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Oral Nano Medicine Bio Interaction in the Gastro Intstestinal Tract in Health And Diseases : A Review

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Abstract: Oral nanomedicines are emerging as a significant advancement in drug delivery, aiming to overcome the complex barriers of the gastrointestinal tract (GIT) and improve therapeutic outcomes. The GIT presents challenges such as variable pH, mucus layers, digestive enzymes, epithelial barriers, microbiota, and immune defenses, which limit the effectiveness of conventional oral drugs. Nanoparticles with customized physicochemical properties offer enhanced mucus penetration, targeted cellular uptake, specific interaction with gut microbiota, and modulation of immune responses. This review examines various oral nanomedicine systems—including liposomes, polymeric nanoparticles, micelles, solid lipid nanoparticles, and dendrimers—focusing on their mechanisms of interaction within healthy and diseased GIT conditions. It also discusses recent preclinical studies, clinical trials, and approved formulations, highlighting advances in translational research. Understanding these biointeractions is vital for designing future oral nanomedicines to treat gastrointestinal disorders such as inflammatory bowel disease, infections, ulcers, and cancers. Continuous innovation in nanocarrier technology promises improved drug stability, targeted delivery, enhanced bioavailability, and better patient outcomes in gastrointestinal therapeutics.

I. INTRODUCTION

Oral nanomedicine utilizes nanoparticles as advanced drug carriers designed specifically for oral administration. These nanoparticles are engineered to interact effectively with the gastrointestinal tract (GIT), which presents a complex environment consisting of mucus layers, epithelial barriers, digestive enzymes, and resident microbiota. The primary aim of such designs is to improve drug stability, enhance mucoadhesion for prolonged retention, and facilitate mucus penetration, ensuring precise drug release and absorption at target sites such as the stomach or intestines. To succeed, nanoparticles must overcome multiple barriers, including mucus penetration, acidic gastric conditions, and enzymatic degradation, before reaching the absorptive surfaces. They can exploit cellular pathways, such as endocytosis, to cross the intestinal barrier and enter systemic circulation[1], [2].

A. Importance of Oral Drug Delivery

Oral delivery is favored for its convenience, patient compliance, and suitability for repeated dosing. It is non-invasive and cost-effective compared to parenteral routes. However, conventional oral drugs face limitations such as poor solubility, degradation under acidic gastric conditions, enzymatic metabolism, and restricted absorption. Nanomedicine offers solutions to these challenges by protecting vulnerable drugs, enhancing solubility, and enabling targeted delivery, thereby improving bioavailability and therapeutic outcomes

B. Nanomedicine in Oral Delivery

Various nanoparticle systems — including polymeric, lipid-based, inorganic, and mucoadhesive types — are being developed for oral delivery. These systems can be engineered for sustained drug release, targeted delivery, and increased cellular uptake. By protecting drugs from harsh GIT conditions, nanoparticles can reduce dosing frequency and side effects. Moreover, strategies such as floating nanoparticles or mucoadhesive formulations can increase gastric retention time, enabling more efficient treatment of diseases like Helicobacter pylori infection and inflammatory bowel diseases.[1], [2]

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C. Challenges in the GIT Environment

The GIT is a complex and dynamic system with variable pH levels (acidic in the stomach and neutral to alkaline in the intestines), mucus layers of varying thickness (50–450 μm), and diverse motility patterns affecting drug residence time. Mucus acts as a physical barrier, trapping foreign particles, while the epithelial barrier regulates drug uptake through specialized cells and immune defense mechanisms. Digestive enzymes further complicate drug stability. Additionally, physiological variations, such as fed or fasted states and individual differences in microbiota, add further challenges. Developing nanoparticles capable of penetrating mucus, resisting degradation, enduring variable pH, and employing appropriate transport mechanisms remains a critical focus in oral nanomedicine research

II. GATROINTESTINAL TRACT IN HEALTH

A. Gastrointestinal Tract Physiology

The gastrointestinal tract (GIT) is a highly specialized and dynamic organ system that plays a central role in digestion, nutrient absorption, and immune defense. Structurally, it comprises distinct regions—the stomach, small intestine, and large intestine—each of which possesses unique physiological properties tailored to specific functions.

