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A Review on Solid-lipid Nanoparticle

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Abstract: ***Hydrophilic and hydrophobic medicines can both be carried by solid lipid nanoparticles (SLNs), which are solid core lipid nanocarriers. They are one of the favoured options for medication delivery since they may be constructed of components that are biocompatible. Surface alterations of SLNs may also provide them distinctive qualities like mucoadhesiveness or targeting capacity. A wide range of drug delivery technologies are being developed at an astounding rate. The two main compounds that are widely delivered to target areas are various manufactured nanoparticles and medications with poor pharmacokinetic and solubility characteristics. The features of biodegradability and nontoxicity make nanolipid dispersions (liposomes, deformable liposomes, virosomes, ethosomes, and solid lipid nanoparticles) the best colloidal carriers for administration. Solid lipid nanoparticles (SLNs), which may be manipulated to demonstrate a variety of benefits over liposomes and polymeric nanoparticles, are the most prevalent among them.***

The writers of this paper have discussed everything from the fundamentals of SLNs to how they are used in controlled medication delivery. More precisely, the authors covered SLN-related patent disclosures for the years 2014–2022, although they also included a summary of those for the years 2008–2019.

I. INTRODUCTION

Materials now come in a variety of particle sizes, from microscopic to nanoscale, thanks to technological advancements over the past two decades. Materials' total surface area is increased by several orders of magnitude as their particle size is reduced at the nanoscale scale. Nanoparticles are defined as particles with a size between 1 nm and 1000 nm. Although the term "nano" is simple to define, it has a wide range of applications. Several nano-based systems made up of various materials that can be used as nanocarriers are shown in Fig. 1.

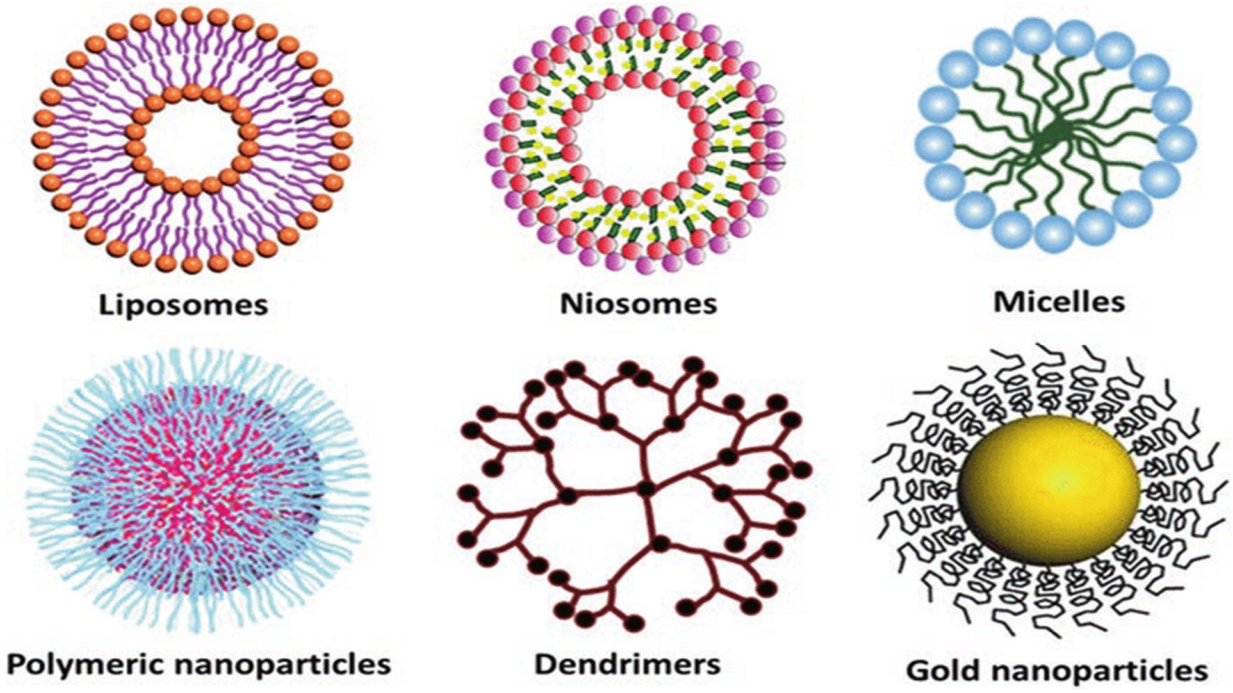

Figure: 1 Schematic diagram of the different types of nanoparticles.

