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Formulation and Evaluation of Floating Microspheres of an Antidiabetic drug

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Abstract: ***The primary objective of this work was to create Metformin floating microspheres to achieve longer retention in the upper GIT, which improves absorption and bioavailability. The microspheres were created using a solvent evaporation process with various ratios of rate controlling polymers ethyl cellulose and Carbopol 940, with Metformin employed at a fixed ratio in each formulation. A (1:1) mixture of dichloromethane and ethanol, with tween 80 as a surfactant. The produced microspheres were tested for percentage yield, particle size, entrapment efficiency, buoyancy, and drug release in vitro. The influence of polymer concentration on various parameters was studied. According to the findings, increasing the concentration of ethyl cellulose improved drug release from floating microspheres. The formulation F6 was selected as best formulation, and it has drug release of 94.22% at 12 hrs. entrapment efficiency 98.8%, buoyancy 94.2%.***

Keyword: Diabetes, Metformin, Floating microspheres, Drug release .

I. INTRODUCTION

Diabetes is one of the leading causes of death and disability worldwide. The most recent WHO estimate for the number of diabetics globally in 2000 is 171 million, with a probable increase to at least 366 million by 2030. The medical community's focus is on disease prevention and treatment, as seen by the increasing number of research papers published on the issue each year. (1)

Oral administration has been the most popular and convenient method of drug administration. Floating microspheres are a non-effervescent gastro retentive drug delivery technique.

They are low density systems with enough buoyancy to float over gastric contents and remain in the stomach for an extended period of time. As the device floats over the gastric contents, the drug is gently released at the correct rate, resulting in enhanced gastric retention and fewer variations in plasma drug concentration. When microspheres come into contact with stomach fluid, the gel formers, polysaccharides, and polymers hydrate to produce a colloidal gel barrier that limits the rate of fluid entry into the device. and resultant drug release. As the dosage form's external surface dissolves, the gel layer is maintained by the hydration of the next hydro colloidal layer. The air captured by the expanded polymer reduces density and gives the microspheres buoyancy. (2) Metformin is an anti-diabetic, insulin-sensitizing medication from the Biguanide class of oral anti-hyperglycaemic agents. Metformin HCl is a safe medication with a half-life of 1.5-3 hours. It is not entirely absorbed, resulting in a low bioavailability concern. Approximately 80-100% of the medication is excreted intact. Metformin HCl has a total daily need of 1.5-3g, resulting in a significant prevalence of GI side effects and toxicity. Slow but complete drug release in the stomach increases drug bioavailability and utilisation, resulting in fewer doses and GI side effects. Keeping the above facts in consideration the present study is performed with a view to formulate and evaluate floating microsphere of metformin hydrochloride in order to maintain a sustained drug concentration for longer period of time.

II. MATERIAL AND METHODS

A. Sample Collection

Metformin hydrochloride was a received from aarti Parma, Mumbai. Ethyl cellulose (14 cps), Carbopol 940, dichloromethane, ethanol, tween 80, distilled water was collected from Pharmaceutics research lab. All other chemicals were of analytical grade.

B. Preparation of Microspheres

Floating microspheres containing Metformin HCL were prepared by solvent evaporation method using Ethyl cellulose and Carbopol 940. Briefly drug and polymer were mixed in the mixture of dichloromethane and ethanol in 1:1 ratio. The slurry was slowly introduced into the 100ml water containing 0.02% tween 80 while being stirring at 500rpm by a magnetic stirrer for 2 hr. at 40^0C to allow solvent to evaporate completely. Microspheres were washed with petroleum ether. The collected microspheres were dried at room temperature for 24 hr.

Table 1: Formulation of the floating microspheres

Formulation Code	Metformin HCL (mg)	Carbopol 940 (mg)	Ethyl Cellulose (mg)	DCM: ethanol (ml)	Aqueous phase containing 0.02%tween 80 (ml)
F_1	500	100	100	1:1	100
F_2	500	100	250	1:1	100
F_3	500	100	500	1:1	100
F_4	500	250	100	1:1	100
F_5	500	250	250	1:1	100
F_6	500	250	500	1:1	100
F_7	500	500	100	1:1	100
F_8	500	500	250	1:1	100
F_9	500	500	500	1:1	100

III. CHARACTERIZATION OF MICROSPHERES

A. Particle size Analysis

All of the microspheres were sized using optical microspheres equipped with an ocular micrometer and a stage micrometer. The optical microscope was used to measure the size of more than 50 microspheres at random. The total size of the microspheres was divided by the number of microspheres to determine the average particle size. (3) Least count of the ocular micrometer was calculated by the following formula

$$\text{Least count} = \frac{\text{No of Division of Stage Micrometer}}{\text{No of division of ocular micrometer}} \times 100$$

