ T cells. This results in a spontaneous cytotoxic response mediated by IL-15 and an adaptive immune response that is pro-inflammatory and leads to activation of intraepithelial lymphocytes (IELs) and villous atrophy. Therapeutic interventions that interrupt this cascade are indicated by numbered labels: (1) Gliadin Enzymatic Degradation: luminal gluten degradation by oral proteases (AN-PEP, Latiglutenase, TAK-062); (2) Gluten (3) Sequestration uses non-absorbable polymers (BL-7010, AGY) to bind gluten and inhibit absorption; (3) Tight Junction Modulators (Larazotide acetate) close epithelial junctions to prevent paracellular translocation; (4) Transglutaminase Inhibitors (ZED1227/TAK-227) block gliadin deamidation to prevent APC activation; (5) Gluten Tolerization uses nanoparticles (TAK-101), polymers (KAN-101) or epitopes (Nexvax2) to induce immune anergy; (6) Lymphocyte Migration Inhibitors (CCX282-B, Teriflunomide) block cell homing to inflamed tissue; (7) Anti-IL-15 Treatment (AMG714, PRV-015) neutralizes innate cytokines to halt enterocyte destruction; and (8) Probiotics (VSL#3, Bifidobacterium infantis NLS) help with luminal peptide hydrolysis and return microbiome homeostasis. Adapted from Santonicola et al. (19)

Literature Search Methodology

A literature search was conducted to synthesize the available evidence on the applications of nanomedicine in CD. The search strategy was designed to maximize transparency and comprehensiveness within the scope of this emerging field, rather than to serve as a formal systematic review protocol. The primary literature was sourced from two major electronic databases, PubMed/MEDLINE and Science Direct. A supplementary search engine, Google Scholar, was used to provide comprehensive coverage and to track secondary citations. The search strategy was based on Boolean operators between nanomedicine parameters and CD terminology: ("celiac" OR "coeliac") AND ("nano" OR "nanoparticle" OR "nanomedicine" OR "nanodrug" OR "nano platform" OR "drug delivery"). Targeted searches using the modifier ("clinical trial") were performed to identify translational human data and advanced-stage platforms. The search did not have formal date restrictions, but priority was given to literature published from 2020 onwards to reflect recent advances in nanomedicine research, and older foundational studies were included when directly relevant to the mechanistic or historical context of the field. Studies were selected by strict inclusion and exclusion criteria. Articles were included if they met all of the following: (1) were published in English; (2) explicitly discussed the engineering, characterization, or application of a nanotechnology-based delivery system or biomaterial; and (3) directly addressed the pathogenesis, diagnostic targeting, or therapeutic management of CD. Articles were excluded if they studied conventional treatment strategies without a nanoscale material component or studied gastrointestinal or autoimmune diseases not directly associated with celiac disease models. Non-peer-reviewed preprints and standalone conference abstracts were also excluded to maintain standards of evidence. The amount of eligible literature was limited due to the novelty of research on nanomedicine applied to celiac disease. Therefore, all studies that met the inclusion criteria were included in the review, with no further prioritization or exclusion based on date, impact factor, or study design hierarchy. The inclusion of all available evidence reflects the field's early stage and underscores the need for further research.

Nanoparticle Integrated Delivery Systems

Emerging nanotechnology has provided a novel therapeutic paradigm for CD treatment, shifting the strategy from passive dietary management to active, molecularly targeted intervention. Engineered nanomedicines are designed to reach different anatomic routes to effectively block the celiac pathogenic cascade, resulting in two main therapeutic modalities: non-systemic local platforms and systemic tolerogenic networks. Non-systemic approaches employ local oral nanocarriers that act within the gastrointestinal tract, using physiological cues to inactivate toxic gluten fragments or silence inflammatory cytokines in the mucosal wall. Conversely, systemic approaches use biomimetic nanoparticles that are intravenously administered and avoid circulatory immune surveillance. These platforms actively target antigen-presenting cells within the liver and spleen, inducing antigen-specific immune tolerance. reprogramming pathogenic immune memory. Together, these complementary nanoscale strategies offer a powerful platform to overcome the physiological barriers that have historically hindered the development of conventional celiac pharmaceuticals.

Non-Systemic Gastrointestinal Nanomedicine: From Luminal Enzymatic Deactivation to Mucosal Gene Silencing

Developing local therapies for CD faces a primary challenge: the harsh, degradative environment of the gastrointestinal (GI) tract. When administered orally, protein enzymes are rapidly denatured by gastric acid (pH 1.2-2.0) and pepsin, and unprotected nucleic acids such as small interfering RNA (siRNA) undergo rapid degradation by luminal nucleases and are hindered by a thick, negatively charged intestinal mucus barrier.

