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Floating Microspheres: An Overview

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Abstract: ***This following review on Floating Microspheres is to highlight current literature and addition of newer approaches in floating microspheres as drug delivery system. Current studies show that floating microspheres can attain delayed and sustained release oral formulations with ability to achieve various release patterns, low dosage dumping risk, with repeatable and short gastric retention time.***
This paper also covers floating microspheres current condition of along with methods like use of low-density porous carrier. There have been many successful attempts around the globe to research about this drug delivery system according to therapeutic requirements and study its efficacy and compliance. Floating microspheres provide enormous potential for developing innovative controlled and delayed release oral formulations. The current paper discusses the stomach emptying physiology in relation to FDDs, as well as the production methods and various variables that impact the performance and properties of floating microspheres.
An overview of in vitro and in vivo research that aid in the investigation of the efficiency and uses of floating microspheres is also provided. The latest innovations in pharmaceutical industry are guaranteed to create genuine opportunities for the formation of unique and efficient methods in developing potential DDS.
Keywords: Floating microspheres , floating drug delivery system, , porous carrier , drug delivery system gastro retention.

I. INTRODUCTION

Oral drug administration is easiest and a prominent of delivery of drug. The achievement and maintenance of drug concentration within a range that is therapeutically effective takes place only when the drug is administered many times in one day depending upon the dosage[1]. Large number of patients prefer to take drugs orally because they are easy to administer and handle. Alot of development has been done in oral drug-controlled delivery in the recent years but for the drugs with a very short time of absorption throughout the GIT, this is not so successful[2].

These problems led to formation of a new controlled oral drug delivery dosage form which have characteristics of gastro-retention. After the administration of the drug orally, in the stomach, drug is released in a controlled release manner which helps it to reach the absorption sites in a continuous manner[3]. It is a well-known fact that contact time with mucosa of small intestine controls the degree of drug absorption in the GIT, therefore, time of transit in small intestine is an important criterion for the drugs which are absorbed incompletely[4].

Many approaches have been tried to improve the period of stomach emptying of a delivery system, but most promising has been the use of FDDS having lower density as compared to the gastric contents. Floating drug delivery system show buoyancy in a long term manner over gastric contents and increase bioavailability of drug. This increased intra-gastric buoyancy of this type of release system delivers an appropriate approach to continuously transport drug into the stomach and offer local therapeutic effect[5]. There is a decreased level of fluctuations in the therapeutic level which further decreases risk of antibiotic resistance like in case of penicillin, amoxycillin[6]. Controlled drug delivery system is better than the sustained delivery of drugs because gastric retention helps in increasing the solubility of drugs that are poorly absorbed in the gut due to basic pH before gastric emptying[7]. Microspheres, for example, have several unit particle dose forms have the properties of passing uniformly through the GI tract and deliver an adjustable release and as a result, the variation of absorption in different subjects and the local irritation risk factors are reduced[8]. There is a need of deep study and understanding of polymer and molecules of drug to formulate a floating drug delivery system. There are two interesting techniques developed and put into application to enhance the activity and effect of floating microspheres namely – hollow microspheres or microballoons and use of low density porous carriers. The current article discusses the most recent technological advancements and progress in gastro-retentive drug delivery systems, with a particular significance on the methods and benefits of gastro-retentive drug delivery systems, as well as in-vivo and in-vitro studies that aid in the study of the performance and applications of floating microspheres[9].

II. METHOD OF PREPARATION

There is a broad range of methods for the manufacture of floating gastro-retentive microspheres. While preparing floating microspheres, it is very important to choose the most optimal method of preparation which decides the efficient entrapment of active constituents. The preparation method mostly depends on the polymer nature, drug and its intended use[10].

A. Solvent Evaporation Technique

This method includes emulsifying the organic solvent (generally methylene chloride) which contain the dissolved polymer along with the drug that is dissolved or dispersed in excess amount of continuous phase that is aqueous in nature, with the help of an agitator. The shape and size of particle size is affected by how much emulsifier is present in the aqueous phase. The rate of mixing is decreased after the ideal droplet size of the emulsion is formed and the organic solvent is evaporated under required temperature. After dispersion phase solvent is evaporated, solid micro particles coated with polymers are formed, which entrap the medication. Filtration, centrifugation, or lyophilisation are used to recover the solid micro particles from the suspension[11]. This method is widely used by many industries in formulating a delivery system with co trolled release. There are two types of emulsion solvent evaporation – water in oil type and oil in water type[12].