B. Scanning Electron Microscopy Analysis

The shape and surface morphology of microsphere samples were examined using a scanning electron microscope. Microspheres were clustered on double-sided carbon dust, which was placed on a sample carrier (9 aluminum stubs with double adhesive tape) in the shape of a cylinder with a weight of 5 mm and a diameter of 10 mm, and were coated with AU-pd (Gold Platinum) mixture under vacuum (9100 m torr) and sputter coated to a thickness of 50 nm. An electron beam with a voltage range of 5-15 KV was used to image the samples. Surface topography microphotographs with appropriate magnification were taken. (4)

C. Determination of Drug Content

An accurately weighed quantity of the floating microspheres equivalent to 20mg of drug was taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of phosphate buffer (pH 6.8) repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using phosphate buffer (pH 6.8). The solution was filtered and the absorbance was measured after suitable dilution at 233 nm by using UV-visible spectrophotometer. The drug content was estimated in triplicate using a calibration curve constructed in the same solvent.

D. Determination of Percentage Yield

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of all non- volatile components which were used for the preparation of the microspheres. The yield percentage was determined with the following formula of Patel et al. (2009):

Yield (%) = $\frac{\text{Weight of microspheres}}{\text{Total expected weight of drug and polymer}}$ X 100

E. Estimation of Drug Entrapment Efficiency (DEE)

Amount of drug entrapped in to the microspheres is determined by using the formula.

Drug entrapment efficiency (DEE) = $\frac{\text{Experimental drug content}}{\text{Theoretical drug content}}$ = x100

F. Buoyancy Determination

The microspheres about 300mg was weighed and were spread over the surface of USP dissolution type II apparatus which was filled with 900 ml of 0.1 N HCl containing 0.02% of Tween 80. The medium was agitated with a paddle rotating at 100 rpm. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and total mass of the microspheres (Debjit et al., 2009).

Buoyancy % = $\frac{\text{Weight of floating microsphere after time}}{\text{Initial weight of microsphere}}$ x 1000

Floating ability of different formulations was found to be differed according to drug polymer ratio. The percentage buoyancy for different formulation was found in range from 86.0% to 94.31%studies:

The drug release studies were conducted using a six basket dissolution device USP type II. The microspheres were inserted in a nonreacting mesh with a mesh size smaller than the microspheres.

To keep microspheres from escaping, the mesh was knotted with nylon thread. At 37°C, 900 cc of 0.1 N hydrochloric acid was utilized as a dissolving media. At regular intervals of up to 12 hours. After adequate dilution, 5 mL aliquots were taken and analyzed by UV spectrophotometer at 232 nm. The removed volume was replaced with an equivalent volume of fresh 0.1 N hydrochloric acid. (5)

IV. MICROMERITIC PROPERTIES

Microspheres were characterized for their micromeritic properties such as bulk density, tapped density, compressibility index, Hausner`s ratio, and angle of repose

A. Bulk Density

An exact quantity „M" of microsphere was taken and was placed into a measuring cylinder. Volume „V" occupied by the microspheres was noted without disturbing the cylinder and bulk density was calculated using the following equation;

Bulk density (Pb) = M/V

B. Tapped Density

To calculate the tapped density, a cylinder containing a specified amount (M) of microspheres was exposed to a fixed number of taps (about 100) until the bed of microspheres reached the minimum. The following equation was used to obtain the tap density and final volume after tapping, Vo. (6)

Tapped Density (Pp) = M/Vo

C. Angle of Repose

This characteristic was discovered to predict flowability. The angle of repose of the microspheres was calculated using the fixed funnel method and the formula,

Angle of repose (ϕ) = $\tan^{-1}[2h/d]$ - h

Where, h is height and d is the diameter of the microsphere pile that is on a paper after making the microspheres flow from the glass funnel. (7)

D. Carr's Index or % Compressibility

A high Carr's index is indicative of the tendency to form bridges can be calculated by using following formula:

Carr's index or %compressibility Index or C= $\frac{V_t - V_b}{V_t}$ x 100

Where, V_t = Tapped density

V_b = Bulk density

E. Hausner's Ratio

Hausner's ratio is measures of the propensity of a powder to be compressed and the flow ability of granule. A higher Hausner's ratio indicates greater cohesion between particles.

Hausner's Ratio = V_t / V_b

Where, V_t = Tapped density

V_b = Bulk density

Table 2 : Particle size determination.

