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The Need for Oral Insulin

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Abstract: ***Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disorder characterized by immune-mediated destruction of pancreatic β-cells, resulting in absolute insulin deficiency. Conventional insulin therapy, administered via subcutaneous injections, is effective but associated with limitations such as patient discomfort, poor compliance, storage challenges, and unpredictable absorption. Oral insulin represents a promising alternative, potentially improving patient adherence and mimicking physiological insulin delivery through the portal-hepatic system. However, oral administration is hindered by multiple barriers, including enzymatic degradation in the gastrointestinal tract, acidic gastric environment, poor intestinal absorption, and first-pass metabolism, which inactivate the protein. Recent advances in nanotechnology have demonstrated that nanoparticles can overcome these challenges by protecting insulin from degradation, enhancing intestinal uptake, and enabling controlled drug release. This review highlights the need for oral insulin, discusses the limitations of conventional therapy, explores recent developments in novel oral delivery systems, and examines regulatory and commercial aspects, emphasizing the future potential of oral insulin to transform diabetes management.***

Keywords:_Oral insulin; Type 1 Diabetes Mellitus (T1DM); Insulin therapy; Nanoparticle-based insulin delivery; β-cell dysfunction; Glucose regulation; Bioavailability; Controlled drug release; Patient compliance

I. INTRODUCTION

A. GLOBAL BURDENOF DIABETES (T1DM & T2DM)

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. According to the International Diabetes Federation (IDF), over 500 million people worldwide are living with diabetes, and this number is projected to rise significantly in the coming decades. Insulin therapy remains the cornerstone for the management of Type 1 Diabetes Mellitus (T1DM) and is often required in advanced stages of Type 2 Diabetes Mellitus (T2DM).

B. LIMITATIONS OF CURRENT INSULIN DELIVERY ROUTES

Traditionally, insulin is administered via the subcutaneous route. Although this method ensures therapeutic plasma concentrations, it fails to replicate the physiological insulin pathway, where insulin secreted by the pancreas first reaches the liver through the portal circulation. Moreover, the injectable form of insulin poses several limitations such as pain, needle phobia, inconvenience, and risk of local infections, which collectively reduce patient compliance.

C. IMPORTANCE OF DEVELOPING ORAL INSULIN

The development of an effective oral insulin formulation has thus become a major focus in diabetes research. Oral administration would not only mimic the physiological route of insulin secretion but also improve patient compliance and adherence to therapy. However, the gastrointestinal (GI) tract presents several challenges, including enzymatic degradation and poor absorption, which have delayed the successful commercialization of oral insulin products.

II. PHYSIOLOGY OF INSULIN AND GLUCOSE REGULATION

A. ROLE OF INSULIN IN GLUCOSE HOMEOSTASIS

Insulin is a peptide hormone secreted by the Beta-cells of the islets of Langerhans in the pancreas. It plays a central role in maintaining glucose homeostasis by regulating the uptake, utilization, and storage of glucose in various tissues.

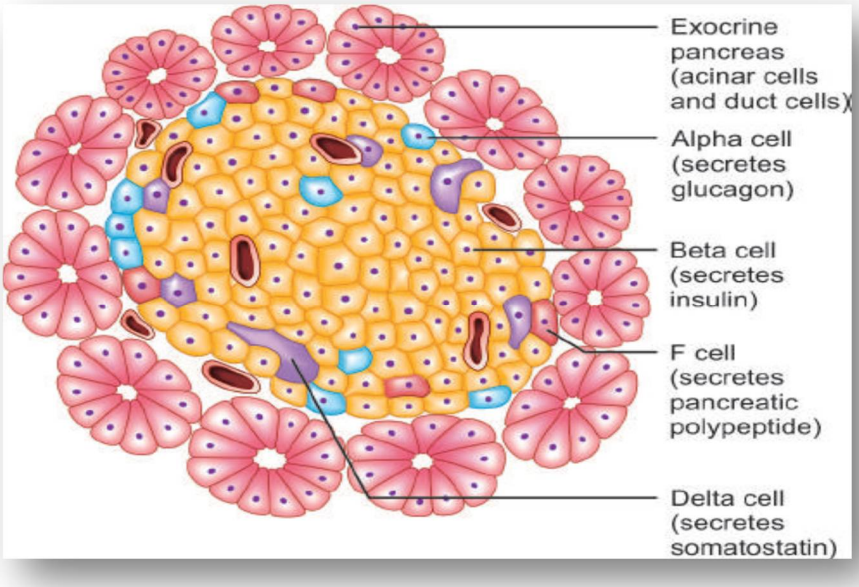

Fig 1:Islets of Langerhans in the pancreas surrounded by exocrine acinar cells.

