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Microneedles: An Approach in Transcutaneous Drug Delivery: A Review

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Abstract: ***Transcutaneous drug delivery carried out a carner in the conveying of drugs to get direct acces across the scin deep into the systemic circulation. Transcutaneous drug delivery has a number of benefits including impoved patient compliance, sustained release, dealy of gastric irritation, as well as elimination of pre-systemic first-pass eflect. It gives attraction to many researchers due to various conventional medicine ben fits. Due to the strong matches of pral drug delivery systern and the pain related with the use of needles case of injections, drug delivery research has greatly adjusted towards the transderntal route. Delivery of drugs via transcutaneous route has proved to be the convenient route for various dinical implications in this review, we tell about different types of microneedles are described and its methods of assemble. Microneedles can be fabricated in different forms like dedicate, solid, and dissolving. There are also hydrogel forming microneedles in relation of hydrogel forming microneedles, special attention, these are ine vative microneedles which does not contain drugs but imbibe interstitial fluid to form continuous conduits between dermal microcirculation and an attached patch-type reservoir. Regulatory give the go ahead approved several microneedles for clinical uses are also examined. The last part of this review discusses concerns and challenges about microneedles use***

Keywords: ***Transcutaneous, Microneedles, skin, Drug Delivery, Permeation, Systemic Circulation, Hydrogel-Forming Microneedles.***

I. INTRODUCTION

protects the human body against Entrance of toxic chemicals and egress of water. In soite of the large surface area of the skin, it is challenging for compounds including drugs and vaccinas to cross the skin in therapeutically appos teamounts. 15/The outer most layer of the skin le. StratDrug delivery via tra cutaneous mute across the skin provides the most convenient route for various clinical inference deep into the systemic circulation and it developed for controlled drug delivery. Tia cutaneous drug delivery system represents a systent which delivers the drug effectual transversely the hurman skin. These are generally describes as the devices which corlain drug molecules of delined surface ered that delivers the causal determinism emount of drug to the entire skin surface at a Causal determinism rata. These systents have been designed to deliver the drug through the skin to the systemic circulation, it is defined as a self-contained. Creative delivery system which is considered to deliver the drug upon application into the skin, at controlled rate to the systemic circulation (1) Hypodermic needles generally used in clinical practice to deliver medications across the skin into the blood flow Injections with hypodermic neesies are essential from a Clinical current situation, but painful. They induce hypersensitivity: bruising and bleeding at the po the spot of administration, and in some cases it associate with risks of contamination.(2) the difficulty in crossing the skin is effected by its anatomical peculiarities. (3,4) The skin is the largest organ in the body. It is about 15 meter so in adults and it provices protection for internal organs and um corneum play a major role of obstruction in the sien. The stratum corneum is 10-15 µm thick 15-20 corneacyta layers. It is made up form carnencytes embedded in an intercellular lipid matrix. In hurman stratum corneum, the important pid class they are free fatty acids, ceramides and cholesterol which form two lamellar phases. These include the short frequently phase and the long periodicity phase with repeat distances of approximately 6 and 13 run. Under the stratum corneum is the applicable epidermis, which is a cellular, avascular tissue measuring 50 100 µm comoact (6) The viable epidermis consists mainly of keratinocytes and approximately -40% protein, 40% water and 15%-20% lipios. The flow epidermal-deral junction consists of capilla that project into the dermis. Calls in the isasal layer of the epidermis forme the most essentialstructural and functional connection to the dermis below (7) The stratum corneum and viable epidermis together form the full epidermis. Base membrane and tight junctions may both offer alive to the transport of molecules across the epidermis (8) Relow epidermis layer is the complicated dennis, made up a compact collagen bundles and coarse elastic fibers. The denne contains blood vessels, lymphatics and nerves, as well as the different skin appendages, Below the complicated dermis lies the hypodermis Subcutaneous fat Uissue), which may have a thickness of up to several millimeters (9)

