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Microspheress Types Preparation Evaluation and Applications: A Review

Hitarth Sah[1], Prof. Dr. G. Ganarajan[2]
[1, 2]*Department of Pharmaceutics, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun, Uttarakhand, India*

Abstract: ***Microspheres, also known as microspheres or "monolithic spheres" are small spherical particles that usually range from 1 to 1000 micrometres (µm). This multi-particulate drug delivery system is used in order to obtain controlled and prolonged drug delivery, thus improving the stability, bioavailability, and site specificity at a desired and predetermined rate. There are various methods in order to prepare/formulate the microspheres, such as emulsion-solvent evaporation, extraction of solvent, spray drying, Coacervation, Electrostatic or Electrodynamic, Template or Moulding methods and various other methods that include Thermally Induced Phase Separation (TIPS) and Supercritical Fluid Extraction of Emulsions (SFEE). Every method has its own benefits and disadvantages therefore, the selection of appropriate method is critical in achieving the desired microsphere characteristic. This review covers the different methods used to prepare the microspheres, the variety of parameters used in order to evaluate their effectiveness and their applications in the field of pharmacy.***
Keywords: Characterization, Evaluation, Microspheres, The preparation methods of microspheres.

I. INTRODUCTION

In the past few years, many studies have been conducted concerning the sustained, prolonged and controlled release of drugs, that aims to prolong the release of drug in order to provide an extended period of time. Thus, various controlled drug delivery system such as microparticles are used. Microparticles can be defined as solid roughly sphere-shaped structures with a diameter ranging from 1 to 1000 micrometres (µm) which can take the form of dispersed medications in certain solutions or microcrystalline crystals. In nature, they are biodegradable particles that are free-flowing and are made up of synthetic polymers or proteins. Two different kinds of microparticles exist, these are:

1) Microcapsules: Micrometric reservoir system (i.e., the substance is entrapped and is clearly encircled with the help of a unique capsule wall.)
2) Microspheres**:** Micrometric matrix system (i.e., the substance that is entrapped is distributed throughout the matrix.)

The terms "microcapsules" and "microspheres" are frequently used analogously. Glass, polymer and ceramic microspheres are all commercially accessible. The microspheres play a critical role in enhancing drug absorption while reducing negative effects. Microencapsulation can be used to delay and alter drug release. Its small size allows wide distribution through digestive tract, enhancing drug absorption and reducing side effects. [1-3]

II. ADVANTAGES OF MICROSPHERES

1) Controlled drug release: Microspheres can be designed to administer drugs in a regulated manner and/or sustained way, allowing for a prolonged and more precise delivery of a drug.
2) Versatility: They can be formulated with a wide range of size, shapes, and compositions allowing for versatility in drug delivery applications.
3) Improved drug delivery: Microspheres can protect drug from degradation, providing improved stability and longer shelf-life compared to conventional drug formulations.
4) Targeted drug delivery: To accomplish targeted dispatch of the drugs, where the drug is given directly into the desired region/ tissue in the body, microspheres can have their surfaces altered. By doing so, you can improve a drug's therapeutic effectiveness while lowering its systemic exposure and off-target negative effects.
5) Enhanced bioavailability: Can improve the bioavailability of poorly or low soluble drugs by encapsulating them, thereby increasing/enhancing their solubility and absorption.
6) Reduced dosing frequency: Microspheres can enable prolonged drug release, reducing the drug administration's frequency resulting in improved medication adherence.
7) Localized delivery/dispatch of the drug: Direct delivery into the target sites (i.e., tumours, inflamed tissues/ specific organs.)

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8) Flexibility in formulation design: Microspheres offer flexibility in formulation design, allowing for the incorporation of various excipients, additives and modifiers to tailor various properties such as drug release rate, size and surface characteristics.