After food intake, blood glucose levels rise, stimulating pancreatic Beta-cells to secrete insulin. This insulin enters the portal vein and first reaches the liver, where approximately 50-60% of the hormone is extracted during the first pass. This hepatic uptake is crucial for regulating glucose production by suppressing gluconeogenesis and glycogenolysis.

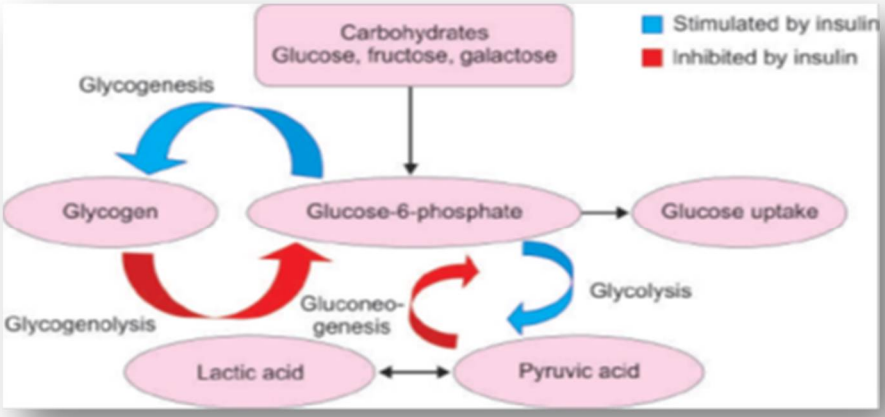

Fig 2: Actions of insulin on carbohydrate metabolism.

The remaining insulin reaches peripheral tissues such as skeletal muscle and adipose tissue. Here, insulin binds to its specific receptor–a tyrosine kinase receptor – initiating a cascade of intracellular events that promote:

- Glucose uptake via translocation of GLUT-4 transporters to the cell membrane.
- Glycogen synthesis in muscle and liver
- Lipogenesis in adipose tissue
- Inhibition of lipolysis and proteolysis

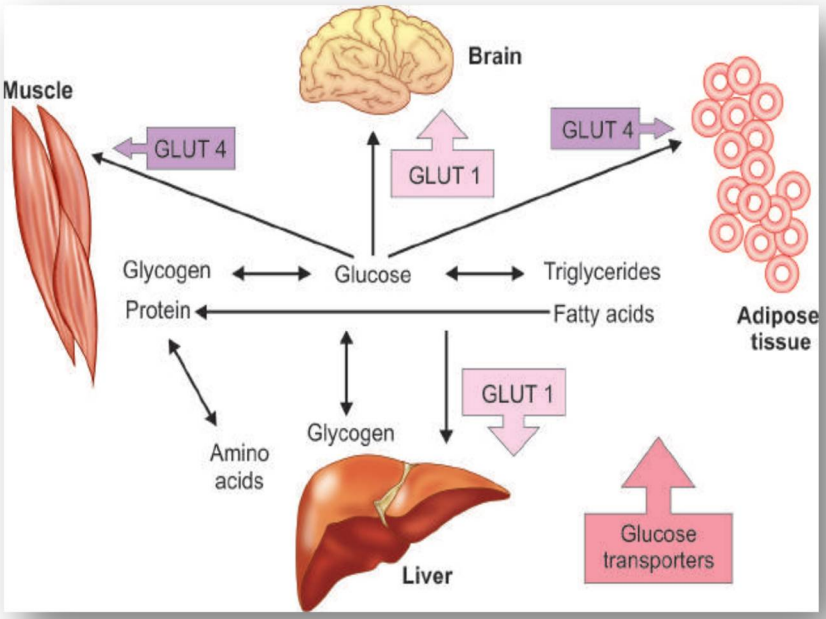

Fig 3:Glucose transporters

B. HEPATIC FIRST PASS EFFECT

In physiological conditions, insulin secreted endogenously passes through the portal circulation before entering systemic circulation. This ensures that the liver – the main site of glucose regulation – is exposed to the highest insulin concentration.