Formulation code	Mean particle size (µm)
F1	290.50 ± 0.705
F2	302.21 ± 0.605
F3	380.42 ± 0.680
F4	340.70 ± 3.121
F5	360.45 ± 4.301
F6	252.50 ± 0.322
F7	314.65 ± 2.31
F8	252.15 ± 0.78
F9	278.89 ± 2.73

Scanning electron microscope (SEM) image

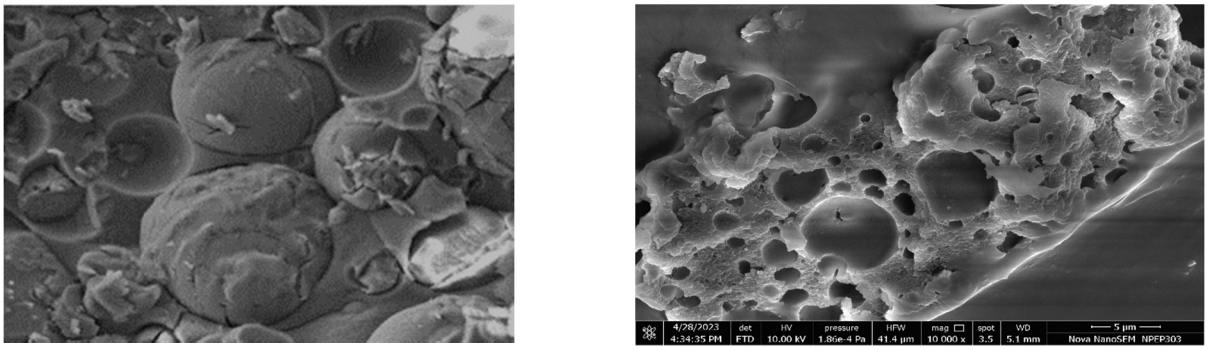

Figure 1 : Scanning electron microscope (SEM) image of F6 formulation .

Table 3 : Result on Drug content , Percentage yield , Entrapment efficiency & Buoyancy determination.

Formulation code	Drug content (%)	Percentage yield (%)	Entrapment efficiency (%)	Buoyancy (%)
F1	41.2±0.41	94.8%	82.8±0.31	82.0
F2	39.2±0.02	91.2%	85.9±0.14	86.3
F3	40.3±0.18	96.1%	87.13±0.2	90
F4	38.4±0.30	85.2%	89.9±0.43	87.3
F5	44.0±0.29	90.1%	91.7±0.18	92.1
F6	48.2±0.32	99.2%	98.6±0.35	94.2
F7	42.3±0.10	92.5%	93.9±0.34	85.1
F8	43.8±0.45	89.3%	97.3±0.47	89.3
F9	46.7±0.26	98.0%	87.4±0.3	91.5

Table 4 : In vitro drug release studies

Time(h)	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	1.65	1.23	1.065	1.56	1.33	1.05	1.532	1.33	1.23
2	2.85	2.34	1.232	1.557	3.32	4.04	3.42	1.435	2.34
3	4.712	3.86	4.243	5.45	8.411	7.56	5.231	4.023	3.55
4	7.567	5.56	8.422	6.32	10.78	9.23	8.78	7.34	9.45
5	13.412	10.34	13.423	11.055	13.45	17.231	15.321	13.345	16.52
6	17.456	14.35	22.661	15.33	18.781	24.89	20.322	19.233	21.234
7	35.612	24.89	36.66	27.344	27.233	38.912	28.57	23.457	30.423
8	43.121	30.451	40.511	34.23	30.431	51.23	49.231	35.333	37.781
9	59.651	47.23	54.231	42.211	47.23	67.453	54.341	40.32	48.450
10	67.142	57.231	60.33	50.211	54.33	77.211	60.32	53.122	57.67
11	78.554	67.12	76.322	65.33	65.234	86.342	68.431	60.245	68.343
12	86.243	74.341	84.231	70.321	78.23	94.22	73.421	71.34	73.231