1) Water in oil

This technique, also called non-aqueous emulsification solvent evaporation, is where polar solvents like ethanol, dichloromethane, acetonitrile etc are used, the drug along with the polymer are dissolved together at room temperature while vigorously agitating for the formation of uniform drug-polymer dispersion[13]. The solution obtained is added to the dispersion medium slowly where the dispersion medium contains heavy or light paraffin with a surfactant that is soluble in oil and then it is stirred at 500 rpm with the help of overhead propeller agitator at room temperature for 2-3 hours to make sure that the solvent evaporates completely. After decantation of liquid paraffin, separation of microparticles is done by filtration using Whitman Filter Paper. The micro particles are then washed, air dried for a day, and stored in desiccators[14].

2) Oil in Water type

In this preparation method, the drug and selected polymer should not be soluble in water[15]. Organic solvents like dichloromethane, ethanol, acetone, ethyl acetate is used in combination or alone, are used to dissolve the polymer by either dissolving it or dispersing it with the assistance of an emulsifying agent or surfactant, into the polymer solution, which is emulsified into an aqueous phase, yielding an oil in water emulsion. After achieving an emulsion which is stable, organic solvent is evaporated by constant stirring and maintaining the required temp and pressure[16]. Studies have shown that, the evaporation of the organic solvent from microspheres causes the polymer precipitation at the oil and water interface, which generates cavities in the microspheres and makes them hollow, giving them their floating capabilities[17].

B. Ionotropic Gelation Method

In this, polyelectrolyte is cross linked with counter ions for the formation of gel matrix. A huge number of drugs' encapsulation is done by using this method.

One common example of polyelectrolyte is sodium alginate which have a property of coating of core of the drug and includes particular anions in their chemical composition and functions as a release rate retardant[18]. Gelation is induced by the formation of mesh network structure when they are combined with polyvalent cations.

Microspheres are made when polymeric solution loaded with drug are placed into a polyvalent cation aqueous solution dropwise. These cations infiltrate into the droplets containing drug and polymer, and a 3D lattice of ionically cross connected moieties formed. The produced microspheres are allowed in the original solution for an extended amount of time to gel internally before being separated by filtering[19].

C. Emulsion Solvent Diffusion Method

In this technique, ethanol and dichloromethane is used first to dissolve the drug in a solution containing the selected polymer. This polymer solution is poured into a solution of SLS and then it is stirred at 150 revolutions per minute for approximately 2 hours with the help of a propeller type agitator. After the stirring, and washing, the formulation is then dried in a desiccator. Floating microspheres developed using emulsion solvent diffusion method results in an increased time of colonic residence[20].

D. Coacervation Process for Phase Separation

The essential idea of this approach is to reduce polymer solubility in an organic phase, hence affecting creation of a phase rich in polymer called co-acervates. After dispersing the drug particles in a polymer solution, in the system, an incompatible polymer is injected, causing the first polymer phase to separate and the drug particles to be eaten[21].

E. Polymerization Technique

There are two methods in this technique which are:-

1) *Regular Polymerization:* It is accomplished by the use of many processes such as precipitation, bulk, emulsion, suspension and micellar polymerization. Bulk polymerization offers the benefit of producing pure polymers.
2) *Inter-facial Polymerization:* This entails interaction among different monomers at the interface of 2 immiscible liquid, resulting in the creation of a film of polymer that basically covers the dispersion[22].

F. Hot melt Encapsulation Method

In this method, PCL micro-particles are developed. This method has a disadvantage that the use of thermo-labile chemicals is prohibited[23].

