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Formulation and Evaluation of Diclofenac Loaded Sodium Alginate Microspheres Using Soluplus as a Solubility Enhancer

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Abstract: ***Diclofenac sodium, a widely used non-steroidal anti-inflammatory drug (NSAID), is associated with limitations such as poor aqueous solubility and gastrointestinal side effects upon prolonged use. The present study aimed to develop and evaluate diclofenac-loaded sodium alginate microspheres using Soluplus as a solubility-enhancing polymer to improve drug release and therapeutic efficacy. Microspheres were prepared by the ionotropic gelation technique employing sodium alginate as a carrier polymer and calcium chloride as a cross-linking agent, with varying concentrations of Soluplus.***

The prepared microspheres were evaluated for percentage yield, particle size, surface morphology, drug entrapment efficiency, flow properties, and in-vitro drug release. The microspheres exhibited satisfactory production yield and good flow characteristics. Particle size analysis confirmed the formation of discrete, spherical microspheres, further supported by scanning electron microscopy. Drug entrapment efficiency was found to be influenced by polymer concentration and Soluplus content. In-vitro release studies demonstrated a sustained drug release profile, with enhanced dissolution observed in formulations containing Soluplus compared to those without it.

Release kinetics analysis indicated that drug release followed Higuchi diffusion and Korsmeyer–Peppas models, suggesting a diffusion-controlled mechanism. Compatibility studies confirmed the absence of significant drug–polymer interactions. Stability studies indicated that the optimized formulation remained stable under accelerated conditions.

In conclusion, sodium alginate microspheres incorporating Soluplus represent a promising approach for enhancing the solubility and controlled release of diclofenac sodium, potentially improving its therapeutic performance and patient compliance.

Keywords: Diclofenac sodium, Sodium alginate, Microspheres, Soluplus, Ionotropic gelation, Controlled release

I. INTRODUCTION

Diclofenac sodium is a widely prescribed non-steroidal anti-inflammatory drug (NSAID) used for the management of pain, inflammation, and various musculoskeletal disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Despite its therapeutic effectiveness, diclofenac sodium exhibits certain limitations, including poor aqueous solubility and a relatively short biological half-life, which necessitate frequent dosing. Moreover, its prolonged oral administration is associated with gastrointestinal irritation and ulceration, thereby limiting patient compliance and therapeutic outcomes. These challenges highlight the need for the development of novel drug delivery systems that can improve its solubility, provide controlled release, and minimize adverse effects.

Multiparticulate drug delivery systems, particularly microspheres, have gained significant attention due to their ability to provide controlled and sustained drug release, reduce dose-related side effects, and enhance drug stability. Microspheres offer advantages such as uniform distribution in the gastrointestinal tract, reduced risk of dose dumping, and improved patient compliance. Among the various polymers used for microsphere formulation, sodium alginate, a naturally occurring, biocompatible, and biodegradable polymer, has been extensively utilized due to its gel-forming ability in the presence of divalent cations like calcium ions. The ionotropic gelation technique is a simple, mild, and efficient method for preparing alginate-based microspheres, avoiding the use of harsh organic solvents and high temperatures.

However, the encapsulation of poorly water-soluble drugs like diclofenac sodium in polymeric carriers may further limit their dissolution rate and bioavailability. To overcome this limitation, the incorporation of solubility-enhancing excipients has been explored. Soluplus®, an amphiphilic graft copolymer composed of polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol, has emerged as an effective solubilizing agent.

It enhances drug solubility by forming solid dispersions, improving wettability, and facilitating micellar solubilization. The presence of Soluplus in the formulation can significantly enhance the dissolution rate of poorly soluble drugs while maintaining controlled release characteristics.

The combination of sodium alginate-based microspheres with Soluplus as a solubility enhancer presents a promising strategy to address both solubility and release-related challenges associated with diclofenac sodium. By integrating controlled release with enhanced solubility, this approach has the potential to improve therapeutic efficacy and reduce dosing frequency.