To overcome these physiological limitations, nanomaterials are engineered as physical shields to protect sensitive therapeutic payloads from premature degradation and to exploit local physiological triggers, such as pancreatic lipases or cellular endocytic pathways, to deliver therapies directly to the duodenal lumen and mucosa. This is a non-systemic approach that aims to intercept the disease drivers locally before initiation of the inflammatory cascade.

Engineered Silica Nanocomposites for Luminal Enzymatic Deactivation

The earliest stage of celiac pathogenesis begins directly within the intestinal lumen, where the incomplete digestion of wheat gluten leaves behind highly stable, immunogenic 33-mer gliadin fragments. Silica-based nanomaterials provide a robust, rigid matrix that stabilizes protective proteases directly within this fluid cavity.

For this purpose, researchers designed bromelain-loaded nanocomposites (BLNCs), based on spherical silica nanoparticles (~72.5 nm) as a core with a coating of a bio-inspired layer of poly-L-DOPA (10). The role of the polymer coating was to provide rich functional surface groups that stably bind the plant protease bromelain while preserving its catalytic conformation. The silica core served as a physical shield, protecting the immobilized bromelain from peptic cleavage in the stomach, ensuring the enzyme arrived fully active in the duodenum. Upon reaching the

duodenal lumen, the immobilized enzymes actively cleave the immunogenic peptide bonds of gliadin, breaking down the large proteins into non-toxic fragments before they can reach epithelial receptors.

In vitro evaluation was performed on the human colon adenocarcinoma cell line (Caco-2) co-cultured with peripheral blood mononuclear cells (PBMCs) isolated from celiac patients. The results demonstrated that BLNC treatment at an optimal concentration of 20 mg/mL achieved complete enzymatic digestion of toxic gliadin. By degrading these fragments in the lumen, the nanocomposites successfully halt the activation of epithelial chemokine receptors. Specifically, the expression of CXCR3 and CCR5, which normally spikes 6.14-fold upon raw gluten exposure, is suppressed to a baseline level of 0.34-fold. This localized intervention prevents downstream enterocyte cytotoxicity and significantly abrogates the secretion of inflammatory cytokines by patient PBMCs. Characterization and analysis of the anti-inflammatory activity of BLNCs are provided in Figure 2.

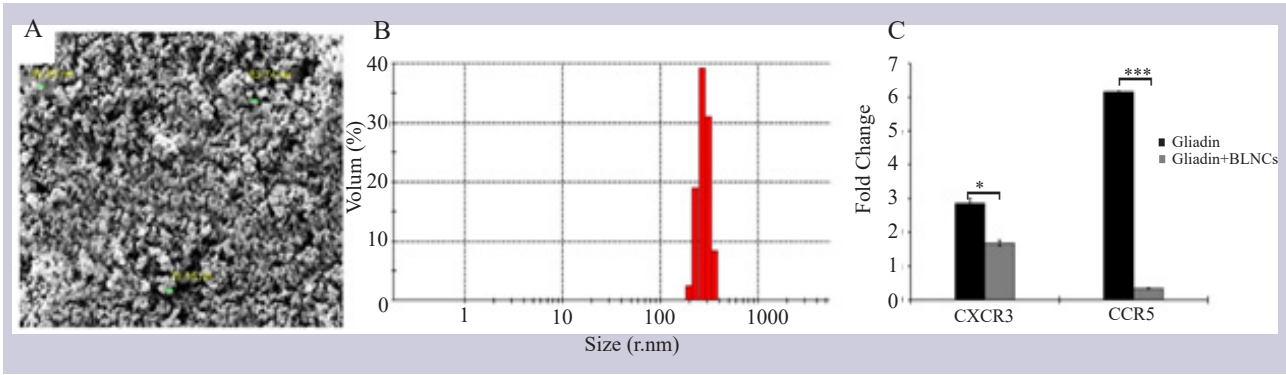

Figure 2. Characterization and anti-inflammatory activity of bromelain-loaded nanocomposites (A) FE-SEM image of BLNCs at a magnification of 20,000×, showing spherical core morphology with an estimated diameter range of 56–84 nm (average~72.5 nm); local particle accumulation and agglomeration are due to the sample drying preparation. (B) Dynamic light scattering (DLS) analysis showing the overall hydrodynamic size distribution profile of the nanocomposites. (C) Relative mRNA levels of chemokine receptors CXCR3 and CCR5 in human Caco-2 cells after exposure to raw immunogenic gliadin and gliadin enzymatically digested by BLNCs (20 mg/mL). Treatment with BLNCs effectively degrades the toxic fragments and suppresses the characteristic 6.14-fold inflammatory spike to a baseline 0.34-fold. Statistical analysis was performed by Student's t-test; error bars represent standard deviation (n=3; $p \leq 0.05$, $p \leq 0.001$). Adapted from Mousavi Maleki et al. (10).