One of the potential pharmaceutical nanocarriers for regulated drug delivery is solid lipid nanoparticles (SLNs), originally known as lipospheres [1,2]. Typically, biodegradable and secure lipidic components make up SLNs. The amazing thing about SLNs is that they can transport a wide range of treatments, including tiny medication molecules, big biomacromolecules (like polysaccharides), genetic material (like DNA or siRNA), and vaccine antigens as well [3,4]. They are able to load both hydrophilic and lipophilic medicines among the tiny drug molecules. The latter ones, which require systemic administration by intravenous route as well as oral route for an instant and substantial effect, are particularly challenging to give via popular and practical means of administration. Lipophilic compounds can fit well in the interior core structure of SLNs. Due to their small size (in the nanoscale range), they have benefits for biopharmaceutical elements of nanoparticle trafficking in vivo, administration, and controlled release of loaded cargos [5]. Solid lipids (mostly physiological lipids) that have been properly disseminated in an aqueous solution that contains a stabiliser (surfactant) are the active key components of SLNs [1,6,7]. Submicron colloidal carriers (SLNs) have therefore been proposed to provide combinatorial benefits of polymeric nanoparticulate systems, fat emulsions, and liposomes while avoiding some of these carriers' drawbacks. From formulation point of view, SLNs offers excellent physical stability, protection of environment sensitive labile drugs, and targeted drug delivery [8–10]. However, insufficient drug loading, drug expulsion especially due to phase transition upon storage and relatively large water content are some of the limitations of SLNs. To minimize these problems nanostructured lipid carriers (NLCs) are being utilized, which are modified version of SLNs [10]. By having both solid lipid and liquid lipid, they differ in the internal core structure than SLNs; where only solid lipid core is available. NLCs provide some imperfections in the core hence resulting into more stable preparation. Due to SLNs' adaptability across a range of research and development fields, multiple therapeutic patents are developing due to their low risk/benefit ratio. The effectiveness of SLNs in transporting antitubercular drugs (Rifampicin [8], Isoniazid, Pyrazinamide [4,15], Vitamins [16], drugs for topical applications (Minoxidil [17], Roxithromycin [18], Tazarotene [19]), anti-inflammatory [20] and antioxidant agents (curcumin) [21,22], enzymes (catalase) [23], low molecular weight heparin (LMWH) With reference to current research publications, we summarise the development of SLNs as therapeutic drug carriers in this review.

II. SOLID LIPID NANOPARTICLE:

Phospholipids are a crucial component of lipid and lipid-based drug delivery systems due to their range of characteristics, including their amphiphilic nature, biocompatibility, and multifunctionality. However, the complex manufacturing process, low percentage entrapment efficiency (% EE), and challenging large-scale fabrication of liposomes, lipospheres, and microsimulation carrier systems, as well as their other shortcomings, have led to the development of the SLN delivery system.26, 27. SLNs typically have a spherical form with a diameter between 50 and 1000 nm. Lipids, which are solid at room temperature, emulsifiers, and occasionally a combination of both, active pharmaceutical ingredients (APIs), and a suitable solvent system are the main components of SLN formulations. Nanocarrier-based drug delivery systems can be subcategorized in many aspects depending on the route of administration, degree of degradability, etc. The route of administration includes nanoparticles for parenteral administration, oral administration, ocular administration, and topical administration, and nanoparticles for protein peptide delivery. Nanocarrier systems can also be subcategorized based on the degree of their degradability as follows.