A defining feature of the GIT is its pH gradient, which varies significantly along its length. The stomach maintains a highly acidic environment (pH 1–3) to activate digestive enzymes such as pepsin and to kill harmful microorganisms. This acidity also aids in breaking down food particles and initiating protein digestion. In contrast, the small intestine has a nearly neutral to slightly alkaline pH (6–7.5), creating optimal conditions for enzymatic activity, nutrient absorption, and microbial homeostasis. The large intestine exhibits a near-neutral to mildly acidic pH (5.5–7), influenced by microbial fermentation and short-chain fatty acid production, which play important roles in colonic health and metabolism.

Enzymatic activity is another critical aspect of GIT physiology. Digestive enzymes such as pepsin, pancreatic amylases, proteases, and lipases break down carbohydrates, proteins, and fats into simpler absorbable units. Brush border enzymes in the small intestine, including maltase and lactase, further process nutrients before absorption.

The mucus layer lining the GIT epithelium acts as both a protective and functional barrier. Composed predominantly of mucin glycoproteins, electrolytes, and water, this viscoelastic gel protects the epithelial cells from mechanical stress, acidic conditions, digestive enzymes, and pathogens, while also facilitating nutrient transport. Mucus thickness and composition vary across different GIT regions, affecting both drug diffusion and nanoparticle interactions.

Another defining feature of the healthy GIT is its microbiota—a diverse population of bacteria, archaea, viruses, and fungi that reside mainly in the large intestine. This microbial community contributes to digestion, metabolism of complex carbohydrates, synthesis of vitamins, immune modulation, and maintenance of mucosal integrity. The composition and activity of gut microbiota are strongly influenced by luminal pH, diet, and host physiology, creating a dynamic environment for oral drug delivery systems to navigate.

B. Nanomedicine Interactions in Healthy GIT

Nanomedicines designed for oral delivery face a series of physiological barriers within the healthy GIT. The first and perhaps most critical barrier is the mucus layer, which can trap or degrade nanoparticles before they reach the epithelial surface. To address this, strategies such as surface modification (e.g.,PEGylation or ligand functionalization) are employed to enhance mucus penetration or promote muco-adhesion for sustained release.

Once beyond the mucus, nanoparticles encounter the epithelial barrier, which they can cross via various mechanisms. Transcellular transport involves uptake into epithelial cells through endocytosis and vesicular transport, while paracellular transport allows passage between cells through tight junctions, though this route is limited in most regions of the GIT. Specialized epithelial cells, such as M cells in Peyer's patches, play a unique role by sampling luminal content and facilitating transport of nanoparticles to underlying immune tissues, thereby enabling both systemic absorption and localized therapeutic action.

The release of drug molecules from nanoparticles can be engineered to occur in specific regions of the GIT in response to physiological cues such as pH changes, enzymatic activity, or the presence of certain biomolecules. For example, pH-sensitive nanoparticles can be designed to remain intact in the acidic stomach but release their payload in the neutral pH of the small intestine. The physicochemical properties of nanoparticles—including size, shape, surface charge, hydrophobicity, and functional coatings—significantly influence their interactions with GIT components, uptake efficiency, and biodistribution. Smaller nanoparticles generally exhibit better mucus penetration, while surface charge can affect both adhesion to mucus and epithelial uptake. Hydrophilic coatings can reduce opsonization and degradation, enhancing nanoparticle stability.

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In a healthy gastrointestinal environment, these interactions are carefully balanced to avoid triggering excessive immune responses while ensuring optimal drug absorption and bioavailability. This delicate interplay highlights the importance of understanding the healthy GIT's physiology—its pH gradients, enzymatic environment, mucus composition, and microbiota profile—to rationally design oral nanomedicine systems capable of overcoming these barriers for effective therapy.

C. Gastrointestinal Tract in Disease

Common Diseases of the Gastrointestinal Tract

The gastrointestinal tract (GIT) is susceptible to a variety of disorders that significantly alter its normal physiology, barrier functions, and microenvironment. Among these, Inflammatory Bowel Disease (IBD)—which includes Crohn's disease and ulcerative colitis—stands out as a chronic inflammatory condition characterized by persistent mucosal damage, dysregulation of immune responses, and disruption of gut microbiota. These alterations result in clinical symptoms such as abdominal pain, diarrhea, rectal bleeding, and nutrient malabsorption, all of which impact drug delivery and therapeutic outcomes.

Peptic ulcers, often arising from Helicobacter pylori infection or prolonged NSAID use, are characterized by erosions in the mucosal lining of the stomach or duodenum. These lesions alter the local pH, mucus structure, and enzymatic activity, posing significant challenges for oral drug stability and absorption.