Intestinal Polymeric Nanoparticles for Mucosal Gene Silencing

If luminal digestion fails to degrade immunogenic gliadin fragments prior to epithelial translocation, the surviving peptides interact with tissue transglutaminase 2 in the lamina propria. TG2 deamidates the gliadin peptides, conferring a negative charge that enables high-affinity binding to the peptide-binding clefts of HLA-DQ2/8 molecules on antigen-presenting cells. This leads to significant upregulation of interleukin-15, the main cytokine responsible for enterocyte death and mucosal injury. Silencing the genes for both TGM2 and IL15 in the mucosal wall is a compelling therapeutic strategy to attenuate disease progression.

To deliver fragile siRNA payloads safely to these mucosal cells, researchers designed carriers with a core matrix composed of type B gelatin (12). Despite its net negative charge at physiological pH, type B gelatin physically entraps and protects the negatively charged siRNA sequences through an ethanol-induced solvent displacement and desolvation process rather than electrostatic attraction. Cross-linked with glyoxal to yield a stable, compact nanostructure with an average diameter of 217 nm, these gelatin cores shield the siRNA payload from extracellular nucleases. Upon reaching the intestinal cell wall, the nanoparticles enter the cytoplasm of epithelial and dendritic cells through established endocytic pathways, where they release the siRNA to downregulate target mRNA. These dual-targeted gelatin nanoparticles achieved a 60% simultaneous suppression of TGM2 and IL15 gene expression in in vitro celiac models. This dual silencing directly safeguards the integrity of the cellular barrier, avoiding the loss of critical tight-junction proteins such as ZO-1, and limiting the apoptotic pathways, which generally result in compromised intestinal permeability and tissue degradation.

Multi-Compartmental Systems for Gastrointestinal Protection and Biodistribution

Bare gelatin nanoparticles demonstrate high efficacy in in vitro cell cultures but require further structural engineering for in vivo oral delivery to a living organism to survive the harsh acids and enzymes of the stomach. This problem has resulted in the development of multi-compartmental "solid-in-solid" and "solid-in-liquid" hybrid systems.

In one approach (14) the active 200 nm siRNA-loaded gelatin nanoparticles were encapsulated in a larger protective 11.4 µm microsphere matrix comprised of poly(ε-caprolactone) (PCL) in the "Nanoparticle-in-Microsphere Oral System" (NiMOS). A parallel platform (17), the "Nanoparticle-in-Self-Emulsifying Oral Fluid system" (NiSEC), disperses the gelatin cores in a protective lipid-emulsion phase that spontaneously emulsifies in gastrointestinal fluids. The outer PCL shell of the NiMOS platform is completely insoluble in the stomach's highly acidic environment, thereby protecting the fragile gelatin-siRNA cores inside. Once in the duodenum, the microspheres are subjected to pancreatic lipases that preferentially hydrolyze the ester linkages in the outer PCL matrix. This results in a targeted controlled release of the active gelatin nanoparticles directly onto the duodenal wall, allowing for transfection of the surrounding mucosa (14).

In celiac-mimetic animal models, oral administration of these multi-compartmental platforms showed excellent protective and therapeutic effectiveness compared with unprotected cores. The liquid-lipid matrix of the NiSEC platform provided maximal duodenal wetting and the longest tissue residency half-life ($t_{1/2}$ = 21.4 hours) (14, 17). Complete disease modification was achieved by structural protection of the NiMOS platform ($t_{1/2}$ =14.8 hours).

These methods showed sustained knockdown of TGM2 and IL15 across the intestinal architecture by enhancing the siRNA local tissue residency compared to bare cores (14, 17). The extended in vivo genetic silencing by NiMOS platform led to total abrogation of mucosal damage, villous height preservation, and inhibition of infiltration of inflammatory cells, thus offering a strong validation for the oral delivery of multi-compartmental celiac nanomedicines (14). A comparison table portraying pharmacokinetic and efficacy metrics for unprotected gelatin, NiMOS, and NiSEC platforms is provided below (Table 1).

Table 1. Pharmacokinetic and efficacy metric comparison between unprotected gelatin, NiMOS and NiSEC delivery platforms (14, 17).