III. VARIOUS TYPES/CATEGORIES OF MICROSPHERES

1) Bio Adhesive Micro-Spheres: The sticking of water-soluble polymers may be defined as the affixation of the drugs to the selective barrier by using the sticking properties. Bio adherence can be defined as the affixation to the mucosal membrane of the drug delivery device, which includes the buccal, ophthalmic, nasal, rectal, etc. These types of microspheres stay at the application site for a long time, interact closely with the absorption site and produce greater therapeutic results. This extended retention time may result in the increased absorption and when used in combination with a controlled- release of drug may result in enhanced concordance and medication adherence by reducing the administration frequency. By affixing the drug to carrier particles such as Liposomes, Nano-particles, Nano-spheres, Microspheres, etc., which can control the absorption and release of the desired medication, thus the carrier-based drug delivery systems offer an innovative and intelligent method of delivery of drugs. [2,4,5]

2) Magnetic Microspheres: The magnetic microspheres are macroscopic molecular particles that, without producing embolic occlusion, can circulate through the capillaries because of their small size (< 4μm). They are important as they localize the drug to the disease affected areas. The precision targeting thus aims to optimize the performance of the drug's delivery and in tandem reduces adverse effects and the toxicity produced. There are different categories of magnetic microspheres such as:

a) Therapeutic microspheres are generally employed to deliver the antineoplastic agents to the tumour in the liver.

b) Diagnostic microspheres that are generally employed for imaging metastatic hepatic diseases and also helps to tell apart bowel loops from other abdominal structures. [6,7]

3) Floating Microspheres: The floating- microspheres are generally prolonged gastric-resident drug carrier systems that follow non-effervescing techniques. These microspheres are empty particles that are spherical in shape and are without a core. They have a size that typically ranges from 1 to 1000 micrometres (μm). Gastro retentive floating microspheres have buoyancy that helps them float in and above the gastric/stomach contents and therefore tends to remain in the digestive system for sustained time period. This helps drugs to slow elution at a sought-after rate. They increase patient compliance by reducing dosing frequency. Diffusion, Erosion and Osmosis are the way through which the drug release mechanism from multi particulate may occur. [8,9]

4) Radioactive Microspheres: Radioactive microspheres are small, tiny beads (usually ranging from 4 to 30 nanometres) or particles that have been incorporated or labelled with a radioactive isotope. These types of microspheres are used for blood flow studies, cancer treatment and liver function testing. The radioactive microspheres always include one or sometimes more radionuclides. These radio-active microspheres tend to transmit intense irradiation dose to the disease-affected sites without harming the regular unaffected neighbouring anatomy.

5) Poly Meric Micro-Spheres: The polymeric microspheres are of various types and can be classified into synthetic-polymeric micro-spheres and bio-degradable polymeric micro-spheres.

a) Synthetic-polymeric microspheres are made from synthetic polymers and are used for cell sorting, drug delivery and diagnostic imaging.

b) Biodegradable polymeric microspheres are made from biological polymers that can be broken down by biological processes in the body. [8,12]

IV. POLYMERS

Polymers are frequently employed in the preparation of micro-spheres. The choice of polymers depends on the intended microspheres-based applications, the attributes of the polymer, and the synthesis approach used.

The polymers used can be classified into natural, synthetic or semi-synthetic polymers based on their source and method of preparation.

The properties of micro-spheres may be tuned through varying the molecular weight, composition and processing condition of the polymers used in their preparation. The polymers used in order to prepare the microspheres can be categorised into the following categories:

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V. TYPES OF POLYMERS

A. The Synthetic Polymers

1) Non-Biodegradable

a) -Glycidyl meth-acrylate
b) -Epoxy polymer
c) -Polyacrylonitrile (PAN)
d) -Polystyrene (PS)
e) -Acrolein
f) -PMMA

2) Biodegredable

a) -Lactides and glycosides copolymer
b) -Poly alkyl cyno acrylates (PCA)
c) -Polycaprolactone (PCL)
d) -Poly [lactic- co- glycolic acid] (PLGA)
e) -Polyanhydrides