This hepatic first pass effect helps in maintaining normal fasting blood glucose levels by controlling hepatic glucose output. However, when insulin is administered subcutaneously, this natural pathway is bypassed, leading to relatively low hepatic insulin levels and high peripheral insulin concentrations, resulting in non-physiological glucose regulation.

C. WHY ORAL ROUTE MIMICS PHYSIOLOGICAL INSULIN DELIVERY BETTER THAN INJECTIONS?

An ideal insulin delivery system should mimic natural insulin secretion patterns, maintaining basal and postprandial levels in a physiological range. The oral route of insulin delivery has the potential to achieve this by directing insulin through the portal hepatic system, similar to endogenous insulin.

Hence, developing oral insulin is not only about improving patient comfort but also about restoring physiological insulin dynamics, providing better glycemic control and minimal side effects.

III. LIMITATIONS OF CURRENT INSULIN THERAPY

Although insulin therapy remains the cornerstone in the management of Type 1 Diabetes Mellitus and advanced Type 2 Diabetes Mellitus, its conventional subcutaneous route of administration has several drawbacks that limit its overall clinical effectiveness and patient acceptance.

1) Pain and Inconvenience

Frequent insulin injections are painful and inconvenient, particularly for children, elderly patients, and those with needle phobia. This discomfort often leads to poor compliance and irregular dosing.

2) Non-physiological Insulin Distribution

Injected insulin enters systemic circulation directly, bypassing the hepatic first-pass effect. As a result, the liver receives less insulin than required while peripheral tissues are exposed to higher concentrations. This imbalance can lead to peripheral hyperinsulinemia, weight gain, and risk of hypoglycaemia.

3) Compliance and Lifestyle burden

The need for multiple daily injections, sterile storage, and careful timing with meals reduces patient compliance. Carrying insulin pens and syringes can be inconvenient and socially uncomfortable.

4) Cold-chain and Cost issues

Insulin formulations require refrigeration to maintain stability. In low resource settings, lack of cold-chain maintenance can lead to drug degradation and economic loss.

5) Psychological impact

Dependence on injections may create emotional distress and a sense of social stigma among patients, decreasing their quality of life.

IV. RATIONALE/ NEED FOR ORAL INSULIN

The development of oral insulin aims to overcome the shortcomings of injectable therapy while restoring the physiological pattern of insulin action.

1) Mimicking the natural pathway

In normal physiology, insulin released from the pancreas first passes through the portal vein to the liver, regulating hepatic glucose output before reaching peripheral tissues. Oral insulin, once absorbed from the intestine, would follow a similar route via the portal circulation, thereby mimicking endogenous insulin kinetics more closely than subcutaneous injections.

2) Improved patient compliance

Oral dosage forms are painless, simple, and familiar to patients. Eliminating the discomfort and stigma of injections significantly enhances treatment adherence, especially in pediatric and geriatric populations.

3) Reduction of systemic side effects

By targeting the liver first, oral insulin can minimize systemic hyperinsulinemia and its associated adverse effects such as hypoglycemia and weight gain. This localized hepatic action results in more physiologically balanced glucose control.

4) Convenient and Cost-effective Therapy

Tablets or capsules are easier to handle, transport, and store. They do not require sterile syringes or refrigeration, reducing overall treatment costs and improving accessibility in developing regions.

5) Psychological and Social benefits

Oral insulin removes the fear and embarrassment associated with injections, improving overall patient satisfaction and quality of life.

V. CHALLENGES IN DEVELOPING ORAL INSULIN

Although the concept of oral insulin offers tremendous therapeutic potential, several biological and pharmaceutical barriers limit its successful development. The gastrointestinal(GI) tract poses the most significant challenge due to its complex environment, which leads to poor insulin stability and absorption.