Delivery platforms	Unprotected gelatin cores	NiMOS platform (11.4 µm PCL)	NiSEC platform (lipid emulsion)
Gastric survival rate	<5% (Rapid degradation)	>92% (Complete protection)	>85% (High stability)
Duodenal tissue half-life (t1/2)	<2.5 hours	14.8 hours	21.4 hours
Duodenal mucosal bioavailability	Minimal	Moderate-to-High (targeted local release)	Highest (enhanced lipid wetting)
In vivo histological impact	Persistent villous atrophy	Complete reversal of blunting; restored Vh:Cd ratio	Not evaluated (PK/ biodistribution only)

Systemic Tolerogenic Nanomedicine: Receptor-Mediated Hepatic Clearance and Antigen-Specific Immunological Tolerance

Local gastrointestinal therapies are aiming at intercepting gluten in the intestinal lumen or mucosa, whereas systemic treatments are directed at the fundamental cause of CD, namely the lifetime persistence of pathogenic, gluten-reactive CD4+ memory T cells (16). Historically, attempts to desensitize patients failed with free soluble gluten peptides. Injecting naked peptides into the bloodstream causes them to bind directly to circulating T cells, eliciting a massive release of systemic cytokines, such as interleukin-2, and leading to severe clinical symptoms. Researchers have engineered intravenous polymer nanoparticles utilizing an immune-evasive strategy as a way to safely administer these immunogenic antigens without provoking an immediate inflammatory reaction (16, 18). These platforms are physically tailored to evade inflammatory immune detection in the blood and to actively target the reticuloendothelial system (RES) in the liver and spleen, thereby inducing antigen-specific immunological tolerance.

Biomaterial Engineering for Hepatic Scavenger Receptor Targeting

The physical and surface chemical features of the tailored matrix determine the successful diversion of nanoparticles away from pro-inflammatory phagocytes and into tolerogenic filtering pathways. To drive this process, researchers designed and validated TIMP-GLIA, an antigen-coupled polymer platform (16). The TIMP-GLIA nanoparticles are prepared in a biocompatible poly (D, L-lactide-co-glycolic acid) (PLGA) polymer matrix and

processed into spheres of around 511 nm average diameter. The key engineering novelty of this platform is its surface charge; the particles are structurally engineered to have a strong negative zeta potential of -45 mV. This particular negative surface charge in the circulation makes the nanoparticles mimic the phosphatidylserine-rich surface of genuine apoptotic cellular debris, a mechanism known as apoptotic mimicry (20, 21). Thus, the nanoparticles evade immune detection by circulating pro-inflammatory cells, enabling them to effectively shield their encapsulated cargo of native, immunogenic gliadin proteins. Instead of inducing a systemic immune response, these negative PLGA nanoparticles are promptly cleared from circulation by directly targeting specialized, tolerogenic antigen-presenting cells, such as Kupffer cells in the liver and spleen. The particles selectively bind to MARCO scavenger receptors on the surface of these cells, facilitating receptor-mediated internalization. The tolerogenic APCs import the PLGA matrix and degrade it by natural hydrolysis. The intact gliadin peptide fragments are presented to circulating memory CD4+ T cells. These filtering cells are in a resting condition; thus, they display the gluten antigen without expressing inflammatory costimulatory molecules such as CD80 or CD86. In the absence of these crucial costimulatory signals, the antigen signal received by pathogenic gluten-reactive T-cell clones leads them into a state of sustained unresponsiveness known as anergy or alternatively, induces their active deletion by programmed cell death. At the same time, this tolerogenic presentation induces a protective phenotypic shift, expanding the population of FOXP3+ Regulatory T cells (Tregs) that actively patrol the intestinal mucosa to mitigate subsequent gluten-driven hypersensitivity.

Clinical Optimization and Suppression of Systemic T-Cell Reactivity

The successful preclinical outcome of the hepatic-homing PLGA platform paved the way to clinical translation and human evaluation under the medicinal designation TAK-101 (18). This platform employs a closely matched design of negative, spherical PLGA nanoparticles (~500 nm) that entirely encapsulate a vast, native pool of gliadin proteins. In a randomized, double-blind, placebo-controlled, human Phase 2a clinical trial, adult patients with CD on a strict gluten-free diet were given two intravenous infusions of TAK-101 on day 1 and day 8 followed by a rigorous 14-day oral gluten challenge starting on day 15 to test for systemic and mucosal protection. The clinical findings show that the tolerogenic nanoparticle process is easily translatable to humans. The active nanoparticles led to a substantial reduction of the systemic immune response in the patients treated. TAK-101 mediated hepatic clearance after oral gluten challenge resulted in an 88% decrease in the frequency of gluten-reactive, interferon-gamma secreting PBMCs compared to placebo, suggesting that pathogenic circulating T-cell clones were effectively silenced. Importantly, this systemic silence was also seen in direct physical protection of the digestive organs. Following the oral gluten challenge, the placebo cohort exhibited severe intestinal mucosal deterioration, whereas patients receiving the tolerogenic nanoparticles demonstrated complete protection against tissue degradation. Biopsies indicated that treatment with TAK-101 successfully prevented the entry of inflammatory cells into the tissue and completely preserved the structure of the gut wall, maintaining a steady and healthy villous height to crypt depth ratio (Vh:Cd) throughout the entire period of gluten challenge. In a pioneering clinical milestone for systemic nanomedicine, TAK-101 showed that an intravenous polymer nanoparticle may arrest an active autoimmune reaction and safely reset immunological tolerance in human patients.