B. The Naturally-Occuring Polymers

1) Proteins

a) -Collagen
b) -Gelatin and Albumin
c) -Silk fibroin

2) Carbohydrates

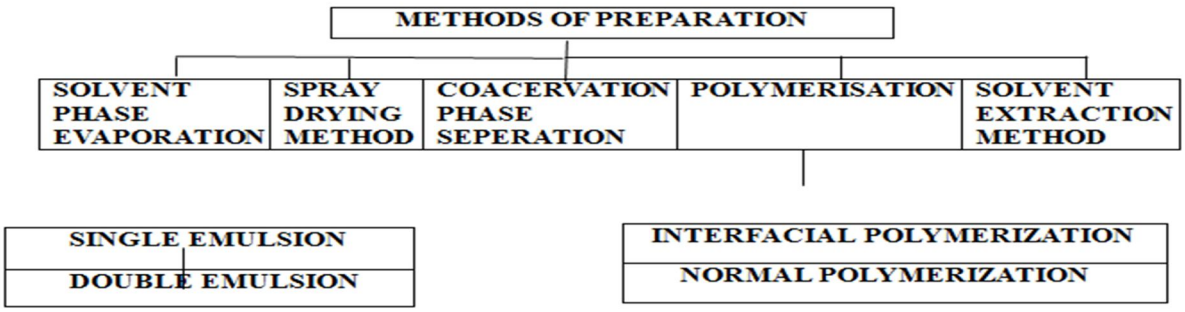
a) -Chitosan
b) -Alginate
c) -Starch and agarose
d) -Hyaluronic acid
e) -Carrageenan
f) -and cellulose derivates

3) Chemically-Modified Carbohydrates

a) -Poly starch
b) -D E A E cellulose
c) -Poly [acryl] dextran

VI. PREPARATION OF MICRO-SPHERES

Micro-spheres may be formulated from various methods. Several approaches exist. The common methods are listed below:



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A. Solvent Evaporation Technique

In this precipitation method, the polymer is added in an appropriate water-immiscible solvent and the drug is dissolved dispersed in this solution- containing- polymer. The generated solution is then homogenized in an aq. continuous phase to form distinct and independent drop-like structures or spheres. Thus, for the micro-spheres' formulation, the solvent (organic) must firstly spread out into the aqueous phase and then must evaporate at the air-water intermediate layer (mechanical stirrer or magnetic stirrer are usually set at desired speed and temperature for the solvent phase to evaporate). Microspheres are then collected or obtained after suitable filtration or drying. [13,14]

1) *Single Emusion Technique:* In single emulsion technique, the multi-particle natural polymer carriers, such as those of proteins and carbohydrates, are created or formulated. After dissolving or dispersing in an aq. media, the naturally-occurring polymers are then distributed in a non-aq. medium, like oil. In the following stage, the cross-linking of scattered droplets is conducted. Either heat energy or chemically-infused cross-linking agents are used to produce the cross linking. Acid halide, Form-aldehyde, Glutaral aldehydes, etc. are used as cross-linkers. The Mo labile components are not suitable for heat denaturation. If an active component is applied during preparation and afterwards exposed to filtration, extraction or fractionation. This Cross-linking may/may not have the limitation of unveiling the active components present to the chemicals greater or rapidly than what is needed/necessary. [15,16]
2) *Double Emulsion Technique:* The method of preparation employed by this technique involves complex emulsion structures i.e., water- in oil- in water emulsion and is prepared by dispensing the (1º) primary water in oil emulsion to the aq. solution of cold Polyvinyl alcohol. This W/0/W emulsion is constantly stirred for about 30 minutes. In the next step, water is added slowly to the emulsion for a period of about 30 minutes. Microspheres or microcapsules are then collected by filtration and are then vacuum dried. Water-soluble drugs, vaccines, proteins, and peptides are best suitable. The use of naturally occurring or synthetic polymers are suitable for the manufacturing of micro-spheres. The solution (aq.) containing protein is then subjected in a lipid-soluble continuous phase (organic in nature). The solution containing protein that is being dispersed must contain the active substances. The initial (1º) emulsion is then put through sonification before its summation to the aq. solution of (cold) PolyVinyl alcohol. This results in a double- emulsion creation. This emulsion is then subjected to the elimination of the solvent either by solvent- extraction or by evaporation of solvent. A no. of water-loving (hydrophilic) drugs are then successfully blended into the microspheres. [17,18]