Gastrointestinal infections, whether bacterial, viral, or parasitic, disturb the balance of normal gut microbiota, cause mucosal inflammation, and damage epithelial cells, creating barriers to drug penetration and altering pharmacokinetics.

Gastrointestinal cancers, including gastric and colorectal cancer, involve abnormal and uncontrolled cell proliferation. These conditions are often linked to chronic inflammation, genetic mutations, or exposure to carcinogens. They change the tissue architecture, increase vascular permeability, and produce a distinct tumor microenvironment, all of which influence nanoparticle delivery strategies. Celiac disease, an autoimmune condition triggered by gluten consumption, leads to atrophy of the intestinal villi, resulting in impaired nutrient absorption and chronic inflammation. This change in epithelial structure significantly impacts drug uptake and the behavior of nanomedicines.

D. Barriers and Opportunities in Disease Conditions

Disease states of the GIT cause substantial alterations to natural barrier mechanisms, creating both challenges and potential opportunities for nanomedicine-based drug delivery.

1) Barrier Disruption: Conditions such as IBD, ulcers, and infections compromise epithelial integrity by damaging tight junctions and degrading the mucus layer. This leads to increased intestinal permeability, commonly referred to as a "leaky gut," which allows greater nanoparticle access to deeper tissue layers. However, this also exposes underlying tissues to enhanced immune surveillance and inflammatory responses, potentially reducing therapeutic efficacy or causing off-target effects.

2) Mucus Alterations: Changes in mucus composition, thickness, and viscosity during disease can either hinder nanoparticle penetration or increase retention, depending on the disease condition. For instance, inflammation may increase mucus secretion, while infection may degrade the mucus barrier.

3) Immune Activation: Disease-associated infiltration of immune cells and elevated pro-inflammatory cytokines affect the uptake, clearance, and targeting of nanoparticles. This immune activity can either impede drug delivery or be leveraged for targeted therapy.

4) Microbiota Dysbiosis: Disease conditions often cause imbalances in the gut microbiota (dysbiosis), which modify enzymatic activity, pH, and metabolite production. These changes influence nanoparticle stability, drug release kinetics, and therapeutic efficacy. These altered conditions present opportunities for engineering disease-specific nanomedicine systems, such as pH-sensitive carriers for ulcer treatment, ligand-functionalized nanoparticles for targeting inflamed tissue, or microbiota-responsive delivery platforms. However, the heterogeneity and dynamic progression of diseases make it essential to design flexible and adaptable nanomedicine approaches.[3], [4]

III. DIFFERENCES IN NANOMEDICINE BEHAVIOR IN DISEASE

Nanomedicine performance in a diseased GIT differs markedly from that in healthy conditions.

1) Enhanced Permeability: Increased gut permeability in disease states facilitates deeper nanoparticle penetration into tissue but also raises the risk of off-target delivery and systemic exposure.

2) Altered Microenvironment: Disease-related oxidative stress and changes in enzymatic activity can lead to premature degradation of nanoparticles, affecting drug release and bioavailability.

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3) pH and Mucus Changes: Altered pH profiles and mucus properties influence nanoparticle stability, transport, and release profiles. For example, acidic microenvironments in ulcers require pH-resistant nanoparticle coatings to ensure stability.
4) Immune Modulation: Immune cell infiltration at disease sites offers both challenges and advantages—while clearance of nanoparticles may increase, immune cells can also act as targets for drug delivery in immunomodulatory therapies.
5) Targeting Opportunities: Disease-specific changes in cell surface receptors or microenvironment characteristics can be exploited using ligand-functionalized nanoparticles for site-specific targeting, improving therapeutic precision while minimizing systemic side effects.

In essence, developing nanomedicine for GIT disorders demands a deep understanding of disease-induced physiological and immunological changes. Tailored nanoparticle systems that consider altered barrier function, inflammation, mucus composition, and microbiota dynamics hold significane promise for enhancing drug delivery efficiency, therapeutic outcomes, and safety profiles in gastrointestinal diseases.[5], [6]

IV. TYPES OF ORAL NANO MEDICINE

Oral nanomedicines represent a significant innovation in drug delivery, designed to overcome the physiological and biological barriers of the gastrointestinal tract (GIT). The GIT is a complex environment with fluctuating pH, digestive enzymes, mucus layers, and diverse microbiota, all of which contribute to challenges like drug degradation, poor solubility, limited absorption, and rapid clearance.