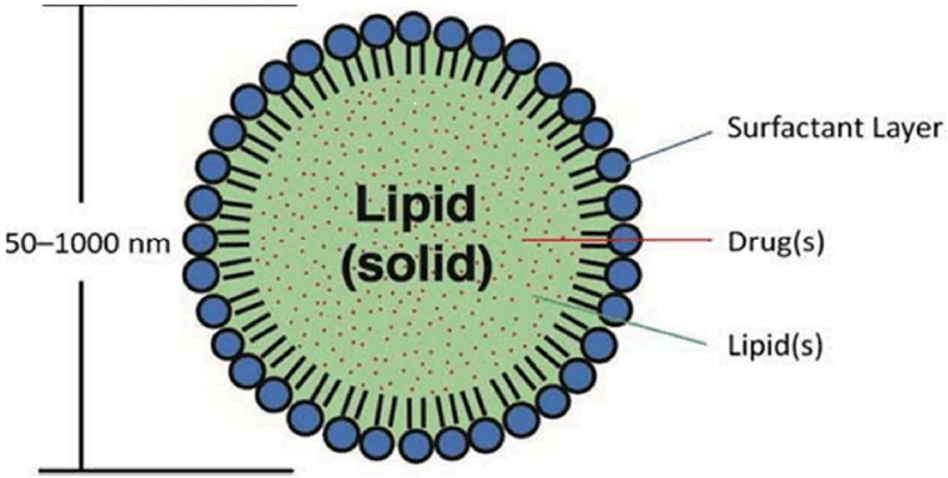

Figure 2: Schematic presentation of the complete structure of solid lipid nanoparticles.

III. SLNS AS THERAPEUTIC DELIVERY SYSTEMS

However, SLNs have been created for a variety of uses, including biomedical, pharmacological, cosmetic, and nutraceutical. To help the readers comprehend the relevance of SLNs in many fields of regulated and targeted administration of therapeutic substances in next sections, the final two applications described above are being summarised. Table 2 shows some current study findings on the use of SLNs for medication delivery.

IV. CONTROLLED AND TARGETED DRUG DELIVERY USING SLNS

Using the solid lipid core matrix of the SLNs, the encapsulated medicine may be released in a regulated way both in vitro and in vivo. For particular uses, it is possible to load biomacromolecules like proteins and peptides as well as tiny medicinal molecules into tailored and well made SLNs. For instance, proteins/peptides like insulin typically have issues when oral administration since the majority of their molecules disintegrate while travelling through the hostile GIT environment. In order to achieve endosomal escape for oral protein (insulin) medication administration, Xu et al., 2018 loaded an endosomal escaping agent in the lipidic core of the SLNs [28]. Authors reported that hemagglutinin 2 (HA2) peptide when loaded into SLN promoted the escape of the loaded insulin from the acidic endosomes significantly vis-a-vis preserved the biological activity of insulin remarkably during the intracellular transport after oral administration. During animal studies, in diabetic rats, a significant hypoglycemic response was achieved by the research group indicating suitability of SLNs coencapsulated HA2 peptide and insulin.

Table 1: List of the recent reviews published discussing various aspects of solid lipid nanoparticles