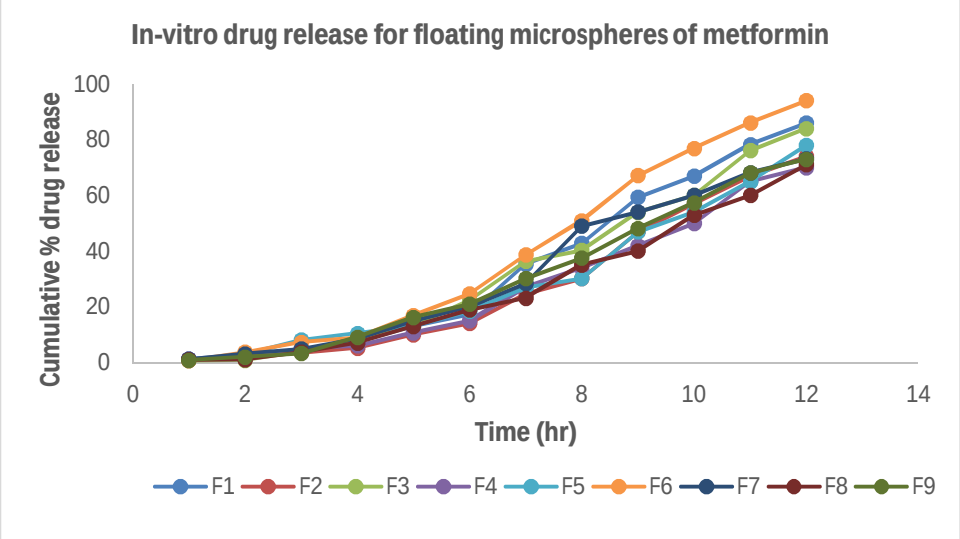

Figure 2: Graph for In-vitro drug release studies of metformin HCl in 0.1 N HCl

Table 5: Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio.

Formulation code	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.52 ± 0.15	0.63 ± 0.24	25.5 ± 0.12	17.46 ± 0.34	1.20 ± 0.40
F2	0.54 ± 0.57	0.67 ± 0.12	23.2 ± 0.33	13.12 ± 0.12	1.24 ± 0.26
F3	0.46 ± 0.44	0.53 ± 0.23	29.3 ± 0.22	13.20 ± 0.46	1.15 ± 0.12
F4	0.49 ± 0.14	0.61 ± 0.11	27.6 ± 0.12	19.67 ± 0.56	1.24 ± 0.34
F5	0.51 ± 0.56	0.62 ± 0.11	26.1 ± 0.11	17.74 ± 0.41	1.35 ± 0.33
F6	0.53 ± 0.34	0.65 ± 0.19	23.7 ± 0.13	17.18 ± 0.13	1.25 ± 0.52
F7	0.49 ± 0.23	0.58 ± 0.22	28.5 ± 0.19	15.51 ± 0.23	1.25 ± 28
F8	0.54 ± 0.16	0.68 ±0.26	24.7 ± 0.32	20.58 ± 0.12	1.20 ± 0.49
F9	0.53 ± 0.14	0.66 ± 0.12	26.7 ± 0.22	19.69 ± 0.54	1.53 ± 0.67

V. RESULTS AND DISCUSSION

A. Particle size Determination.

The particle size of microspheres was analyzed using optical microscope. Mean particle size of floating microspheres varies between 252 µm to 380 µm. (Table 2)

B. Scanning Electron Microscopy Analysis

The shape and surface morphology of microsphere samples were examined using a scanning electron microscope. Microspheres were found to be spherical in shape. (Figure 1)

C. Drug content, Percentage yield, Entrapment efficiency & Buoyancy determination.

Drug content, percentage yield Entrapment efficiency & Buoyancy determination of the prepared microspheres were carried and the results are summarized in Table 3. The range of drug content varies from 38.4 % to 48.4%. Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 85.2 % to 99.2 %. Percentage yield increases with increasing polymer concentration in the formulation. Drug entrapment efficiency increases from 82.8 % to 98.2 % as polymer concentration increase respectively. Floating ability of different formulations was found to be differed according to drug polymer ratio. The percentage buoyancy for different formulation was found in range from 82.0% to 94.2 %. (Table 3)

D. In vitro drug release

At the end of 12 hrs. the percentage cumulative release of Metformin Hydrochloride from microspheres were found to be 86.2%, 74.3%, 84.2% for formulations F1, F2, F3 respectively. The percentage cumulative drug release from microspheres were found to be 70.3%, 78.2%, 94.2% for formulations F4, F5, F6 respectively. The percentage cumulative drug release for microspheres were found to be 73.4%, 71.3%, 73.2% for formulations F7, F8, F9 respectively. (Table 4) The cumulative percentage drug release for higher concentration of ethyl cellulose microspheres was found to be maximum. The rank order for cumulative percentage drug release was found as follows:

F6>F1>F3>F5>F2>F7>F9>F8>F4

E. Bulk density, Tapped density, Angle of repose, Carr's index & Hausner's ratio.

Angle of repose (excellent) and compressibility index were indicated good flowability of microspheres, showing no need for addition of glidants to enhance flowability. The better flow property of microspheres indicates that the microspheres produced were non aggregated.