Nanomedicines, owing to their nanoscale size and tunable properties, can effectively address these issues. Carriers such as liposomes, polymeric nanoparticles, micelles, solid lipid nanoparticles, and dendrimers interact uniquely with GIT components to enhance drug stability, targeted delivery, and controlled release. Surface modifications further improve mucoadhesion or penetration, prolonging retention or enabling deeper tissue access.

Their uptake occurs through mechanisms like membrane fusion, endocytosis, or specialized transport pathways, allowing delivery to local GIT sites or systemic circulation. However, challenges such as gastric instability, premature release, mucus entrapment, and immune responses remain.

The following table summarizes the major types of oral nanomedicines, their interactions within the GIT, and the key advantages and limitations that shape their clinical potential.[7]

Nanomedicie type	Description	Specific interaction with GIT	Advantage in GIT	Challenges in GIT
liposomes	Drug loaded vesicles made of phospholipid bilayer	Merge with mucus and epithelial layers to enhance absorption	Safe carriers that protect drugs and target mucus	Acid instability and mucus trapping
Polymeric nano particles	Composed of bioderadable plymers sach as PLGA	Adheres to or penetrates mucus,enters cells via endocytosis	Regulated drug release,enzyme shielding targeted inflamed tissues	Early drug leakage,mucus obstruction
Micelles	Amphillic compounds creating a core-shell structure	Enhance solubility and mucus penetration	Boost bioavailability of low-low solubility drugs	Can detach in GI fluids ,causing instability
Solid lipid nanopartcles	Solid lipid matrix nanoparticles	Binding the mucusa and epithelial cells	Stability good ,sustained realease	Mucus trapping,targeting challenges
dendrimers	Branched polymers with modified surfaces	Engage with mucus and cells through charge and size	Efficient drug loading with targeted delivery	Possible toxicity and immune removal

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V. MECHANISM OF BIO INTERACTION

A. *Mucus Penetration*

- Role of Mucus: The intestinal mucus serves as a protective gel-like layer composed mainly of mucin glycoproteins. It functions to trap and remove foreign particles, protecting the underlying epithelial cells.
- Challenge for Nanomedicines: For oral nanomedicines to be effective, they must either adhere to this mucus or penetrate it efficiently without being removed prematurely.
- Strategies to Improve Penetration:
  - Surface Modification: Coating nanoparticles with hydrophilic and neutral-charged substances, like polyethylene glycol (PEG), to minimize adhesion to mucus components.
  - Size and Shape Optimization: Designing nanoparticles with suitable dimensions and shapes to navigate through mucus mesh pores.
  - Active Transport Methods: Using stimuli-responsive nanomotors powered by magnetic or acoustic forces to propel particles through mucus.
  - Hybrid Designs: Combining mucoadhesive and mucopenetrating properties, e.g., by applying biopolymer coatings or engineering size-switchable carriers.

Outcome: These methods improve drug retention in the intestine, increase penetration efficiency, and prevent premature drug clearance caused by mucus turnover.

B. *Cellular Uptake (Endocytosis and Transporters)*

- Barrier after Mucus: Once nanoparticles cross the mucus layer, they encounter the intestinal epithelial cells that regulate uptake.
- Key Uptake Mechanisms:
  - Endocytosis Pathways: Includes clathrin-mediated, caveolin-mediated, and macropinocytosis, depending on nanoparticle features.
  - Receptor-Mediated Endocytosis: Functionalizing nanoparticles with ligands to target receptors on epithelial cells or specialized M cells enhances uptake.
  - Transporter Utilization: Nanoparticles can exploit transporter proteins to gain entry into cells.
  - → Transcytosis: M cells over Peyer's patches can transport nanoparticles across the epithelium, aiding systemic delivery and immune interaction.

Significance: These pathways control intracellular trafficking of nanoparticles, influencing where and how the drug is released and its overall bioavailability.

C. *Interaction with Microbiota*

- Microbiota Role: The gut microbiota consists of trillions of microorganisms that influence metabolism, immune responses, and mucosal barrier function.
- Nanomedicine-Microbiota Interactions:
  - Metabolism and Degradation: Microbiota can break down nanocarriers or drug molecules, affecting therapeutic efficiency.
  - Microbial Modulation: Certain nanoparticles can alter microbial populations, potentially correcting imbalances in disease states.
  - Immune Influence: Microbiota-mediated signaling can affect the immune response elicited by nanomedicines.
- Emerging Strategy: Designing nanomedicines to target microbiota specifically for treating metabolic and inflammatory diseases.
- Importance: Understanding these interactions is essential to improve drug efficacy and minimize unwanted effects.