A. Advantages Of Transcutaneous Drug Delivery

1) Avoids first cass hepatic metabolism
2) Continue unchanging bland levels for longer period of time
3) Decrease the dose of administration.
4) Decrease unwanted/ side effects
5) Decreases gastro-intestinal side effects.
6) Easy to discontinue in matter of toce effects.
7) Increased patient compliance.
8) Great benefit for patients who are unconscious.
9) Provices an abe ty to modify the properties of biologica postruction to better absorption

B. Disadvantages Of Transcutareous Drug Delivery System

1) Drug must have some desirable physico-chemical properties to penetrate through stratum conium.
2) Drugs for daily dose ess than 5 mg/day are alternative. Il drug dose is than 10-25 mg/day the TDD will be hard.
3) Local exasperate at the site of administration may be caused by drug adhesive/ other extender in patch,
4) Clinical need must be clearly established.
5) The barrier function of skin modify form one on the spot to another from person to person and with age.
6) Foor skin penatrable limits the number of crug that can be delivered in this route
7) TDD can not deliver innic dinig
8) Drugs of large molecular. Can not he conceptualisation as TDD
9) TOD can not deliver the drugs in throbbing lashion.

II. MICRONEEDLES

Microneedles are innovative drug delivery systems that resemble traditional needles, but they differ in that they are engineered at the micron scale, measuring between 1-100 microns in length and 1 micron in diameter. Defined as micro-scale needles, these are organized on a transdermal patch. Microneedles are now being employed to improve the transdermal absorption of both small and large molecules. (Gupta et al., 2011) Transdermal microneedles create tiny pores in the skin, facilitating the drug's passage through the dermis. When these microneedles are arranged in arrays on a backing suitable for skin application akin to a bandage, the resulting device is referred to as a microneedle patch. (Henry et al., 1998) Microneedles can be classified into four types: hollow, solid, coated, and polymer. Hollow microneedles function similarly to standard hypodermic needles but are shorter in size, allowing a liquid formulation of the drug to be delivered through openings in the mic

A. Characteristics of Microneedles

The characteristics of micro needles include ruggedness, microneedles developed must becapable of insertion deep into the skin without breaking. (Hong et al., 2013) They should be manufactured by taking optimum size and if they are too long, upper portion of micro needles may not have enough rigidity and could undergo breakage. Before penetration. Microneedles generally used in controlled drug released, they should deliver the controlled amount of drug at a definite and predetermined rate. The micro needles should be able to penetrate the drug to the required depth in the tissues of the body. (Chen et al., 2013) Generally, the dimensions of micro needles can vary depending on the types of microneedles.

Typical microneedles. Geometries may ranges from 150-1500 microns in length, 50-250 microns in base width, and 1-25 microns in tip diameter. The tips of microneedles are of different shapes like triangular, rounded or arrow shaped. (Pearton et al., 2012) Most of microneedles make by materials includes. Glass, silicone (of brittle nature), metals such as stainless steel, solid or coat of gold over nickel, palladium, cobalt and platinum and biodegradable polymers. (Khan et al., 2014) Effective characteristics in case of ideal microneedles, designing of microneedles can be such so as to minimize the pain. Various studies revealed that specific micro needles of about a couple hundred microns length were reported to be painless. It was reported by various authors that 13-times increment in needle length (i.e., 500-1500 microns) increases the pain by 7 times (i.e., 5-35% caused by hypodermic needle). If the length remains constant, an Increase in number of microneedles (l.e., 620 micron long) 10 fold from 5- 50 also increases the pain by 3 folds. (Ma Y et al., 2014) (Alvarez et al., 2001

B. Fabrication of Microneedles

Microneedles can be produced using micro-electromechanical systems (MEMS). The fundamental process can be broken down into three stages: deposition, patterning, and etching. Deposition specifically refers to the creation of thin films with thicknesses ranging from a few nanometers to approximately 100 micrometers. Patterning involves transferring a design onto the film. Lithography is utilized to imprint a pattern onto a photosensitive substrate through targeted exposure to a radiation source such as light. This method can encompass photolithography, ion beam lithography, and electron beam lithography. Diamond patterning is also an effective lithography technique. Etching is a method of employing strong acids or mordants to carve into the exposed areas of a material's surface, thereby creating a design, and it can be classified into two types: wet etching or dry etching. The choice of any of the aforementioned techniques primarily depends on the construction material and the specific type of microneedles. Microneedles can be fabricated in various forms, including hollow, solid, and dissolving types.