B. Spray Drying

In this method of preparation of microspheres, a liquid solution containing the desired material to be encapsulated is atomized into small droplets with the help of a spray nozzle. Nitrogen gas is then used to rapidly dry the droplets resulting in the formation of solid microspheres. A suitably volatile organic solvent, such as DCM and DCM (methylene chloride), is used in order to dissolve polymer. Under agitation at high speed, the drug is now blended into the polymeric solution. Small droplets or fine mist are produced by thermal convection lifting of particles is atomized. This results in the rapid solvent evaporation, forming microspheres of the size ranging from 1-100µm. Using a cyclone separator, the microspheres are then separated with the help of hot air flow. Formation of microspheres through this process leads to the formation of rapid/ porous microparticles, that can be used for the drugs with poor solubility. The principle of spray drying involves: Atomization, mixing and drying. [5,18,19]

C. Coacervation Phase Seperation

The phase separation method is primarily made to prepare reservoir-type systems. When the medication is hydro-phobic in nature, like steroids, this approach may be utilized to encapsulate water soluble pharmaceuticals, such as proteins peptides and certain preparations with matrix type. This method follows the principle that by reducing the solvency of polymers in organic phase, coacervates (i.e., a polymer-rich phase), are more likely to develop. The coacervation is brought by this system being given a third component, which causes the system to divide into two phases, one of which is supernatant, i.e., depleted of polymer and the other of which is rich in polymer. There are several techniques that may be used to coacervate phase separation. [20,21]

D. Polymerization

Polymerization is a commonly used formulation process of microspheres. This method involves dissolving of an individual unit or a blend of units in a suitable solvent. A cross-linking agent and an initiator are then added to this solution.

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In the next step, the solution is then homogenized in an aq. phase in which a surface-active agent is present to form small drop-like structures, which initiates the polymerization reaction. The monomers then react to form a polymer network, thus resulting in the formation of solid microspheres. This method can be further classified into the following:

1) *Normal Polymerization:* The normal polymerization is conducted using techniques like large-scale, settling, emulsion, suspension, etc. In this method, a polymer-precursor containing an initiator is warmed for starting polymerizing in the mass polymerization method. To increase the response rate quickly, the originator is introduced. The subsequently acquired polymer is divided into microspheres when the polymerization-sequence during treatment is incorporated. The Suspension polymerization is a.k.a bead / or pearl polymerization when performed at frigid/cool temperatures. [22,23]
2) *Interfacial Polymerization:* A polymer- film that effectively engulfs/shrouds the dispersed phase is created by the engagement of different polymer precursors at the demarcation between the two liquid phases that are immiscible in nature. This procedure follows the principle that lowering the polymer's solubility within the organic phase will have impact on how quickly coacervates, a phase rich in polymers, develop. In this method, the polymer solution containing the drug particles is mixed with an incompatible polymer, which causes the 1st polymer's phase-separation & encapsules/shrouds the drug particle. The solidification is done by adding of the non-solvent. Upon mixing the two phases, a polymerization reaction occurs at the interface between the two phases, resulting in the formation of solid microspheres. [24,25]

E. Solvent Extraction

Microsphere preparation is frequently done using solvent extraction. In this method, organic solvents that are soluble in water, such as Dimethyl sulfoxide (DMSO) is used and water is used for the extraction of organic phase. In this, a polymer solution is combined with a solvent-solute mixture of the desired material to be confined in a capsule, such as a medication or protein, in a suitable solvent. The resultant mixture is then emulsified to create tiny droplets in an aqueous phase that contains a surfactant. The solvent is then routinely extracted or vapourised from the droplets, leaving behind solid microspheres. [25,26]