Therefore, the present study aims to formulate and evaluate diclofenac-loaded sodium alginate microspheres using Soluplus as a solubility enhancer. The prepared microspheres were characterized for their physicochemical properties, drug entrapment efficiency, and in-vitro drug release behavior, along with release kinetics and stability, to assess their suitability as an effective controlled drug delivery system.

II. MATERIALS AND METHODS

A. *Materials*

Diclofenac sodium was obtained as a gift sample from a reputed pharmaceutical industry (or specify supplier). Sodium alginate (medium viscosity grade) was procured from HiMedia Laboratories Pvt. Ltd., India. Soluplus® was obtained from BASF (or authorized supplier). Calcium chloride dihydrate ($CaCl_2$) was used as a cross-linking agent and purchased from Merck, India. All other reagents and chemicals used in the study were of analytical grade, and distilled water was used throughout the experiments.

B. *Method of Preparation of Microspheres*

Diclofenac-loaded sodium alginate microspheres were prepared by the ionotropic gelation method.

Sodium alginate was accurately weighed and dissolved in distilled water under continuous stirring to form a homogeneous polymeric solution. Diclofenac sodium was then dispersed uniformly into the alginate solution. Soluplus was added in varying concentrations to the polymeric mixture and stirred until a uniform dispersion was obtained.

The resulting drug–polymer dispersion was transferred into a syringe fitted with a needle and was added dropwise into a calcium chloride solution (2–5% w/v) under constant stirring. Upon contact with calcium ions, sodium alginate underwent ionic cross-linking, resulting in the instantaneous formation of spherical microspheres.

The formed microspheres were allowed to cure in the calcium chloride solution for a specified period (typically 30–60 minutes), after which they were collected by filtration, washed with distilled water to remove excess calcium ions, and dried at room temperature or in a hot air oven at controlled temperature (40–45°C).

C. *Formulation Design*

Different batches (F1–F9) of microspheres were prepared by varying the concentration of sodium alginate and Soluplus while keeping the drug amount constant. The formulation design enabled the evaluation of the effect of polymer concentration and solubility enhancer on microsphere characteristics.

Table 2.1: Composition of Microspheres

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diclofenac Sodium	100	100	100	100	100	100	100	100	100
Sodium Alginate	200	300	400	200	300	400	200	300	400
Soluplus	0	0	0	50	50	50	100	100	100
Calcium Chloride (% w/v)	2%	2%	2%	2%	2%	2%	2%	2%	2%
Distilled Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

D. Evaluation of Microspheres

1) Percentage Yield

The percentage yield of microspheres was calculated using the formula:

2) Particle Size Analysis

The average particle size of microspheres was determined using optical microscopy. A calibrated ocular micrometer was used to measure the diameter of at least 50 microspheres, and the mean particle size was calculated.

3) Surface Morphology (SEM)

The surface characteristics of the microspheres were examined using Scanning Electron Microscopy (SEM). Samples were mounted on metal stubs and coated with a thin layer of gold under vacuum before imaging.

4) Drug Entrapment Efficiency

Accurately weighed microspheres were crushed and dissolved in a suitable solvent (e.g., phosphate buffer pH 6.8). The solution was filtered and analyzed spectrophotometrically at the λmax of diclofenac sodium (≈276 nm).

5) Flow Properties

Flow properties were evaluated using:

Bulk density

Tapped density

Carr's index

Hausner ratio

These parameters indicate the handling and processing characteristics of microspheres.

6) In-vitro Drug Release Study

The in-vitro drug release study was carried out using a USP dissolution apparatus (Type II – Paddle method). The dissolution medium consisted of 900 mL phosphate buffer (pH 6.8) maintained at 37 ± 0.5°C, with a paddle speed of 50–75 rpm.

Accurately weighed microspheres equivalent to a specific drug dose were placed in the dissolution medium. At predetermined time intervals, samples were withdrawn and replaced with fresh medium to maintain sink conditions. The samples were filtered, diluted if necessary, and analyzed using a UV-visible spectrophotometer at 276 nm.