VI. CONCLUSION

The incorporation of the highly water-soluble antidiabetic drug metformin hydrochloride was done using ethyl cellulose and Carbopol 940 as the polymer. The formulations exhibited sufficient floating properties. Percentage drug release study was affected by the polymer concentration. From this study it is concluded that the formulation F6 was a good formulation. Where the formulation was having 94.22% buoyancy with 8 hour control release or longer and would be capable of reducing the frequency of administration depending upon the formulation variable. SEM studies the formulation was found in spherical nature. So, the formulation F6 is more effective and it is concluded that the prepared floating microspheres of metformin HCl may prove to be potential candidate for safe and effective sustained drug delivery over an extended period of time which can reduce dosing frequency.

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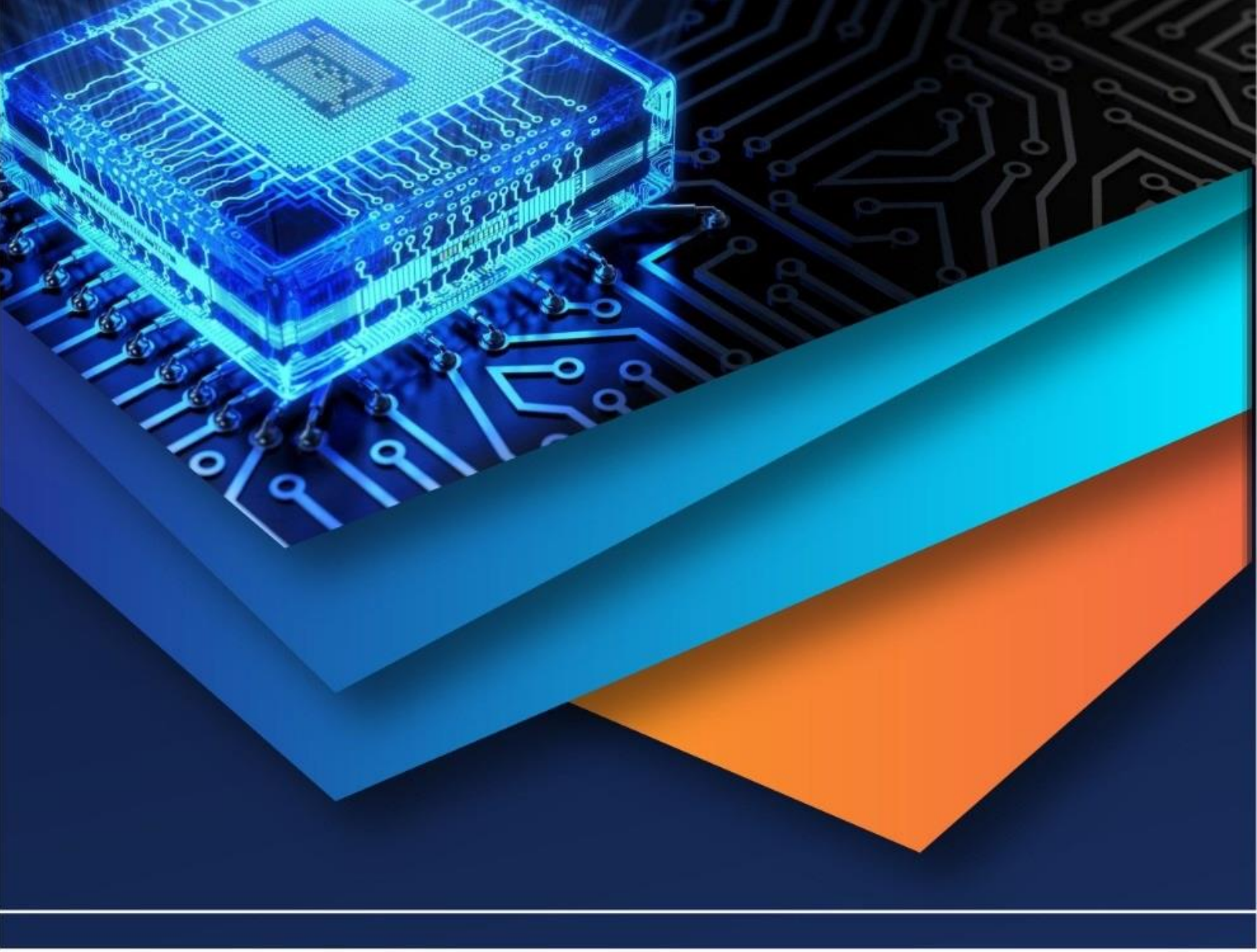

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