Sr. No	Area Covered	Title	Reference
1	Brain targeted delivery	Brain targeted delivery of anticancer drugs: prospective approach using solid lipid nanoparticles	29
2	Drug and gene delivery	Solid Lipid Nanoparticles as Efficient Drug and Gene Delivery Systems: Recent Breakthroughs	30
3	Topical immunization	A highlight on lipid based nanocarriers for transcutaneous immunization	31
4	Topical delivery of retinoids	Lipid nanoparticles for the topical delivery of retinoids and derivatives	32
5	Targeting strategies with SLNs	Drug targeting using solid lipid nanoparticles	33
6	Routes of administration for SLNs	Effective Delivery Routes And Strategies For Solid Lipid Nanoparticles (SLN) And Nanostructured Lipid Carriers (NLC)	34
7	Patent perspective	SLN, NLC, LDC: state of the art in drug and active delivery.	35
8	Applications in gene therapy	Solid lipid nanoparticles for applications in gene therapy: a review of the state of the art	36
9	Nucleic acid delivery	Solid lipid nanoparticles as nucleic acid delivery system: properties and molecular mechanisms	37
10	Breast cancer	Lipid-based nanocarriers for breast cancer treatment – comprehensive review	38
11	Antioxidant delivery	Hyperglycemia-induced oxidative stress in isolated proximal tubules of mouse: the in vitro effects of myricitrin and its solid lipid nanoparticle	39
12	Preparation and characterization of SLNs	Carvacrol Loaded Solid Lipid Nanoparticles of Propylene Glycol Monopalmitate and GlycerylMonostearate: Preparation, Characterization, and Synergistic Antimicrobial Activity	40
13	Enhances the oral absorption through SLNs	Slowing down lipolysis significantly enhances the oral absorption of intact solid lipid nanoparticles	41

The chitosan-modified SLNs are better carrier system for mucosal routes of drug delivery; where it provides longer residence time. SLNs have been formulated using ultasonication method composed of tripalmitin lipid as core material and lecithin as dispersion stabilizer [42]. Chitosan was coated over these quercetin loaded SLNs. When tested for their cellular uptake by colorectal carcinoma (Caco-2) cells, uncoated SLNs (size nearly about 110 nm) were well taken up by Caco-2 cell than free drug; however, chitosan-coated SLNs have shown less uptake as observed by the authors.

V. RESENT UPDATE OF SLNS

LNs have been researched for a number of uses in food chemistry, including preservation, cosmetics, topical application, noninvasive methods (transdermal or ophthalmic), targeted delivery of anticancer medications to different malignant cells, and co-delivery of numerous treatments [43]. A variety of methods for creating SLNs or encapsulating medicinal substances in SLNs or NLCs have been created or patented. Table 3 especially for the time period of 2008-2013 presents an overview of the patents relating to lipid-based carriers and their composition. 6 R. PALIWAL ET AL. Starting with the most recent patents, we have discussed patents in this article. Table 4 covers some of the most recent (2014–2019) patents for lipid-based carriers, including both SLNs and NLCs.

Topical delivery of drugs particularly for the treatment of skin diseases such as psoriasis may be more beneficial using SLNs as drug carrier for the same.

An invention has been claimed in order to develop SLNs as a carrier for a therapeutically effective agent called tazarotene or it pharmaceutically acceptable salts. Inventors claimed for a pharmaceutical composition comprising this delivery system and a process for the preparation of such composition thereof. Sorafenib is a choice of drug for the treatment of various cancers like renal cell carcinoma, hepatic carcinoma, and as a tyrosine kinase inhibitor; particularly useful as targeted anticancer drug in case of thyroid cancer. However, this molecule suffers with the problem of poor bioavailability. An invention has been disclosed related to SLNs of sorafenib and a preparation method thereof [44]. High-speed shearing followed by ultra-sonication was the selected method. Inventor claimed that sorafenib solid lipid nanoparticles were having small particle size, high encapsulation efficiency and good stability

VI. TECHNIQUES FOR THE FABRICATION OF SLNS

A. Preparation Method

1) High Pressure Homogenization or HPH (hot/cold) (45)

HPH is a method that uses high pressure (100 to 2000 bar) to force a liquid or dispersion through a small, micrometer-sized opening in order to create submicron-sized particles. The particles are broken down by cavitational forces and a high shear stress, which leads to a reduction in particle size.

The HPH procedures known as hot-HPH and cold-HPH can be carried out at high temperatures or below room temperature, respectively. Both techniques begin with heating the lipid(s) and drug(s) to a temperature that is 5–10 °C higher than the lipid's melting point in order to dissolve or scatter the drug(s) within the melted lipid. (46) Lipid concentrations typically range from 5% to 20% w/v. In the second step of the HPH technique, the aqueous phase containing the amphiphile molecules is added to the lipid phase (at the same temperature as the lipid melting) and the hot pre-emulsion is obtained using a high-speed stirring device. The lipid (more added for homogenization) is forced at high pressure (100–1000 bar) through a narrow space (few μm) for 3–5 times, which depends on the formulation and required product.