VII. EVALUATION PARAMETERS OF MICROSPHERES

A. Size And Shape Of Molecular Entities

The Scanning electron microscopy (SEM) and light microscopy (LM) techniques are most often used for the regular depiction of microspheres. Both of the mentioned methods may have the choice of determining the microspheres' external structure and condition. LM provides a control over coating parameters in case of double walled microspheres. Before and after coating the microspheres, structures can be visualized and the change can be measured microscopically. The LM provides a lower resolution as compared to SEM. Investigations of double walled systems, microsphere surfaces and after cross-section is done by SEM. The characterization of multi-walled microspheres is done by confocal fluorescence microscopy. Other techniques performed for particle size analysis include laser diffraction, dynamic light scattering and multi size coulter counter. [27,31]

B. Density Determination

A multi volume pycnometer may be used to determine the density of the prepared microspheres. A cup containing a precisely weighed sample is inserted into the multi volume pycnometer. In the chamber, helium is supplied at a steady pressure and rate, and given room to expand. It is noticed that there are two consecutive observations of pressure decrease at various beginning pressures. The volume and subsequently the density of microsphere carrier are calculated from two pressure readings. [28]

C. Electron-Spectroscopy [Esca -Analysis]

Electron spectroscopy for chemical analysis (ESCA) is a method to determine the surface chemistry of microspheres. This method provides a mean for the surface's atomic composition determination. The surface science of the assurance of the microspheres is relevant for the Electron Spectroscopy for Substance investigation (ESCA). The electron spectroscopy for the compound examination technique (ESCET) serves as a proxy for the nuclear arrangement of the surface. This spectrum provides proof of the biodegradable microsphere's surface deterioration. The ESCA is used to get these spectra. [29]

D. Vibrational Spectroscopy Using Ft-Ir

The degradation of the polymer structure of a transporter framework can be determined by using a technique called Fourier-transform infrared spectroscopy (FT-IR). To measure the surface of microspheres, a method called Attenuated Total Reflectance (ATR) is used.

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In ATR, an infrared beam is passed through the ATR cell and is reflected by the sample, which provides IR spectra mainly of the surface material. The surface arrangement of microspheres depends on the manufacturing process and conditions, and this this information can be obtained through ATR-FTIR. [30]

E. Angle Of Contact

To access a microparticle carrier's wetting ability, the angle of contact is assessed. It influences whether microspheres are hydrophilic or hydrophobic in nature. The solid specific thermodynamic characteristic is influenced by the presence of the adsorbed component. At the interface of the solid, air and water is measured. By putting a droplet in an annular cell that is positioned above the objective of an inverted microscope, the advancing and retreating angle of contact is recorded. After the microspheres have been deposited for a minute or so, the angle of contact is measured at 20ºC. [31]

F. Loading Efficiency

By allowing the wash micro-spheres, lysate may determine the microsphere's capacity to capture or the percentile of the capture. The lysate is subjected to the influence of various dynamic factors adhering to the monograph requirements. The mathematical expression below can be employed to determine the entrapment efficiency: [29,31]

$$\%\textit{Drug entrapment efficiency (DEE)} = \frac{ESTIMATED\ DRUG\ CONTENT}{THEORETICAL\ PERCENTAGE\ DRUG\ CONTENT} X100$$

G. Invitro And Invivo Methods

There is a need for experimental technique that makes it possible to assess a drug's permeability across a membrane and its release characteristics. Numerous invitro and in vivo techniques have been reported for this purpose.