Firstly, enzymatic degradation is a major issue. Insulin, being a peptide hormone, is highly susceptible to breakdown by proteolytic enzymes such as pepsin in the stomach and trypsin and chymotrypsin in the intestine. This results in rapid loss of biological activity before it can be absorbed.

Secondly, acidic pH in the stomach(pH~1.5-3.5) leads to structural denaturation of insulin molecules, further reducing their effectiveness.

Thirdly, the intestinal epithelial barrier restricts the passage of large hydrophilic molecules like insulin(molecular weight~5800Da). Tight junctions between epithelial cells prevent insulin from diffusing across the intestinal wall, leading to extremely low permeability.

Additionally, insulin shows poor bioavailability(<1%) when administered orally, mainly due to limited absorption and extensive first-pass metabolism. Formulation stability during manufacturing, storage, and transit through varying pH conditions also remains a technical hurdle.

Therefore, this challenge is twofold-protecting insulin from degradation and ensuring its effective transport across the intestinal mucosa into systemic circulation.

VI. STRATEGIES TO OVERCOME BARRIERS

To overcome these biological and physiological obstacles, several innovative drug delivery strategies have been explored to improve insulin`s stability, absorption, and bioavailability.

A. Use of Enzyme inhibitors

Protease inhibitors such as aprotinin, soybean trypsin inhibitor, and bacitracin are incorporated in formulations to protect insulin from enzymatic degradation. These agents temporarily inhibit the activity of GI proteases, allowing insulin to remain intact for absorption.

B. Permeation enhancers

Absorption enhancers like bile salts, fatty acids, and surfactants (e.g., sodium lauryl sulfate, sodium cholate) increase intestinal epithelial permeability by opening tight junctions or modifying membrane fluidity, facilitating paracellular transport of insulin.

C. Nanoparticle and Lipid based carriers

Nanocarriers such as polymeric nanoparticles, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) protect insulin from enzymatic attack and enable controlled release.

Lipid-based carriers also improve mucosal adhesion and lymphatic uptake, bypassing hepatic metabolism.

D. Mucoadhesive and pH sensitive polymers

Polymers like chitosan, carbopol, and Eudragit are used to form mucoadhesive coatings that help insulin adhere to the intestinal wall for longer residence time. Enteric coatings or pH sensitive polymers ensure insulin release only in the intestine(pH>6), protecting it from gastric acid.

E. Microencapsulation and Ionotropic Gelation

Microencapsulation using biodegradable polymers (e.g., alginate, PLGA) forms protective microcapsules around insulin, enhancing stability. Ionotropic gelation techniques enable encapsulation in calcium-alginate gels, creating a protective barrier against enzymatic attack.

F. Self-emulsifying Drug Delivery System (SEDDS)

These lipid-based systems form fine oil-in-water emulsions upon contact with GI fluids, promoting solubilisation and enhancing absorption through lymphatic transport pathways.

G. Co-delivery with Absorption Modifiers

Combination of insulin with agents like Vitamin B12 analogues or lectins helps in receptor-mediated transport across the intestinal mucosa.

VII.RECENT DEVELOPMENTS IN ORAL INSULIN RESEARCH

A. ORAMED-ORMD-0801 (Oral insulin capsule)

Oramed`s ORMD-0801 is an enteric-coated oral insulin candidate designed with protease inhibitors and absorption enhancers to deliver insulin to the small intestine. Company data and corporate presentations report promising early-phase signals, but a later pivotal trial did not meet its primary endpoints, prompting reanalysis and program adjustments. The program has had mixed outcomes and Oramed announced reinitiation/targeted trials after reviewing data.

B. BIOCON-Insulin tregopil and related programs

Biocon`s oral insulin analogues (e.g., insulin tregopil) have advanced through multiple clinical evaluations examining PK/PD, food effects, tolerability, and efficacy. Recent published reviews and company reports summarize trials showing proof-of-concept for prandial glucose control in some cohorts, but overall bioavailability and consistent glycemic benefit remain limited, requiring further formulation optimization.

C. DIASOME-Hepatic directed vesicle (HDV) insulin lispro

Diasome is developing a hepatic-directed vesicle formulation of insulin lispro (HDV-Insulin Lispro) intended to improve hepatic targeting after oral or subcutaneous administration. The company has completed enrolment in Phase 2b OPTI-2 trials and reported ongoing clinical evaluation for Type-1 diabetes to examine efficacy and hypoglycemia outcomes.