In summary, engineered nanomedicine provides a proactive, molecularly targeted alternative to passive dietary restriction, from the local interception of gluten in the gut using oral nanocarriers to the induction of sustained immune tolerance via intravenous biomimetic particles. Table 2 summarizes these strategies and platforms.

Critical Evaluation ff Nanomedicine Platforms

The translation of designed nanomedicines for CD necessitates a transition from descriptive platform design to an analytical evaluation of their clinical, regulatory, and physical limitations (22). Laboratory-scale achievements provide strong proof-of-concept mechanisms, but the transfer of these technologies to clinical applications is dependent on the resolution of specific biophysical trade-offs between the local and systemic delivery modes (23).

Comparative Analysis of Delivery Platforms

Engineered nanomedicines for blocking the celiac pathogenic cascade are categorized into two modalities: non-systemic local platforms and systemically delivered tolerogenic networks (10, 18). Local oral structures, including bromelain-loaded silica nanocomposites, gelatin-siRNA nanoparticles, and multi-compartmental vehicles such as the Nanoparticle-in-Microsphere Oral System, have therapeutic effects in the gastrointestinal lumen and mucosal wall. These platforms have a highly localized safety profile that reduces the likelihood of systemic off-target toxicities (12). However, their therapeutic potential is intrinsically limited by the serious gastrointestinal challenges such as stomach acidity (pH 1.2-2.0), proteolytic endopeptidases, and a thick intestinal mucus layer (13). Oral platforms require sophisticated multi-layer protective coatings and

Table 2. Summary of engineered nanoparticle platforms and delivery strategies

Strategy	Platform composition	Size & Charge	Primary mechanism	Key outcome	Source
Luminal deactivation	Polymer-coated silica nanocomposites	72.5 nm	Encapsulates bromelain proteases to resist stomach acid and cleave gluten in the duodenum.	Suppresses inflammatory CXCR3/CCR5 receptor spikes down to baseline.	(10)
Mucosal gene silencing	Type B gelatin nanoparticles	217 nm; 6.2 mV	Entraps and shields dual siRNA sequences to safely enter intestinal cells via endocytosis.	Achieves 60% dual knockdown of TGM2 and IL15; protects ZO-1 tight junctions.	(12)
Oral protection (solid-in-solid)	Nanoparticle-in-microsphere system (NiMOS)	11.4 µm PCL microspheres	Encapsulates gelatin-siRNA cores inside an acid-resistant shell digested by pancreatic lipases.	Extends duodenal half-life to 14.8 hours; reverses villous blunting in vivo.	(14)
Oral protection (solid-in-liquid)	Nanoparticle-in-self-emulsifying fluid (NiSEC)	Liquid-lipid matrix	Disperses gelatin cores in a lipid matrix that spontaneously emulsifies in gastric fluids.	Maximizes mucosal wetting to yield the longest duodenal half-life (21.4 hours).	(17)
Systemic tolerance	Antigen-encapsulating PLGA particles (TAK-101)	500 nm; -45 mV	Mimics apoptotic debris to target MARCO receptors on liver/spleen Kupffer cells.	Delivers gliadin safely to silence memory T cells; drops reactive PBMCs by 88%.	(16, 18)

consistent, lifelong adherence to chronic dosing schedules for efficacy (22). Alternatively, systemic delivery platforms such as the antigen-encapsulating PLGA nanoparticle network TAK-101 target the underlying etiology of CD by inhibiting pathogenic immunological memory (16). These intravenous formulations encapsulate native gliadin proteins in a biomimetic polymer matrix, thereby completely avoiding luminal degradation and allowing sustained restoration of antigen-specific immunological tolerance (18). The main disadvantage of the systemic approach is its specific toxicological susceptibilities (22). The administration of nanocarriers via the intravenous route leads to dynamic interaction with the circulation, which can cause harmful non-specific innate immune responses such as complement activation-related pseudo allergy (CARPA), acute cytokine release syndrome, or rapid blood clearance (24). Furthermore, systemic regimens necessitate particular intravenous therapeutic infusions, shifting celiac therapy from a self-directed dietary regimen to an invasive, provider-mediated clinical protocol (2).