In vitro drug release studies have been used as a quality control process in the manufacturing of pharmaceuticals, in the development of new products, etc. Sensitive and reliable release data obtained from physio chemically and hydrodynamically specified conditions are essential. Numerous invitro release methods for buccal formulations have been developed, however there is still no standard invitro approach available due to the effect of technology specified circumstances and the difficulty of imitating in vivo conditions. Various workers have utilized equipment with varying designs and under varying circumstances, depending on the shape and application of dosage form developed. [33]

In vivo drug release studies take advantage of an organism's biological reaction, either locally or systematically, as well as those that entail direct local assessment of absorption or build-up of penetrants at the surface, are used to research the permeability of intact mucosa. Some of the earliest and most basic research or mucosal permeability relied on how medicines' systemic pharmacological effects affect the oral mucosa. However, in vivo investigations utilising animal models, buccal absorption assays, and perfusion chambers for investigating drug permeability are the techniques that are most frequently employed. [35]

H. In Vivo And In Vivo Correlation

The phrase "in vitro – in vivo correlations" refers to the relationship between in vitro dissolving rates and the rate and degree of availability as assessed by blood concentration and/or urine excretion of medication or metabolite. Using these relationships, one may create product specification that take bioavailability into account. [36]

VIII. APPLICATIONS OF MICROSPHERES

1) *Microsphere in the delivery of vaccines:* The necessary factor of a vaccine is its ability to provide protection against the microorganism or its hazardous product. An optimal/ideal vaccination should meet the criteria for effectiveness, safety, ease of use, and cost. Safety and minimizing, and detrimental outcomes are a complicated concern. The degree of antibody formation and the safety factor are directly correlated with the application method. The drawback of traditional vaccinations may be solved by biodegradable delivery technologies for vaccines administered parenterally. Parenteral (Subcutaneous, Intramuscular, and Intradermal) carriers are alluring as they provide a number of benefits such as:

a) Adjuvant-mediated improvement of antigenicity.
b) Modulation of the release kinetics.
c) Stabilisation of antigen.

2) *Achieving Drug Targeting Via Microparticulate Carriers:* Targeting or localized medication delivery, is a thoroughly researched paradigm which is now receiving loads of attention. The ability of the drug to access and engage specifically with its candidate binding sites is essential to its therapeutic effectiveness. Drug activity is centred on the capacity to exit the pool in a proficient, accurate/ consistent way, which is facilitated by a carrier-vehicle system. When granules are placed in a certain anatomical compartment, either the environment's physical characteristics or the particle's biophysical interactions with the target tissue's cellular composition allow the particles to be retained.
3) *Monoclonal Antibodies mediated microsphere targeting:* Microspheres that are immune to mAbs are called stealth particles/microspheres. This targeting is a strategy for achieving particular site-specific targeting. Monoclonal antibodies (mAbs) are generally used to target microspheres laden with bio-active compounds to specific regions due to their great selectivity. mAbs can be covalently coupled to the microspheres directly to form an attachment. These antibodies are coupled to the amino, free aldehyde or hydroxyl groups on the outer layer of microspheres. There are a variety of ways to connect the mAbs to microspheres, some of the methods are:

a) Specific absorption
b) Coupling via reagents
c) Non-specific adsorption
d) Specific adsorption

4) *Imaging:* The usage of microspheres for targeting has been well researched. Microspheres that have been radio-labelled can be used to imaging different cell types, cell linings, cell's tissues, and various organs. The spectrum of microspheres' particle sizes has a significant impact on how specific areas are imagined. Apart from the portal vein, the intravenously administered particles will become stuck in the lung's capillary bed. When utilising microspheres labelled with human serum albumin for scintigraphy imaging of lung cancer masses, the phenomenon is taken advantage of.
5) *Chemoembolization:* Chemoembolization is an endovascular treatment that entails the local administration of a chemotherapeutic drug concurrently with or after the selective arterial embolization of a tumour. Theoretically, such embolization will have the benefits of both vascular blockage and prolonged therapeutic doses of chemotherapeutics in tumour affected regions. A development of conventional percutaneous embolization methods is chemotherapy.

IX. CONCLUSION

The overall result is that microspheres are good drug carriers for targeted drug administration. Microsphere drug delivery is safe and efficient and is used in multitude of practical applications, including floating, targeted drug delivery, vaccine delivery, and other fields. Procedures for creating and evaluating microsphere formulations are easily reproducible and generally available. Microspheres drug delivery targets a wide region; hence a consistent performance research was needed to compare in vivo performance.