C. Hollow Microneedles

Hollow microneedles feature a hollow center within the needle. These microneedles can be produced using standard 30 gauge hypodermic needles. The pressure and flow rate in hollow microneedles can be adjusted for rapid bolus injection, slow infusion, or varying delivery rates. Additionally, hollow microneedles can facilitate the administration of a larger volume of drug solution. When inserted into the skin, the hollow bore bypasses the stratum corneum and creates a direct pathway to the deeper layers of the epidermis. A pattern of 4 x 4 holes was created in a polyetheretherketone mold (with a diameter of 9 mm). The needles were then inserted through these holes at predetermined lengths of 300, 550, 700, and 900 µm. Afterward, the needles were trimmed and secured at the back of the mold. A manual applicator was also developed for the array of microneedles (Donnelly et al., 2013). These microneedles are primarily used to inject drug solutions directly into the skin. They are costly to produce and require sophisticated microfabrication techniques. With a hollow bore design, these microneedles enable drug transport through the well-defined needle interiors by diffusion or expedited delivery through pressure-driven flow. The mechanical properties and biocompatibility potential of silicon microneedles have been evaluated. However, issues such as high production costs and fragility have motivated researchers to explore alternative materials (Chen et al., 2007). Hollow silicon microneedles were created using a process of isotropic etching followed by anisotropic etching to achieve a tapered tip. This technique resulted in silicon microneedles that are 300 µm tall, with an outer diameter of 130 µm and an inner diameter of 110 µm at the tip, tapering to an 80 µm inner diameter and a 160 µm outer diameter at the base. To enhance the biocompatibility of these microneedles, they were coated with 500 nm of titanium using a sputtering method, followed by a gold coating applied through electroplating. Hollow microneedles can also be manufactured using other systems like micro-electro-mechanical systems (MEMS) technologies, including laser micromachining, deep reactive ion etching, integrated lithographic molding, and wet chemical etching, as well as X-ray photolithography. The AdminPen microneedles have also been developed, consisting of hollow stainless steel microneedles ranging from 600 to 1500 µm in length, which can be connected to a syringe for delivering liquid formulations. AdminStamp devices incorporate AdminPatch microneedle arrays fixed to an applicator with six stainless steel screws. These can also perforate the skin without liquid. When utilized in this manner, they function like solid microneedles, initially creating holes before drug solution application (Sheer et al., 2011). Hollow microneedles can directly deposit compounds into the viable epidermis or dermis, thus bypassing the stratum corneum. This is particularly beneficial for delivering compounds with high molecular weights, such as proteins, oligonucleotides, and vaccines. The transdermal delivery of insulin remains a substantial scientific hurdle. Cheung et al. employed 1100 and 1400 µm long stainless steel microneedles to deliver insulin through porcine skin.

D. Solid Microneedles

Solid microneedles utilize passive diffusion for drug delivery by creating microchannels that enhance skin permeability, followed by placing a drug-loaded patch over these channels. From a safety standpoint, it is preferable for the microchannels to seal quickly after the needle is removed, to avoid the permeation of harmful toxic substances or the risk of infection from pathogenic microorganisms. Henry et al. employed a deep reactive ion etching technique to produce silicon microneedles, starting with the deposition of a chromium masking material on silicon wafers which was then patterned into dots with a diameter similar to the base of the intended microneedles. The wafers were subsequently placed into a reactive ion etcher and subjected to plasma etching, allowing the areas shielded by the metal mask to form microneedles. Vinayakumar et al. developed a series of rectangular cup-shaped silicon microneedles that potentially decrease drug leakage, enhancing drug delivery efficiency, and allowing for the incorporation of multiple drugs. The resulting solid microneedles with a rectangular cup-shaped tip are 200 µm tall. The dimensions of the cup-shaped tips are 60x60 µm (length x breadth) with a depth of 60 µm. Drug filling into the cups was achieved using a unique drop coating