G. Process of Spray-Drying

This method relies on polymer mist drying and medication drying in the air. To dissolve the polymer, volatile organic solvents such as dichloromethane, acetone, ethyl acetate and others are utilised. Following that, the drug is disseminated in solid form in the solution of polymer using high speed homogenization. After that, the atomization of dispersion in a hot jet of air. Atomization produces microscopic droplets from which the solvent quickly evaporates, resulting in creation of the microspheres with sizes ranging from 1 to 100 micrometre. The two processes are known as spray drying, depending on whether the solvent is removed or the solution is cooled[24].

III. FORMULATION FACTORS TO BE CONSIDERED

A. Polymer Solution

We know, polymer solidification and collection on aqueous phase surface is due to the high tension of water. Scientists have developed a new method for continuous process of microsphere preparation where the polymer solution interaction with the air-water interface is minimised.

In this method, a glass tube is submerged in an aqueous phase, avoiding contact with the water's surface, the polymer solution is introduced via the tube and.

Microsphere yield is improved by using this technique and there is reduction in extent of formation of aggregate. With the continuous addition of polymer solution in the main vessel, there will be an overflow of the polymer solution from the vessel top along with the microspheres that are prepared because most of them float on the aqueous phase surface. These overflown microspheres can be collected in a container at the bottom with the help of a suitable sieve size.

B. Effect of Rotation Speed

It is a well-known fact that the distribution and yield od microsphere is affected by the propeller rotation speed. With an increasing speed, particle size of microspheres is decreased while maintaining the morphology.

C. Temperature

The temperature of the dispersion media is an important component while forming microspheres because it influences the solvent evaporation rate.

The developed microspheres have irregular and crushed shape and microsphere shell becomes semi-transparent at low temperatures like 10 degrees Celsius.

The turning of shells into translucent is because of slower rate of diffusion of solvents like dichloromethane and ethanol. But on increasing temp like 40 degrees celcius, the microsphere shell becomes thin and this happens because alcohol in the droplet diffuses quicker into the aqueous phase, and solvent evaporates instantly after being introduced into the medium[25].

IV. CHARACTERIZATION OF FLOATING MICROSPHERES

A. *Percantage Yield*

After microspheres are dried, % yield is calculated and it is done by,
Percentage yield= weight of microspheres formed / weight of drug and polymer (total) X 100[26].

B. *Size of Particles*

The eyepiece micrometre is calibrated and then floating microspheres are transferred on one clean slide and 2 drops of liquid paraffin added. The sample is then dispersed uniformly by using a brush and cover slip is placed to prevent air bubble entrapment. Excess liquid is drained out by a blotting paper. The slide is magnified at a low magnification (10x). When an individual particle is detected, the microscope is adjusted to high power (45x) and the slide is focussed again. Each particle's size is measured in terms of eye-piece divisions. Tabulation of the particle is divided into eye-piece divisions and particle numbers then the number of eye-piece divisions is multiplied by the calibrated value. Diameters are classified into size ranges as well as the determination of the number of distributions is also done after that.[27].

C. *Bulk Density*

This property is the relationship between the powder mass and the volume of the powder in bulk. This density is calculated, determining the volume of taken quantity of the powder fed through a screen and into a volume measuring device.

Bulk density = Mass/Volume in Bulk
i.e., B= M/V[28].

D. *Tapped Density*

The bulk density apparatus is also used to measure the tapped density. The granules of the powder are placed in the apparatus and then the volume of powder which is the total volume, is noted. The cylinder is then tapped up to a 100 times and again the cylinder volume is measured. The formula was then used to calculate Tapped Density:
Tapped Density = Powder mass initially/ Total powder volume noted after 100 tapping.
3 readings were recorded and an average was calculated

E. *Compressibility Index*

The next flow property i.e., compressibility index was calculated by filling a measuring cylinder with powder granules and noting the volume (V0) before tapping. Volume (V) was measured again after 100 taps.

Compressibility index = [BD– TD/BD] x 100.
3 readings were recorded and an average reading of compressibility index was calculated.

A value than 15% suggests a powder has good flow properties, and a value more than 25% means a powder has low flow capabilities.

F. *Hausner's ratio*

Microsphere Hausner's ratio can be calculated by talking the ratio of tapped density to bulk density using the equation.
Hausner Ratio = BD/TD[29].