Before homogenization the drug is dispersed or dissolved in the lipid melt. However, there are certain drawbacks to this method as follows: (1) it cannot be used for heat-sensitive drugs because of their degradation and (2) an increase in the number of rotations or pressure of homogeneity often results in an increase in particle size-46. However, these limitation can be overcome using cold-HPH to prepare SLNs. As discussed earlier, the first step involves the formation of a suspension of melting lipids and drugs, followed by rapid cooling in dry ice and liquid nitrogen. In the third step, the powder is converted into micro-particles by milling. Then, the micro-particles are dissolved cold aqueous surfactant solution. In the last step, to create SLNs, homogenization is usually performed for 5 cycles at 500 bars.

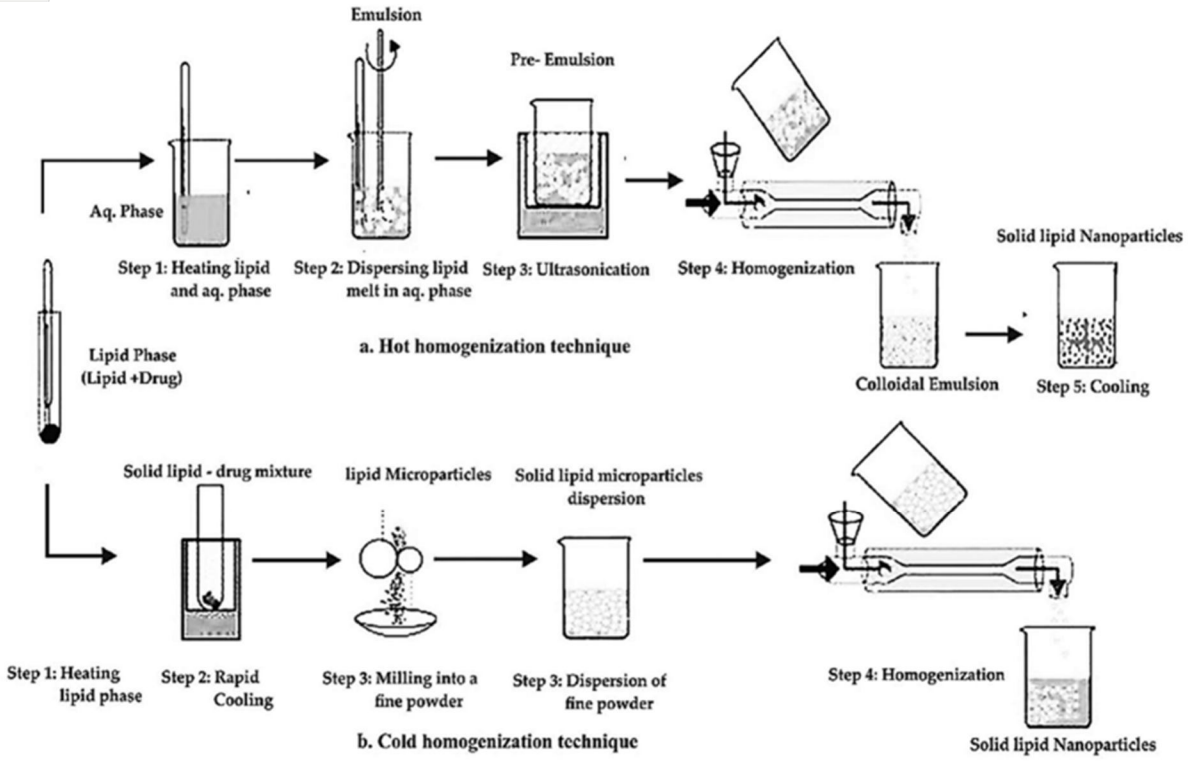

Figure 3: Homogenization technique: (a) Hot homogenization technique and (b) Cold homogenization technique.