technique. Solid microneedles can be constructed from silicon, metal, and polymers. (Nolan et al., 2003) (Bendas et al., 2007). Microneedles manufactured from polymers have also been explored. Olatunji et al. created microneedles from biopolymer films derived from tilapia fish scales (Oreochromis sp.) using a micromolding method. The microneedles were effectively inserted into porcine skin and demonstrated gradual dissolution at 0, 60, 120, and 180 seconds after insertion. The microneedles contained methylene blue as a model drug and successfully penetr Solid microneedles facilitate drug delivery through passive diffusion by creating microchannels that enhance skin permeability, followed by placing a drug-loaded patch on these channels. From a safety standpoint, it is important for the microchannels to close shortly after the removal of the needles to avoid the permeation of harmful toxic agents or infection from pathogenic microorganisms. Henry et al. utilized a deep reactive ion etching technique to produce silicon microneedles, beginning with the deposition of a chromium masking layer onto silicon wafers, which was then patterned into dots approximating the diameter of the desired microneedles. The wafers were subsequently placed into a reactive ion etcher and exposed to plasma etching. The sections protected by the metal mask remained intact, forming the microneedles. Vinayakumar et al. created an array of rectangular cup-shaped silicon microneedles. These microneedles demonstrate the potential for decreased drug leakage, thereby enhancing drug delivery efficiency and allowing for the possibility of administering multiple drugs. The solid microneedles produced have a height of 200 µm, with the cup-shaped tips measuring 60x60 µm (length x breadth) and a depth of 60 µm. The cups are filled with drug utilizing a novel drop coating method. Solid microneedles can be made from materials such as silicon, metal, and polymer. Olatunji et al. developed microneedles from biopolymer films derived from tilapia (Oreochromis sp.) fish scales using a micromolding approach. These microneedles were successfully administered into porcine skin and displayed gradual dissolution at 0, 60, 120, and 180 seconds post-insertion. The microneedles incorporated methylene blue as a model drug and effectively penetrated porcine skin.

E. Dissolving Microneedles

Dissolving microneedles provide several benefits, including a convenient one-step application process for patients. These microneedles are designed based on the ”poke and release” concept. They are constructed from polysaccharides or other polymers. Upon application and subsequent dissolution, these microneedles deliver the encapsulated medication directly into the skin. Micromoulding is the preferred method for producing dissolving microneedles (Bendas et al., 2007). Some drugs and vaccines are sensitive to heat, so molds are typically filled with solutions of medications and excipients and subsequently dried under gentle conditions.

The production process involves pouring the polymer solution into female molds, filling the microcavities with vacuum or pressure, and drying it under ambient conditions, along with methods like centrifugation or additional pressure (Kumar et al., 2011). Master structures for microneedles, along with supporting arrays and pressing tools, were developed by Chen et al. using a specialized electro-discharge-machining technique. Each master structure was composed of 64 (18x8) microstructures. Polydimethylsiloxane (PDMS) molds were manufactured as exact inverse replicas of the master structures. To avoid adhesion to PDMS molds, all master structures underwent a sputter-coating process with platinum. The PDMS molds were created by pouring the PDMS solution over the master structure and allowing the polymer to cure overnight at room temperature. After curing, the PDMS molds were carefully removed from the master structures and utilized for producing chitosan microneedles, polylactic acid supporting arrays, and polycaprolactone pressing tools.

F. Coated Microneedles

Coated microneedles are defined as microneedles that have a drug-containing dispersion applied to their surface. Numerous methods have been documented in the literature for the fabrication of coated microneedles. (Saroha et al., 2011) A method utilizing electrohydrodynamic atomization principles to produce smart coatings for microneedles has been discussed.

Stainless steel microneedles, ranging from 500 to 900 µm in height, were linked to a ground electrode within the setup for electrohydrodynamic atomization, with variations in deposition distance and collection techniques employed for an ethanol: methanol (50:0) vehicle system.