D. *Immune Response*

- GIT Immune Surveillance: The gastrointestinal immune system monitors luminal contents through epithelial cells, macrophages, dendritic cells, and gut-associated lymphoid tissue.
- Nanoparticle-Immune System Interaction:
  - Clearance: Nanoparticles may be captured and degraded by macrophages and dendritic cells.
  - Inflammatory Response: Nanoparticle composition and surface properties can trigger cytokine production.

- Immunomodulatory Design: Nanomedicines can be engineered to target or regulate immune cells for treating inflammatory or autoimmune gut diseases.
- Design Strategies: Use of biodegradable materials, control over particle size, and PEGylation of surfaces help reduce unwanted immune activation while improving tolerance.[8], [9], [10]

VI. PRE CLINICAL AND CLINICAL STUDIES

A. *Preclinical Studies*

- In the preclinical phase, comprehensive in vitro and in vivo studies are conducted to assess the safety, efficacy, and pharmacokinetic behavior of oral nanomedicines.
- Animal models commonly used include rodents such as mice and rats, as well as larger animals that closely mimic human gastrointestinal physiology and pathological conditions like inflammatory bowel disease (IBD), gastric ulcers, and colon cancer.
- These models provide essential insights into nanoparticle performance, including mucus penetration, cellular uptake, biodistribution, and clearance mechanisms in the gastrointestinal tract.
- In vitro systems utilize human intestinal cell lines, mucus analogues, and organoid models to evaluate nanoparticle stability, absorption efficiency, and cytotoxicity under controlled laboratory conditions.
- Advanced techniques such as confocal microscopy, electron microscopy, and fluorescent labeling are applied to quantitatively assess drug delivery efficiency and site-specific targeting.
- Specialized nanoparticles, including enzyme-responsive and microbiota-targeted formulations, are examined using these preclinical mode replicate the complex and dynamic environment of the gastrointestinal tract.
- These studies are fundamental for optimizing the formulation before entering clinical trials, ensuring safety, and enhancing therapeutic potential.

B. *Clinical Trials*

- Several oral nanomedicine formulations have progressed to clinical trials, aiming to improve bioavailability of poorly soluble drugs and enhance targeted delivery within the gastrointestinal tract.
- These trials often target gastrointestinal disorders such as Crohn's disease, ulcerative colitis, and gastric infections.

- The focus of clinical studies includes:
  - Assessing safety profiles and potential adverse effects.
  - Determining optimal dosage regimens for effective treatment.
  - Evaluating therapeutic benefits such as symptom improvement, mucosal healing, and inflammation reduction

- Both ongoing and completed trials are registered in international clinical trial databases, providing transparency and reliable data for further development.
- Clinical translation of oral nanomedicines focuses on improving formulation stability, enhancing patient compliance, and developing scalable manufacturing processes to facilitate commercialization.
- Representative examples of trials include nanosuspensions and polymeric nanoparticles designed for targeted drug release and enhanced absorption in the gastrointestinal tract.

C. *FDA-Approved Formulations*

- Currently, relatively few oral nanomedicine products are specifically FDA-approved for gastrointestinal tract targeting.
- Some examples include:
  - Nanosuspension-based formulations that improve solubility and absorption of poorly soluble drugs (e.g., Fenofibrate nanosuspensions).
  - Liposomal drug formulations that enhance drug stability and mucosal targeting within the GIT.
  - Emerging oral peptide and biologic formulations encapsulated within nanocarriers to protect against degradation in the gastrointestinal environment.

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- These FDA-approved products represent important milestones in the translation of nanomedicine from bench to bedside.
- The field is rapidly evolving, with several candidates in late-stage clinical development, increasing the likelihood of future regulatory approvals.
- Regulatory considerations emphasize patient safety, batch-to-batch consistency, and a thorough understanding of the mechanisms of action for these nanomedicine systems[11], [12], [13].