2) Oil/water (o/w) Microemulsion Breaking Technique

Gasco was the inventor of this technique. The lipid melt is first combined with a drug, surfactant, and co-surfactant combination that has been heated to a temperature equivalent to the lipid's melting point to create the microemulsion. The resulting microemulsion is then dispersed in water at a temperature between 2 and 10 °C.

Figure 3: Preparation of solid lipid nanoparticles by oil/water (o/w) microemulsion method

3) Solvent-emulsification Diffusion Technique

Shows how to create solid lipid nanoparticles using the solvent-emulsification diffusion method. In this procedure, the lipid is dissolved in a water-saturated organic solvent, and the resulting solution is then further emulsified with water and a water-saturated organic solvent while being constantly stirred. Water is added to the produced emulsion to create lipid nanoparticles, which causes the organic phase to diffuse into the continuous phase. With the use of an ultra-filtration process and a dialysis membrane with a cut-off of around 100 000 kDa, the SLN dispersion may be made purer.

4) Solvent Injection Method[46]

The parameters of the process for the synthesis of nanoparticles in this method include the nature of the injected solvent, lipid concentration, and injected amount of lipid solution, as well as viscosity and the diffusion of the lipid solvent phase into the aqueous phase.

5) Water/oil/water (w/o/w) Double Emulsion Method[47]

Demonstrates how to make SLNs using the double emulsion method. SLNs loaded with hydrophilic medicines and certain biological molecules, such as peptides and insulin, are primarily prepared using this technique. The w/o/w multiple emulsions are converted into SLNs using the solvent in water emulsion diffusion method. Insulin is dissolved in the inner acidic phase of the w/o/w multiple emulsion, and lipids are dissolved in the water-miscible organic phase. As a result, the SLNs precipitate and the organic solvent diffuses into the aqueous phase. This technique of preparation is impacted by the type of the solvent and how the hydrophilic medication interacts with the excipients and solvent.

6) Ultrasonication[48]

This technique is based on the idea of using sound waves to reduce particle size. This technique creates SLNs with sizes between 80 and 800 nm by concurrently using high pressure homogenization and ultrasonication.

7) Membrane Contractor Technique[49]

This process involves pressing a lipid through a membrane contactor at a temperature over its melting point. Water circulating beyond the pores flows with the formed droplets of melted lipid, which is then further cooled at room temperature.

8) Electrospray Technique[50]

The most recent innovation in SLN preparation uses electrodynamic atomization to create spherical SLNs that are narrowly scattered and less than 1 m in size. SLNs are directly obtained in powder form using this approach.

9) Preparation of Semisolid Solid Lipid Nanoparticles

For the creation of SLNs, particularly semisolid formulations, a quicker and more efficient single-step technique was created. The procedure involves melting a lipid, dispersing it in a heated surfactant solution that is approximately 10 °C above its melting point, and rotating the mixture for one minute at a speed of 9500 rpm. Then, dispersion is carried out three times at 500 bar pressure and 85 °C. After the first cycle is finished, the dispersion thickens and is used for the following two cycles. Finally, room temperature cooling is applied to the hot, viscous Nano emulsion. The SLNs become semi-solid compatible when the lipid droplets recrystallize and form a gel network. For this procedure, a lipid concentration of 30–50% w/v is necessary.[50]

VII. CONCLUSION

It The literature makes it abundantly clear that SLNs-based formulations have been created and patented for a variety of purposes, such as oral bioavailability, molecule stability, deeper skin penetration of the bioactive, cosmetic applications, targeted drug delivery using ligand anchoring over surface, and code livery of MDR reversal agents, among others. However, because of their adaptable qualities, they are also being changed for the low-cost manufacture of formutations that have received FDA approval.