This method was utilized to create both nano- and micrometer-sized pharmaceutical coatings. Fluorescein dye, which can function as a potential drug, sensory material, or marker for disease states, and polyvinylpyrrolidone, which acts as a polymer matrix, made up the other components of the coating formulation. By altering the excipients and the coating process, particles ranging from 100 nm to 3 µm and fibers between 400 nm and 1 µm were deposited on the microneedles in a controlled and selectable manner. (Tabassum et al., 2011)

G. Hydrogel-Forming Microneedles

Recently introduced to the market, the first two microneedle-based products, Soluvia and Micronjet, utilize metal and silicon as their foundational materials, respectively. However, the current trend in microneedle research has acknowledged the biocompatibility issues linked with silicon, as well as the risk of improper re-use of silicon or metal microneedles, which can remain intact after being removed from a patient's skin. This recognition has spurred the development of various technologies aimed at addressing these challenges. In this context, recent studies have concentrated on microneedles made from aqueous polymer gels. One notable approach involves utilizing hydrogel-forming microneedles. Unlike traditional dissolving polymer microneedles, this drug delivery system allows for the administration of drug and biomolecule doses unrestricted by

III. EVALUATION PARAMETERS (VANDERVOORT ET AL., 2008)

The evaluation of microneedles in vitro is conducted using various media such as agarose gel and methanol for the insertion of the microneedles. In vitro assessments are employed to analyze the properties of newly tested devices or compounds. The primary objectives of in vitro evaluation for microneedles include optimizing the microneedles, determining the penetration and bending forces, assessing the strength of the microneedles, evaluating the dissolution rate of the coating materials, and estimating the efficiency of drug delivery. The following methods are utilized for conducting in vitro studies:

1) *Method 1:* In vitro techniques assess the delivery effectiveness of the microneedles. This assessment involves integrating the microneedles with a Paradimethylsiloxane biochip, into which black ink is injected by the microneedles into a petri dish containing methanol. Right triangular microneedles with taper angles of 8.5 and 15 degrees, as well as isosceles triangular microneedles with taper angles of 9.5 and 30 degrees, have been utilized for this purpose.
2) *Method 2: This* approach involves injecting a diluted solution of Rhodamine B dye through the microneedles into 1% agarose gel to investigate the penetration and flow of the solution once it has permeated the gel.
3) *Method 3:* This method evaluates microneedles by inserting them into porcine cadaver skin and pig cadaver skin for durations of 10 to 20 seconds and up to 5 minutes, respectively. It is used to assess delivery efficacy and the dissolution rate of the coated material—coating applied to the microneedle tips that may include vitamin B, calcein, or sulforhodamine. (Yadav et al., 2011)

IV. IN VIVO TESTING OF MICRONEEDLES

Preclinical in vivo studies typically involve subjects such as mice, rabbits, guinea pigs, monkeys, and more. The primary aim of in vivo testing is to evaluate the safety and potential toxicity of the tested compounds. Key goals of in vivo microneedle testing encompass conducting skin toxicity evaluations, determining penetration forces in various skin types, assessing mechanical stability, analyzing bending and breakage forces, and carrying out a variety of non-clinical safety and pharmacological studies, including the examination of immunogenicity, genotoxicity, skin sensitization and allergenicity, developmental toxicity, acute and chronic dermal toxicity, and carcinogenicity. (Yadav et al., 2011) (Paik et al., 2003)

1) *Method 1:* This in vivo method involves inserting microneedles into the veins of the tails of hairless mice. It serves to determine the penetration force of the microneedles into the skin.
2) *Method 2:* In this in vivo testing method, Rhodamine B is injected into the tail of a laboratory mouse, followed by anesthesia, to ascertain the penetration and bending breakage forces.
3) *Method 3:* This method is designed to evaluate vaccine delivery using microneedles. Ovalbumin serves as a model protein antigen, which is administered into hairless guinea pigs via solid metal microneedles at a dosage of 20 µg over a span of 5 seconds, escalating up to a total of 80 µg.
4) *Method 4:* In this approach, rabbits are used to assess vaccine delivery. They receive the anthrax vaccine containing recombinant protective antigen (rPA) sourced from Bacillus anthracis through solid and hollow microneedles.