Regulatory, Manufacturing, and Physiological Hurdles

International regulatory pathways are key to advancing celiac nanomedicines. The FDA's 2022 Guidance for Industry for Drug Products Containing Nanomaterials requires regulators to use a case-by-case, risk-based framework that requires a thorough analysis of structure-function relationships (25). However, the existing paradigms continue to evaluate polymeric nanotherapeutics using the rules for small molecules and biologicals rather than nanomedicine-specific policies (22). From a Chemistry, Manufacturing and Controls (CMC) perspective, the main regulatory challenge for celiac disease therapies is the validation of the batch-to-batch reproducibility of critical quality attributes (CQAs) according to Good Manufacturing Practice (GMP) guidelines (25). Regulatory agencies require strict monitoring of average particle size, polydispersity and surface charge (zeta potential) (22). The strong negative charge added to TAK-101 (-45 mV) is an important aspect that has to be strictly standardized, as surface charge affects colloidal stability and non-specific cell interactions (16, 25). The European Medicines Agency reflection paper on surface coatings (24) demands developers to test the chemical adherence kinetics of the coating process thoroughly. In platforms with specialized polymer matrices, such as poly-L-DOPA, surface coverage heterogeneity is considered a major impurity that can lead to physical aggregation or aberrant tissue targeting for luminally active BLNC silica cores protected by a shell (10, 24).

Beyond manufacturing, physiological and systemic safety barriers remain. For systemic tolerogenic platforms, vascular geometry, localized hemodynamics, and portal venous blood flow exert a profound impact on biodistribution. Computational fluid dynamics (CFD) and Lagrangian particle tracking have shown that high velocity blood flow within the human celiac trunk produces large hydrodynamic drag forces that move 100 nm particles beyond crucial local artery branches (26). Furthermore, the regulatory focus is moving towards biopersistence and long-term safety. Once in systemic circulation, nanomedicines interact with plasma proteins to form a dynamic protein corona. This corona changes the biological identity of the particle and

enables clearance through phagocytosis by macrophages of the mononuclear phagocyte system in the liver and spleen (24,25). Systemically active networks, such as TAK-101, use this pathway to induce tolerance. However, this tissue localization requires extensive multi-year absorption, distribution, metabolism, and excretion (ADME) profiling (18,25). Organic and biodegradable matrices have shown good short-term biocompatibility, but the fate of persistent nanomaterials underlines the importance of researching long-term intracellular clearance. For instance, common food-grade inorganic nanoparticles (e.g. 15 nm gold and 20 nm silver) were found to accumulate extensively within intestinal crypt cells, downregulating TOM1 receptors and leading to an autophagic blockade, preventing cells from clearing toxic components such as the p31–43 gliadin peptide (27).

Clinical Stratification and Patient Heterogeneity

CD is a clinically heterogeneous disease. Patient profiles vary significantly based on individual sensitivity thresholds, genetic backgrounds, and clinical disease states. The choice of an optimal nanomedical platform should be based on an evidence-based matching of the design of nanoparticles and the specific celiac subtypes defined in the European Society for the Study of Coeliac Disease (ESsCD) 2025 Updated Guidelines (2).

Non-Responsive Celiac Disease (NRCD)

NRCD is defined as adult patients with persistent chronic symptoms or ongoing villous atrophy after more than 12 months on a presumed gluten-free diet. These cases are attributed to continuous intentional or unintentional gluten intake, often from cross-contamination in the commercial food supply, which accounts for up to 80% of these cases. In particular, for subjects with pronounced gluten sensitivity, in whom exposure to traces beyond the safe daily threshold of 10 mg/day triggers local immune activation, non-systemic oral delivery systems represent an ideal intervention (2). Luminal silica nanocomposites (BLNCs) or oral gene-silencing microspheres (NiMOS) counteract toxic gliadin fractions directly in the duodenal microenvironment, protecting the intestinal mucosa from systemic immunity (10,14). Furthermore, the 2025 ESsCD guidelines clarify that symptomatic NRCD is often complicated by the presence of coexisting functional or metabolic overlays. Secondary lactase deficiency occurs in 50–70% of untreated celiac patients, and exocrine pancreatic insufficiency (EPI) is present in up to 26% of newly diagnosed adults and 28% of patients with persistent symptoms (2).

Refractory Celiac Disease (RCD) Subtypes

If enteropathy remains in a persistent state of enteropathy despite documented adherence to the diet, then the patient has true RCD (2). RCD occurs in about 1% or less of adult celiac patients and is classified into two biologically and prognostically distinct entities based on small-bowel lymphocyte immunophenotyping:

RCD type I (RCD-I): Phenotypically normal intraepithelial lymphocyte population RCD-I usually has a benign clinical course with 5-year survival rates of over 90%.