VII. CONCLUSION

Oral nanomedicine offers a novel and promising strategy to overcome the complex physiological and pathological barriers of the gastrointestinal tract. By engineering nanoparticles with specific properties, oral formulations can efficiently cross mucus layers, improve cellular uptake through various mechanisms, engage positively with gut microbiota, and modulate immune responses. These interactions enhance drug stability, enable targeted delivery, allow controlled release, and reduce systemic side effects, resulting in better therapeutic outcomes for gastrointestinal disorders such as inflammatory bowel disease, infections, ulcers, and cancer. Preclinical research using in vitro models and animal studies has shown notable improvements in drug absorption and targeted site delivery. Early clinical trials support the potential of these approaches, with several formulations advancing toward regulatory approval. Despite these advances, challenges such as variability in disease states, nanoparticle safety, and scalable manufacturing remain. Continued collaboration across nanotechnology, pharmacology, and clinicalg research is essential to refine these platforms. Strategically designed oral nanomedicines hold great promise for transforming gastrointestinal therapy, offering safer, more effective, and patient-friendly treatments that can improve global healthcare outcomes.

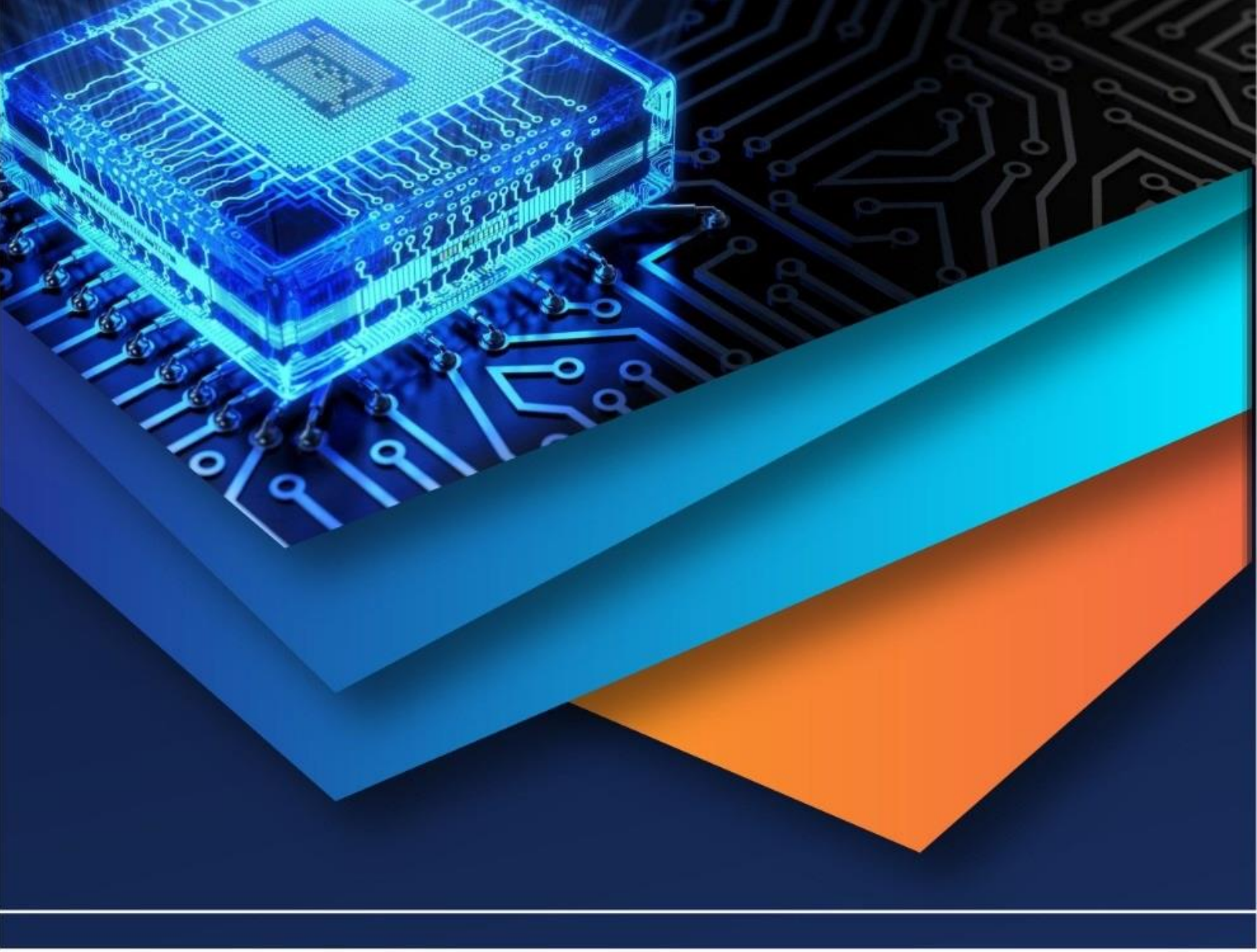
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