V. CLINICAL TRIALS AND MARKETED PRODUCT OF MICRONEEDLES (Jepps et al., 2013)

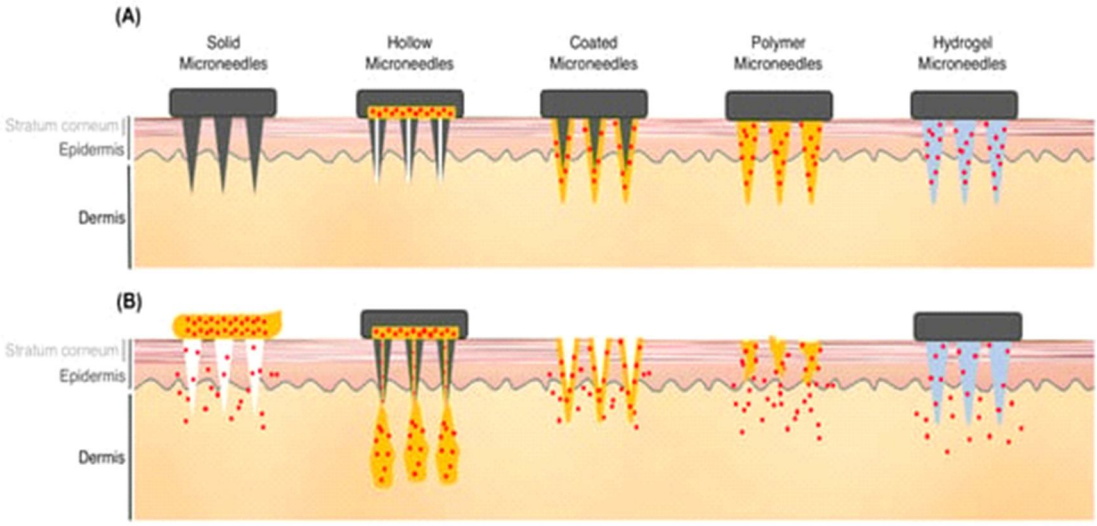
Microneedles were developed as a technology for administration. of peptides, proteins, immunobiological, cosmetics and drugs as well as for biofluidic analysis. Intanza/IDflu is the first intradermal influenza vaccine marketed in Europe, Canada and Australia. Recently it was approved by the USFDA for marketing in the USA. ZP-PTH is a product developed by Zosano Pharma for the treatment of severeosteoporosis, which demonstrated excellent efficacy and safety in Phase. II clinical trials and now is ready for Phase III study. Few examples of marketed products based on microneedle technology, together with their possible use given table. (Pearton et al., 2012) It would appear that many of the currently marketed applicators are utilized for improving the efficacy of cosmetic products.

In 2009, six-month, randomized, multicenter, blinded, multi-dose, Phase 2 clinical study using MN to deliver recombinant human parathyroid hormone 1-34, teriparatide was carried out. The product has completed Phase 2 clinical trials and is scheduled for Phase III trials. If approved, it will be used for the management of osteoporosis. The product is based on titanium microneedle arrays produced by photochemical etching. The MN come with a reusable applicator, NanoPass Technologies also has an intellectual property-backed product called MicronJet". It is a single use, microneedle-based device for intradermal delivery of protein, drugs and vaccines

Table 1. Marketed product of microneedles (Pearton et al., 2012)

Brand Name	Manufacturer	Application
Micro-Trans	Valeritas Inc., USA	It can easily deliver the drug into dermis without limitations of drug size, structure or the patient's skin characteristics.
Onvax Becton	Dickinson, USA	It is a skin micro abrader having plastic microneedles for disruption of stratum corneum for the delivery of vaccines.
AdminPen	AdminMed, USA	Liquid pharmaceutical formulation or cosmetics can be conveniently injected into the skin.
NanoCare,	NanoPass Inc.	Israel It is a small hand-held device for rejuvenation of skin and to boosts the cosmetic effect of topical applications.

Images of type of microneedles based on drug delivery



VI. CONCLUSION

Microneedles, whether utilized as patches or arrays, have emerged as promising vehicles for the efficient transdermal administration of various macromolecular medications. Numerous research studies have validated that microneedles can serve as effective carriers to enhance permeation into systemic circulation, offering a painless, efficient, and safe method for drug delivery. In the future, microneedles are expected to play a significant role in the development and design of controlled drug delivery systems for a range of medications. These pain-free systems are gradually gaining recognition and are likely to become key devices for controlled drug release going forward. Consequently, it is concluded that these systems represent an effective and superior option compared to traditional needle-based formulations for transdermal delivery.