D. OTHER ACADEMIC/INDUSTRY EFFORTS

Multiple groups are working on nanoparticle carriers (PLGA, chitosan), SLNs/NLCs, pH sensitive micogels, mucoadhesive systems, glucose-responsive nanoparticles, and receptor-mediated uptake (e.g., vitamin B12 conjugates). Recent systematic reviews and articles summarize that while many systems improve insulin stability or local intestinal uptake in animals, translation to robust clinical glucose lowering in humans remains the major barrier.

Although none of the formulations have yet received FDA approval, the ongoing progress indicates that a commercially viable oral insulin product may become available in the near future. Continued improvements in formulation design, material science, and clinical translation are key to achieving this milestone.

VIII. REGULATORY ASPECTS OF ORAL INSULIN

The development of oral insulin involves both pharmaceutical and biological regulations because insulin is a biotechnologically derived peptide hormone.

Regulatory approval requires proof of safety, efficacy, quality, and stability just like any other insulin formulation- but oral insulin faces additional scrutiny due to its novel route of administration and complex formulation design.

A. Preclinical Requirements

Before testing in humans, oral insulin formulations must undergo:

- Toxicity studies on animals to ensure no damage to the gastrointestinal (GI) tract.
- Absorption and bioavailability studies to show that insulin remains active after oral administration.
- Stability testing to confirm that insulin is not destroyed by stomach acid or enzymes.

B. Clinical Trial Phases

- Phase I: Conducted on healthy volunteers to test safety, tolerance, and how much insulin is absorbed.
- Phase II: Small studies on diabetic patients to check dose range and early effectiveness in lowering blood sugar.
- Phase III: Large trials comparing oral insulin with conventional subcutaneous insulin to confirm long-term efficacy and safety.

Regulating authorities like the U.S. FDA, EMA and CDSCO evaluate these results before granting marketing approvals.

C. Quality and Manufacturing Controls

- Oral insulin requires strict manufacturing standards under Good Manufacturing Practices (GMP).
- Special attention is given to formulation stability, batch-to-batch consistency, and packaging integrity to maintain the peptide`s biological activity.
- Excipients used as absorption enhancers or enzyme inhibitors must be proven safe for long-term use.

D. Current Status

- No fully approved oral insulin is yet in the market, but several candidates (like ORMD-0801 by Oramed, HDV-I by Diasome and Biocon`s oral insulin) are in advanced clinical stages.
- Regulatory agencies are showing more openness to novel delivery technologies, provided safety and reproducibility are demonstrated.

IX. COMMERCIAL ASPECTS OF ORAL INSULIN

The commercial potential for oral insulin is huge, driven by the global burden of diabetes and patients need for a convenient therapy.

A. Market Demand

- Over 530 million people worldwide live with diabetes, many requiring insulin therapy.
- Studies show that over 70% of insulin-dependent patients would prefer oral tablets if they were equally effective as injections.

B. Economic Impact

- Oral insulin could reduce long-term healthcare costs by improving patient compliance and decreasing hospital admissions related to poor glucose control.
- It may also reduce costs related to needles, syringes, and disposal waste, making it more eco-friendly.

C. Industry Interest

- Major companies like Novo Nordisk, Eli Lilly, Sanofi, Oramed, and Biocon are investing heavily in oral and non-invasive insulin technologies.
- Collaboration between biotech firms and academic institutions is helping to overcome formulation challenges.

D. Market Barriers

- High R&D costs and manufacturing complexity make oral insulin more expensive to develop initially.
- Regulatory approval delays and low bioavailability have slowed commercial launches.

X. CONCLUSION

Insulin remains the cornerstone in the management of diabetes mellitus, yet its injectable route poses significant limitations such as pain, inconvenience, and poor compliance.

The concept of oral insulin emerges as a patient-friendly and physiologically superior alternative, capable of mimicking the natural insulin pathway through the liver.

Despite numerous scientific and regulatory challenges- such as instability in the GI tract, poor absorption, and complex manufacturing – recent advances in nanotechnology, formulation science, and drug delivery systems are bringing this vision closer to reality.