RCD Type II (RCD-II): Defined by the presence of a clonal intraepithelial lymphocytes (IELs) population with a highly aberrant phenotype with loss of surface CD3 and CD8 markers. RCD-II is a severe pre-malignant condition with a 5-year survival rate of 44%–58%, primarily due to progression to Enteropathy-Associated T-cell Lymphoma (EATL). EATL occurs in up to 50% of all RCD-II patients and has a clinical presentation of severe catabolic wasting, with a median survival of less than 1 year.

For high-risk populations, specific interventions are indicated, as conventional immunosuppressants such as azathioprine are absolutely contraindicated in RCD-II due to the risk of malignant transformation. Crucially, the emergence of autonomous, gluten-independent clonal expansion in RCD-II represents the physiological boundary of current antigen-specific nanomedicines. Because platforms like TAK-101 target gluten-reactive CD4+ T-cells to induce tolerance, they are theoretically ineffective against the aberrant, gluten-independent IELs driving RCD-II. Therefore, while systemic tolerogenic platforms offer a molecular modality to silence pathogenic memory and potentially prevent the initial progression to refractory states (16, 18). Patients who have already transitioned to RCD-II require distinct pharmacological interventions, such as targeted anti-IL-15 therapies or chemotherapeutics (2). This highlights the absolute necessity of rigorous immunological phenotyping prior to nanomedicine administration.

Genetic Risk Stratification

The pathogenesis of CD is strongly dependent on genetic predisposition, especially the expression of human leukocyte antigen class II molecules HLA-DQ2 and HLA-DQ8 (2). In accordance with the 2025 ESsCD guidelines, upfront HLA-DQ2/8 genotyping is a highly effective primary screening modality, given its near-absolute negative predictive value. Crucially, HLA-DQ2 homozygosity substantially elevates celiac risk according to clinical risk prediction models, associated with a much earlier disease onset and a more aggressive enteropathic phenotype. This genetic stratification is highly relevant for the design of antigen-specific tolerogenic nanomedicines (22). Existing platforms, such as TAK-101, encapsulate a comprehensive native pool of total gliadin proteins to provide broad epitope coverage; however, the T-cell receptor response generated

by patients with high-risk HLA-DQ2 homozygosity is highly amplified and predictable (2, 18).

Challenges and Future Perspective

Engineered nanomedicines have shown great therapeutic promise in preclinical and early-phase clinical testing. However, a number of multifaceted challenges prevent translation from controlled laboratory settings to broad clinical adoption. Researchers must overcome complex biophysical, translational, and longitudinal safety barriers to successfully commercialize and deploy both non-systemic luminal platforms and systemically targeted tolerogenic networks. Critical bottlenecks in manufacturing scalability, long-term biocompatibility, and sophisticated pharmacokinetic optimization must be overcome to fully realize the potential of these targeted therapies and integrate them into the clinical algorithm for celiac disease.

Overcoming Scale-Up and Manufacturing Bottlenecks

The transition from laboratory proof-of-concept to clinical application heavily depends on overcoming the inherent manufacturing bottlenecks associated with multi-compartmental platforms. Conventional batch manufacturing is often not suitable for industrial scale-up, as systems such as NiMOS and NiSEC involve delicate multi-step solid-in-solid encapsulation or very specific lipid-to-surfactant ratios (14,17). Thus, future studies should focus on integrating continuous manufacturing methodologies. The production of nanomedicines requires advanced techniques such as microfluidic encapsulation and coaxial electrospraying as essential evolutionary steps. This shift to these continuous processes will allow developers to synthesize complex and multi-stage vehicles with the necessary high batch-to-batch reproducibility, stringent dimensional control, and stable drug-loading efficiencies required for successful clinical translation and commercialization.

Longitudinal Safety and Advanced Intracellular Profiling

Demonstrating the longitudinal safety of these platforms represents a critical mandate for future translational studies. Given that CD is a chronic, lifelong condition, any non-dietary therapeutic intervention will necessitate chronic administration over decades. While the transition from persistent inorganic materials to biodegradable matrices, such as PLGA and cross-linked gelatin, mitigates the immediate risk of autophagic blockade, the long-term intracellular fate of these organic platforms remains a critical frontier.

Regulatory agencies demand rigorous evidence that the chronic administration of these matrices does not compromise the host's intrinsic autophagic and lysosomal pathways (22). Future safety profiling must extend beyond short-term biocompatibility assays to definitively establish that the accumulation of chronic clearance products does not cumulatively overload the lysosomal or autophagic machinery of enterocytes, hepatocytes, or splenic macrophages over extended physiological timescales.

Active Navigation and Hemodynamic Targeting

Future systemic nanomedicines must overcome complex hemodynamic forces such as high-velocity blood flow and severe hydrodynamic drag within the celiac trunk to ensure efficient distribution to tolerogenic organs. Consequently, the next frontier in pharmacokinetic optimization is the development of "active navigation" strategies that integrate patient-specific computational fluid dynamics with external physical guidance mechanisms.