G. *Angle of Repose*

The height and radius of the powder pile are determined as the powder bed is formed by pouring it into the funnel placed upon a graph sheet. A 4-inch funnel attached to the stand with a clamp, with the funnel stem set approximately at height of 2-3 cm above the graph sheet below . The funnel then filled with powder and was left to flow freely into the graph sheet. Using a pencil, the area covered by the powder bed is marked by making a circle around it and then the radius and height of heap were measured and recorded using a scale.
The radius was measured 3 times as r1,r2 and r3 and an average was noted. (n = 3).
The angle of repose is calculated as;
Tan ø = h /r.
3 readings are recorded and an average is calculated[30].

H. Drug Entrapment Efficiency

The microspheres formed are evaluated for % entrapment efficiency by takin an amount of the prepared formulation in equivalent quantity of a buffer solution. It is then ultracentrifuged at approximately 17000rpm for some time. In the supernatant there is free concentration of drug and it is measured. % Entrapment efficiency is determined by the formula, % Entrapment efficiency= W-w/w X 100

I. Swelling Evaluation

Swelling experiments are carried out in dried beads that had been immersed for 5-6 hours in a saline solution. The beads are weighed on an analytical balance after being withdrawn from the solution. The swelling ratio Qs, which was expressed by their ability to absorb water, is measured by;

Qs = Ws – Wd X 100 / Wd

where,

Wd = bead weight dried,

Ws = bead weight after swelling[31].

J. Differential Scanning Calorimetry& X-Ray Powder Diffraction (DSC & XRD)

It is critical to know the physical status of the drug in numerous unit systems. During the procedure, the crystallinity of the medication may alter, and affect the release of drug. The crystallinity of a medication is determined using the X ray powder diffraction method and Differential Scanning Colorimetry[32].

V. IN VITRO ASSESMENT OF DRUG RELEASE BEHAVIOUR

Drug release from floating microspheres in vitro, is a complex process due to floating nature of the microspheres and they also stick to the inside surfaces of the dissolving basket, resulting in microspheres or their surfaces not participating in the release research. Release behaviour of the drug of GRDF is one of the most important parameters that is widely studied. Compendial dissolving test machines are preferred by scientists all over the world for investigating drug release from oral dosage formulations. We all know, conditions in stomach have a significant impact on behaviour of drug release. Quality control procedures are chosen with the physiological state of the human stomach in mind[33,34]. Instruments like the paddle apparatus or the rotating basket apparatus, and simple variations of the instruments, are often used in the testing GRDFs[35]. The outcomes of such testing are heavily influenced by the type of GRDF being tested. Many alternative approaches for stopping floating of oral dose forms while performing dissolution tests have been tried. Helical wire sinks are the simplest and widely used method[36]. However, when inspecting floating and verifying the expanding, the employment of a sinker can alter the swelling behaviour of dosage form. A floating system beneath the ring mesh is an alternate solution[37].

Kong et al. utilised a shaker incubator at 37°C and 100 rpm to explore with another extremely basic approach. The medium and the obtained samples were regularly replaced[38]. Eberle et al. created another method termed "custom-built stomach model." His team attempted to adhere the dose form with the paddle shaft in order to avoid air contact repeatedly. It includes 400 ml Erlenmeyer flasks filled with medium and set in a water bath shaker[39].In comparison to a simple USP II paddle equipment configuration, this testing approach resulted in the apparent acceleration of the drug of a test floating system. Furthermore, the dose form in this paddle system may easily float above the surface of the medium, which is a zone with minimal sheer stress and thus provides an excellent insight into the observed results[40]. Because of the artificial nature of the setup, it may allow for more fruitful measurements, but because to a lack of physiological significance, it is unlikely to be reflected in in-vivo behaviour. Scientists realised an important issue that occurs during the dissolution test of gastro retentive dosage forms when put in combination with drugs that are weakly basic in nature, and the problem is the pH difference of the GI tract. The Rosette-Rice device was used to develop a multi-compartment transfer model that included a stomach, bowel, and absorption compartment. The drug is readily transmitted from the stomach to the intestinal compartment in this configuration, and the absorption and intestinal compartments are separated by a filter membrane. The pH of the medium is changed using reservoirs containing 1N HCl or borate buffer. This experimental setting contributed to showing the potential advantages of an in-vitro system for a controlled release floating system over immediate-release tablets[41]. An updated version of the USP II paddle device utilised, to further study physiological disintegration of new gastro retentive dose formulations. In the procedure, to simulate physiological stress in the stomach, the dissolving capillaries of the paddle device are filled with polystyrol beads[42].