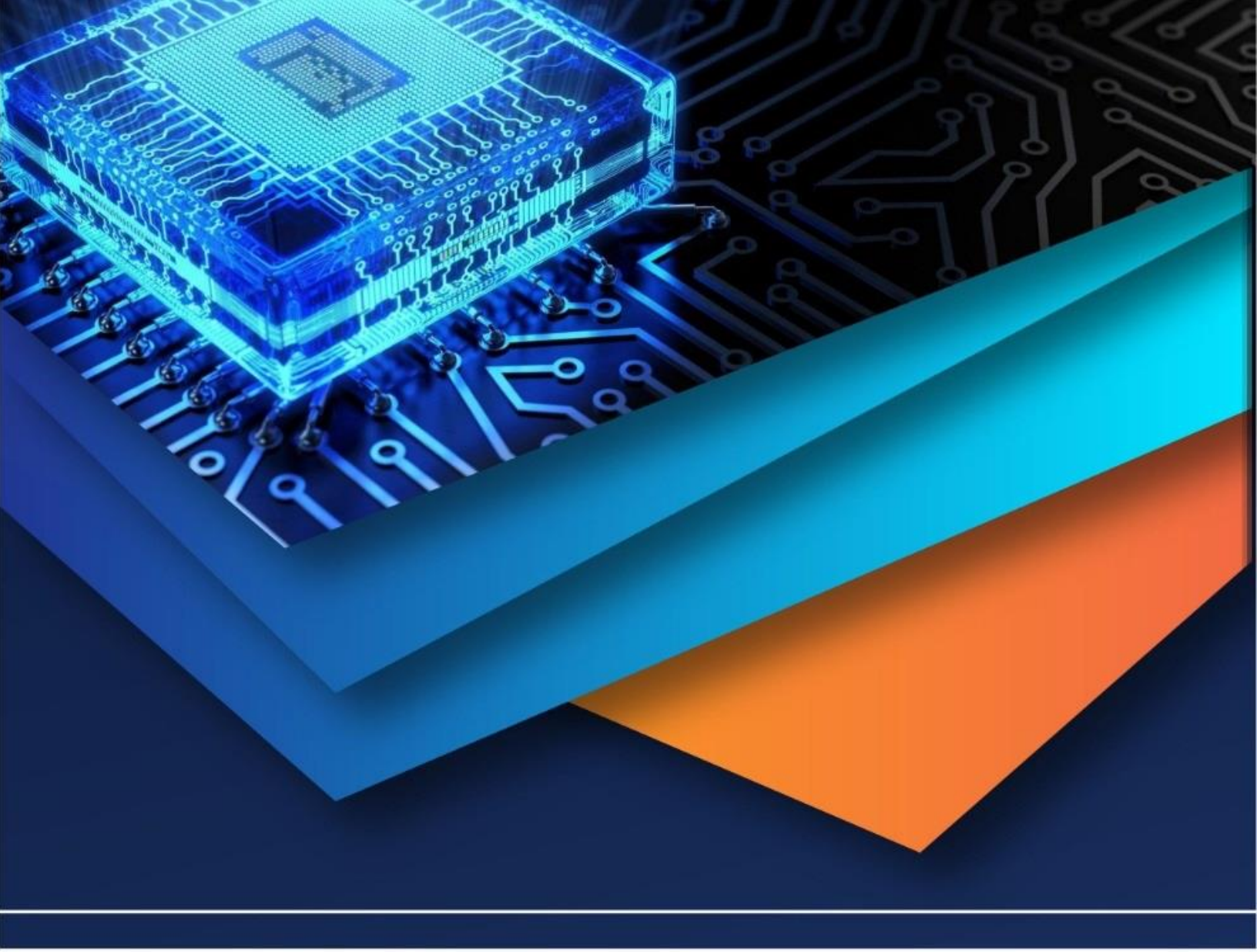
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