As a foundational proof-of-concept for this approach, researchers have modeled the use of highly dense (5240 kg/m^3), 100 nm iron oxide (Fe_3O_4) cores to counteract vascular drag forces (26). With the use of well-controlled localized external magnetic field gradients, it could be theoretically possible for clinicians to steer these nanotherapeutics away from the main systemic circulation and actively guide them into particular localized networks, such as the hepatic or splenic arteries. Individual vascular flow mapping combined with active magnetic targeting will eventually enable precise control of injection parameters and particle trajectories. This synergy will result in optimal therapeutic delivery to the liver and spleen with minimal rapid off-target systemic clearance.

Personalized Delivery Strategies

In the context of the clinical stratification framework presented above, future research needs to define clinical criteria to guide the choice between local and systemic regimens for individual patients.

While systemic interventions such as the platform TAK-101 have the potential for complete dietary liberalization, they require invasive intravenous infusions (18). In the future, individual HLA haplotyping may be used to optimize these systemic regimens by customizing specific epitope densities and intravenous infusion schedules to the precise immunogenetic architecture of the patient.

The specific biophysical behavior of gluten at the nanoscale in the gastrointestinal tract has to be considered, too, for evidence-based stratification. For example, indigestible γ-gliadin fragments spontaneously self-assemble into rigid positively charged 143.6 nm nanospheres that can penetrate the negatively charged intestinal mucus layer (28). This biophysical phenomenon offers a clinically relevant reframing of the local-versus-systemic paradigm: patients whose primary disease driver is rapid disruption of the mucosal barrier by these endogenous nanostructures represent fundamentally distinct clinical candidates

from those whose pathology is dominated by systemic autoantibody production and deep immunological memory. Future biomarker-driven patient profiling that characterizes this distinction will enable clinicians to move beyond empirical platform assignment, facilitating the development of a precise, mechanism-matched therapeutic strategy. Therefore, the strategic pairing of the nanomaterial platform with the individual clinical disease state is not merely a future aspiration, but the essential foundation for translating celiac nanomedicines from laboratory proof-of-concept to definitive clinical utility.

CONCLUSION

Engineered nanoparticles represent a paradigm shift in the treatment of celiac disease, changing the clinical landscape from passive dietary avoidance to active, targeted therapeutic intervention. As reviewed in this paper, nanotechnology overcomes the basic barriers of pharmacokinetics, transport, and structural stability that have traditionally prevented the clinical translation of free, unmodified pharmaceutical candidates. Nanomedicine efficiently intercepts the CD pathophysiological cascade at multiple stages using a variety of engineered delivery systems.

Locally active platforms, such as polymer-coated silica nanocomposites (BLNCs) and multi-compartmental oral systems (NiMOS and NiSEC), are highly effective in neutralizing disease drivers directly within the gastrointestinal tract. They achieve this either via direct proteolysis of immunogenic 33-mer peptides in the duodenal lumen or via targeted, siRNA-mediated genetic downregulation of mucosal TGM2 and IL15. Concurrently, systemically administered tolerogenic PLGA nanoparticles (TAK-101) represent a powerful modality for disease modification through the safe engagement of hepatic and splenic MARCO scavenger receptors. This biomimetic, immune-evasive profile prevents the precipitation of a severe systemic cytokine cascade while safely delivering native gliadin payloads to resting antigen-presenting cells, successfully silencing the established pool of pathogenic, gluten-reactive CD4+ memory T-cell clones.

While the broad clinical use of this approach faces substantial regulatory and manufacturing hurdles, impressive preclinical and early clinical milestones have already been achieved, including a significant physical preservation of human mucosal architecture and an 88% reduction in circulating inflammatory T-cell reactivity. Future studies should focus on bridging the translational gap between lab-scale synthesis and industrial-grade manufacturing by integrating continuous processing techniques, such as microfluidic encapsulation, to ensure rigorous structural reproducibility. Moreover, the chronic nature of celiac disease requires elucidation of long-term intracellular fate and clearance pathways of polymer matrices administered chronically. This remains a critical safety prerequisite to ensure that the accumulation of clearance products does not compromise the host's endogenous autophagic and lysosomal machinery.

The ultimate frontier of celiac nanomedicine is the rational, evidence-based alignment of individual nanoparticle designs with the patient's unique clinical pathophysiology and immunogenetic profile. By integrating advanced, patient-specific fluid dynamics for optimized systemic distribution with a profound understanding of endogenous mucosal interactions, the field is poised to deliver a commercially viable and highly reproducible portfolio of nanotherapeutics. The transformation of celiac disease from a lifestyle-limiting dietary burden into a sustainably managed autoimmune condition represents an achievable milestone for next-generation nanomedicine.

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