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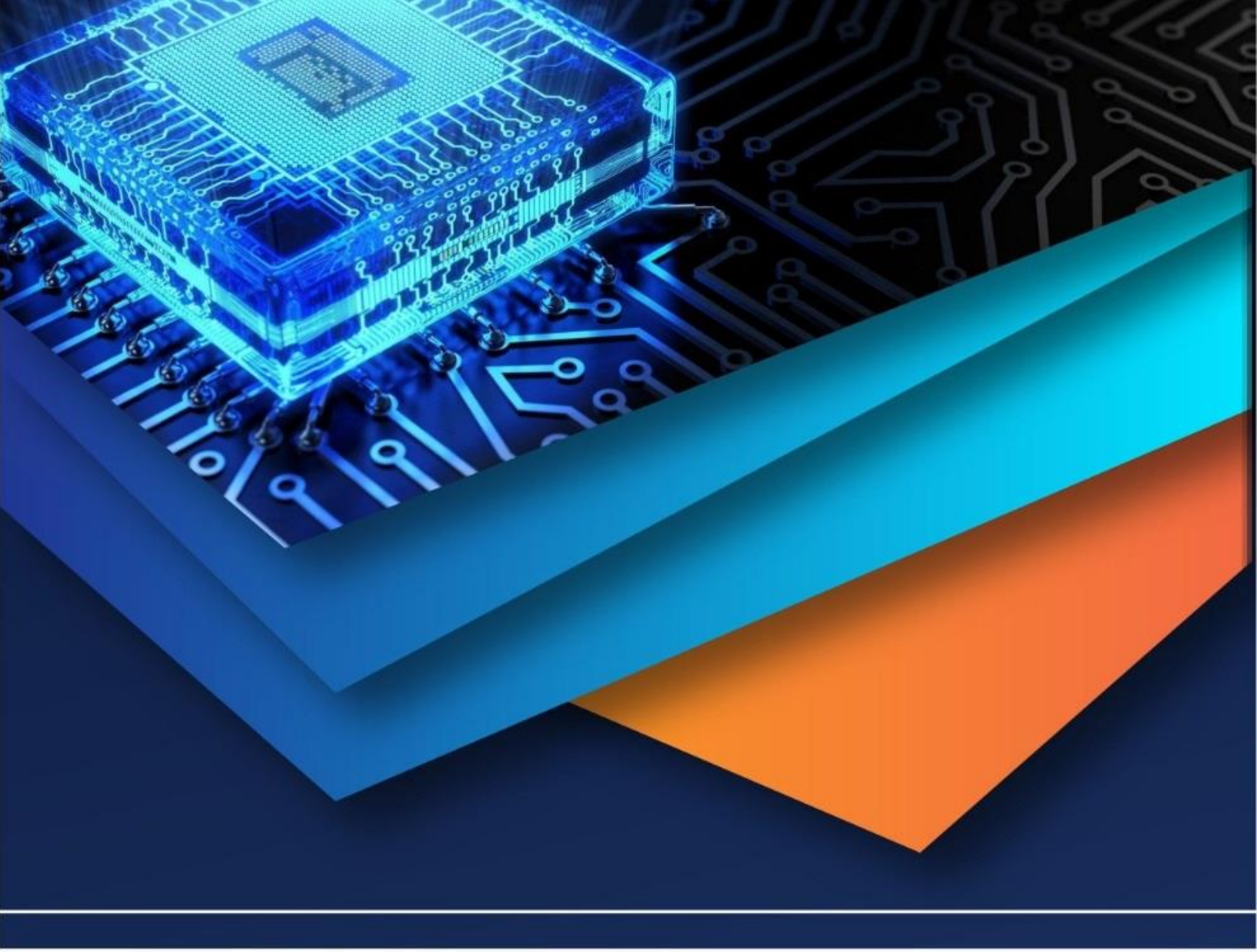

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