VI. IN VIVO STUDIES

The most important requirement of In Vivo studies simulated model of animal or human which gives better information about gastric retention time and drug bioavailability. First, the selection of an animal model is done for an in vivo study and the animals selected can be rats, guinea pigs, rabbits or mice[43].In case of GRDDS, in vivo studies are mostly done on bigger animals like dog or human because gastro retentive time and bioavailability of the drug is difficult to measure in small animals[44]. Gamma scintigraphy is an efficient method for evaluation of gastric retention in humans. Before the development of this method, it was only hypothesized that gastro retentive drug delivery system provides better therapeutic efficacy than conventional dosage forms[45]. Radioisotope, in a very little amount, having shorter half-life is added to the dosage form . After being processed by a computer, the formulation enters source of neutron, allowing it to emit the recorded gamma rays as a picture.[46] To explore the chrono pharmacological effect of diclofenac sodium, scientists created hollow calcium pectinate beads. The floating beads were hollow spheres with less than one gramme per ml of bulk density and more than 30% porosity. This setup was used to execute the study on rabbits (in vivo) with gamma scintigraphy which resulted in 5 hours of gastro retention time of the beads[46].

Magnetic Resonance Imaging is one popular method to study in vivo GRDDs. It is a much safer technique and involves use of radio waves and magnetic fields for studying the structure anatomically along with the dosage form location. The compounds having super paramagnetic properties are used for the process of visualization for example ferrous oxide[47]. Another approach was effectively employed to analyse the stomach retention duration of Iron Oxide black with gadolinium chelates as a super paramagnetic agent and in the investigation of intragastric pill status and residence duration in human volunteers. Another alternative is X-ray or radiology, using a radio opaque material along with the gastro retentive drug delivery system. This method is marked in evaluation process of gastroretentivity, rate of disintegration of dosage formulations and their transit for oesophagus[48]. Gastroscopy is one more widely used method used in the diagnosis and monitoring of the GIT. Fibre optics is used in this method which help in the detection of dosage form. Because this approach is less comfortable, it is occasionally employed to measure stomach retention in any dose form in people under mild anaesthesia[49]. Anti-tumour studies invivo were performed by a group of scientists to look into the potency of 5-fluorouracil of floating beads of calcium alginate. The trial indicated that the multiple unit floating system had the ability to lower the occurrence of stomach tumours in mice by 74%, whereas a standard tablet dosage reduced this incidence by just 25%[50]. Another study by a group of scientists reported increase in bioavailability of atorvastatin calcium, when floating tablets are given to albino rabbits. Tablets with a floating lag time in vitro of 564.16 s when compared to normal pills, a floating period of 6 hours can increase bioavailability by 1.6 times[51].

VII. APPLICATION OF A LOW-DENSITY POROUS CARRIER

The use of porous carriers with low density is a prominent strategy in order to create floating medicine delivery systems. Porous carriers are materials with low density, open or closed pore structures that gives a high exposed drug loading surface area. They have a variable hydrophobicity from a range total hydrophilic carriers that readily dissolve or scatter in water to being fully hydrophobic that float on water for a long time[52]. Porous carriers are used in pharmaceuticals for different applications because of its broad range of effective properties. Some of them includes a new drug delivery development such as FDDS, sustained delivery systems; improved solubility of drugs with poor solubility ; enzyme immobilization etc[53]. There are Several examples of porous carriers used in pharmaceuticals which contain polypropylene foam powder, magnesium aluminometa silicate, porous calcium silicate, porous ceramic, porous silicon dioxide, etc. Streubel led the first group of scientists that tried employing polypropylene foam powder as a porous carrier for the production of floating microspheres containing verapamil HCl. As the carrier material, hydrophobic polypropylene, a highly porous, foam powder with an open-cell structure and low intrinsic density was used. The o/w solvent evaporation process was used to create microparticles of ethyl cellulose, or polymethylmethacrylate (PMMA), Eudragit RS. Dichloromethane was employed as a solvent to dissolve the medication and the polymer that controlled the release rate[54].