Solid lipid nanoparticles (SLNs) are colloidal dispersions with modified properties of other nanoparticles, such as micro emulsions, suspensions, liposomes, and polymeric nanoparticles. The major issues with nanoparticles can be gradually avoided using SLNs, and finally a chemically stable and physiologically appropriate drug delivery system can be achieved with fewer restrictions. Only their gelation tendency seems to be the main issue, but nanostructured lipid capping

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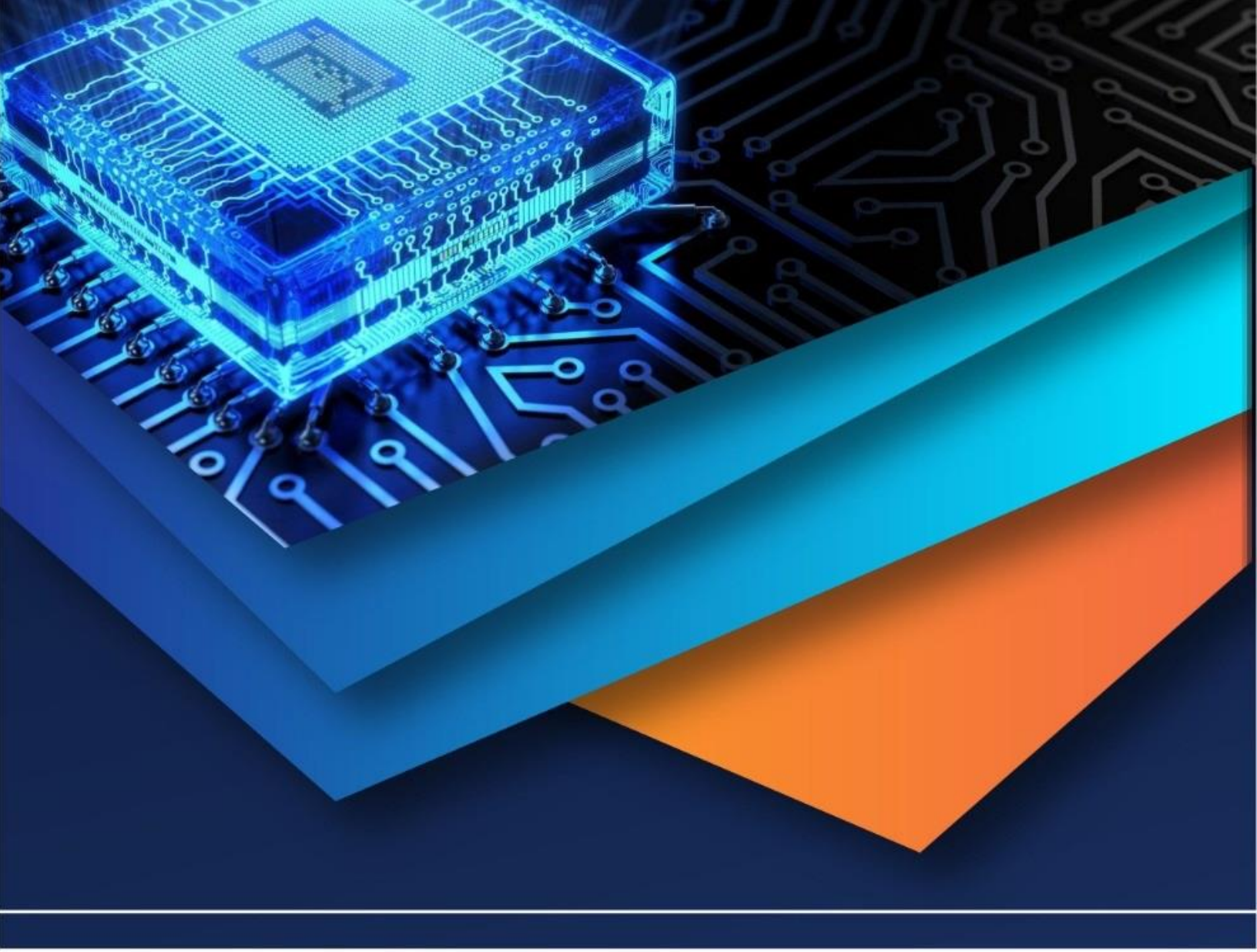

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