Regulatory bodies are cautiously optimistic, and several late-stage clinical trials indicate that oral insulin could soon become a viable therapeutic option. Once commercialized, it is expected to improve patient compliance, enhance quality of life, and reduce the healthcare burden associated with injectable therapy.

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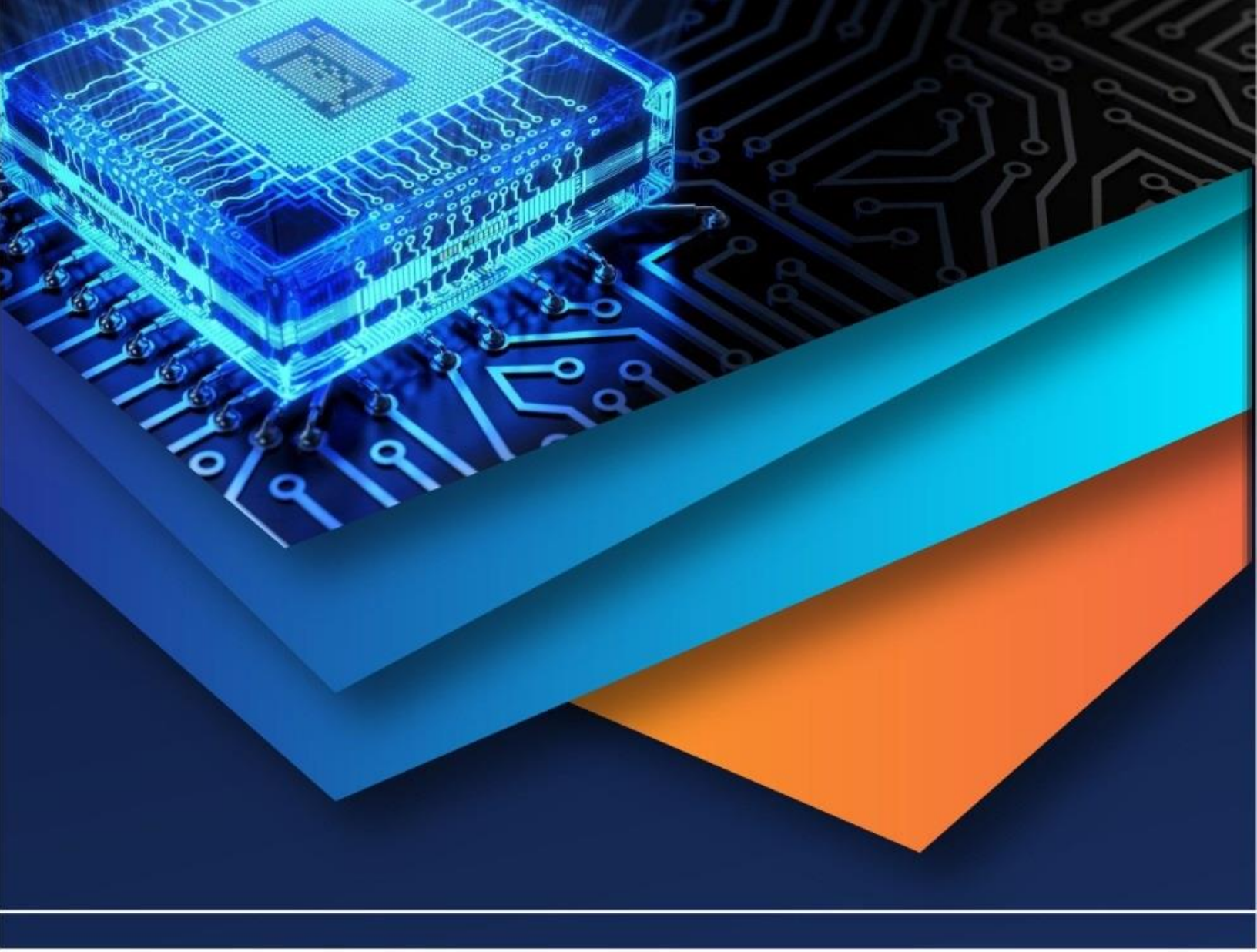

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