Another group of scientists developed repaglinide floating microspheres where calcium silicate with low density was used as porous carriers[55].Calcium Silicate has porous structure with larger pore volume because of which it is used in industries as a powder compressive adjuvant or liquid absorber and it also possess sustained release property. Calcium silicate can float because of the air between its pores when they are surrounded by a polymer[56]. Gamma scintigraphy of the formulations was done on rabbits to study the transit in the Gastro intestinal tract. Microspheres which are non-floating developed from similar polymer was used as a standard to compare the gastroretentive property of the formulation. 6 hours of gastro retentive time was observed in all the animals where repaglinide was used with calcium silicate as the base. The optimized formulation filled with the drug was administered orally to rabbits, blood samples were drawn from them which were then used to study and the pharmacokinetic properties of repaglinide were extracted from floating microspheres and were compared to the pharmacokinetic properties of the marketed tablet formulation.

Floating microspheres relative bioavailability of that drug came out to be increased about 3 times when compared with tablet brand that was available in the market. Muller and Anders have because of the use of at least one permeable structural element, such as foam or a hollow body, devised a floating drug delivery method that is less dense than gastric fluids.

VIII. APPLICATIONS [57]

1) Gastro retentive floating microspheres are particularly efficient in reducing the principal detrimental impact of gastrointestinal irritation; similarly, floating microspheres of nonsteroidal antiinflammatory medications, such as indomethacin, are good for rheumatoid arthritis patients.
2) Floating microspheres are a particularly successful technique for delivering medications with low bioavailability due to restricted absorption in the upper GIT. These systems effectively maximise absorption and increase the bioavailability of a variety of medications.
3) The greater medication dose can be lowered due to an increase in stomach retention time, which results in a lower dosing frequency.
4) Due to site-specific absorption from the upper section of the GIT, drugs with limited bioavailability are considered good candidates for development as floating medication delivery devices to optimise absorption.
5) The systems of floating microspheres can remain in the stomach for long periods of time, allowing the medicine to be delivered gradually. Short stomach residence time issue seen with formulation for oral controlled release can thus be overcome by these methods. These systems can float on the contents of the stomach because their bulk density is less than one.
6) Floating microspheres can significantly enhance stomach pharmacotherapy via local medication release. Thus, removing Helicobacter pylori from the stomach's submucosal tissue can help cure peptic ulcers, chronic gastritis, gastroesophageal reflux disease, and other conditions. Aceto hydroxamic acid floating bio adhesive microspheres have been developed for the treatment of Helicobacter pylori infection. Ranitidine HCl hollow microspheres are also being developed for the treatment of stomach ulcers.
7) These microspheres systems enable sustained drug release behaviour and allow the medication to be released over time. Transilast hollow microspheres are created as a floating controlled medication delivery method.
8) The system of floating microspheres are especially beneficial for medications which are absorbed from the proximal region of the small intestine, or the stomach, such as furosemide, misoprostol and riboflavin. The optimal therapeutic dose might be attained and drug waste decreased by targeting delayed delivery of misoprostol to the stomach.
9) These technologies make it simple to maintain a steady blood level while also making administration easier and improving patient compliance.
10) Prednisolone, Riboflavin, Celecoxib, Lansoprazole, Theophylline, Diltiazem hydrochloride, Piroxicam, Verapamil hydrochloride, and are among the drugs recently found to be made as in hollow microspheres.

IX. CONCLUSION

Floating microspheres have shown to be an efficient approach for increasing bioavailability and controlling the distribution of various medicinal drugs. Significant efforts have been undertaken across the world to investigate these systems for treatment effectiveness with compliance. Gastro retentive dosage forms as floating microspheres accurately regulate the rate of target drug release to a particular region, allowing for a significant influence on health care. These methods also give enormous prospects for creating novel delayed and controlled release oral formulations, therefore expanding the horizon of futuristic pharmaceutical discovery. The increased sophistication of this technology will enable effective improvements in the field of gastro retentive microspheres treatment, allowing for more efficient administration of molecules. Furthermore, current advances in pharmaceutical research will undoubtedly create substantial opportunities for the formation of unique and effective methods in the development of these potential drug delivery systems.

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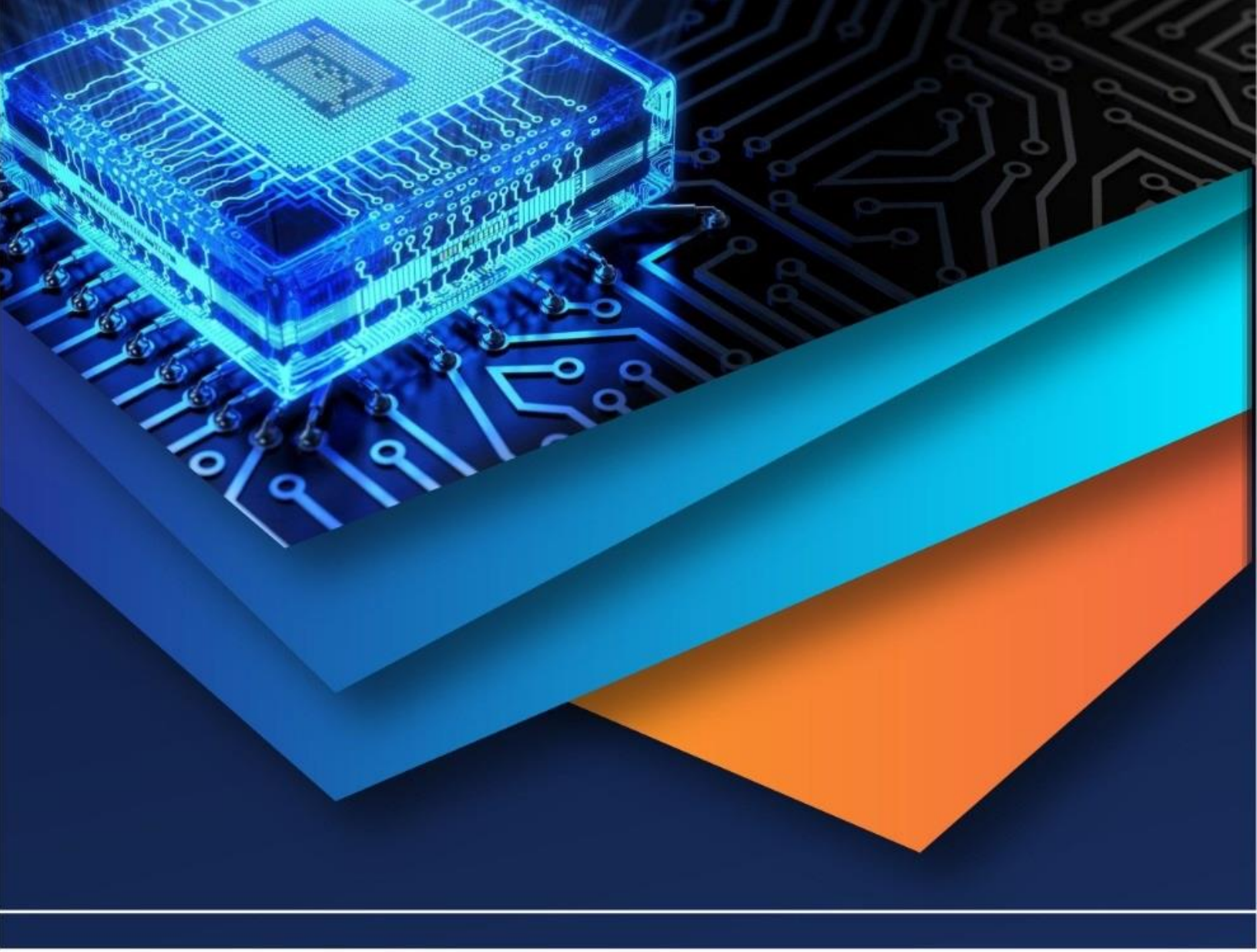

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