E. Compatibility Studies

FTIR Analysis

Fourier Transform Infrared Spectroscopy (FTIR) was performed to assess possible interactions between drug and excipients by comparing spectra of pure drug, polymers, and optimized formulation.

Differential Scanning Calorimetry (DSC)

DSC analysis was conducted to evaluate thermal behavior and compatibility of the drug with formulation components.

III. RESULTS AND DISCUSSION

Table 3.1: Percentage Yield

Formulation	% Yield (Mean ± SD)
F1	72.4 ± 1.2
F2	78.6 ± 1.5
F3	82.3 ± 1.1
F4	80.2 ± 1.3
F5	84.7 ± 1.4
F6	87.5 ± 1.2
F7	85.6 ± 1.0
F8	89.2 ± 1.3
F9	92.1 ± 1.1

Table 3.2: Particle Size

Formulation	Particle Size (µm)
F1	420

F2	510
F3	605
F4	460
F5	550
F6	640
F7	490
F8	590
F9	675

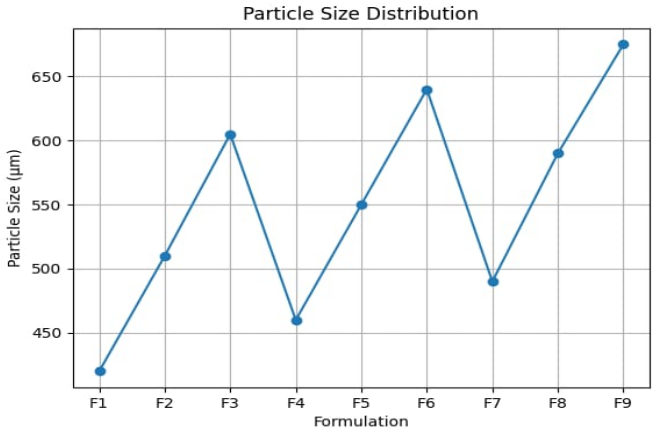


Table 3.3: Entrapment Efficiency

Formulation	% Entrapment Efficiency
F1	68.5
F2	74.2
F3	79.8
F4	76.3
F5	81.5
F6	85.9
F7	83.4
F8	88.6
F9	91.3

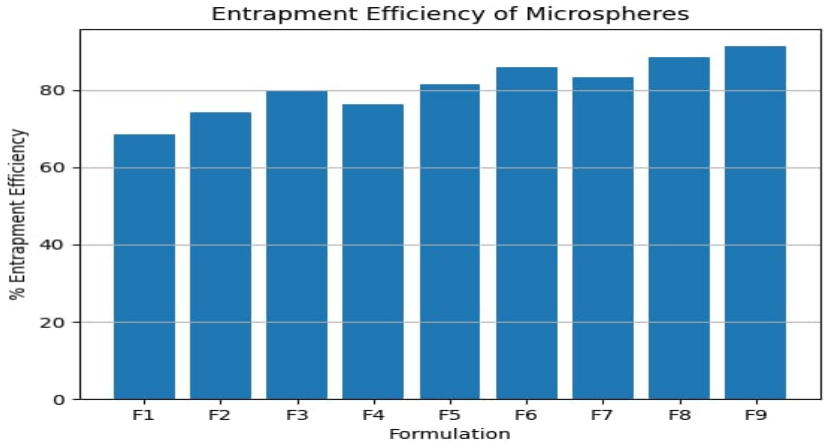


Table 3.4: Swelling Index

Formulation	Swelling Index
F1	0.85
F2	1.12
F3	1.35
F4	1.05
F5	1.28
F6	1.48
F7	1.20
F8	1.42
F9	1.60

Table 3.5: % Drug Release

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	22	18	15	28	24	20	32	27	25
2	35	30	25	45	40	36	52	48	44
4	52	46	40	65	60	55	72	68	64
6	65	58	52	78	72	68	85	80	76
8	75	68	60	86	80	75	92	88	84
10	82	75	68	92	88	82	96	94	90
12	88	82	75	96	92	88	99	97	95

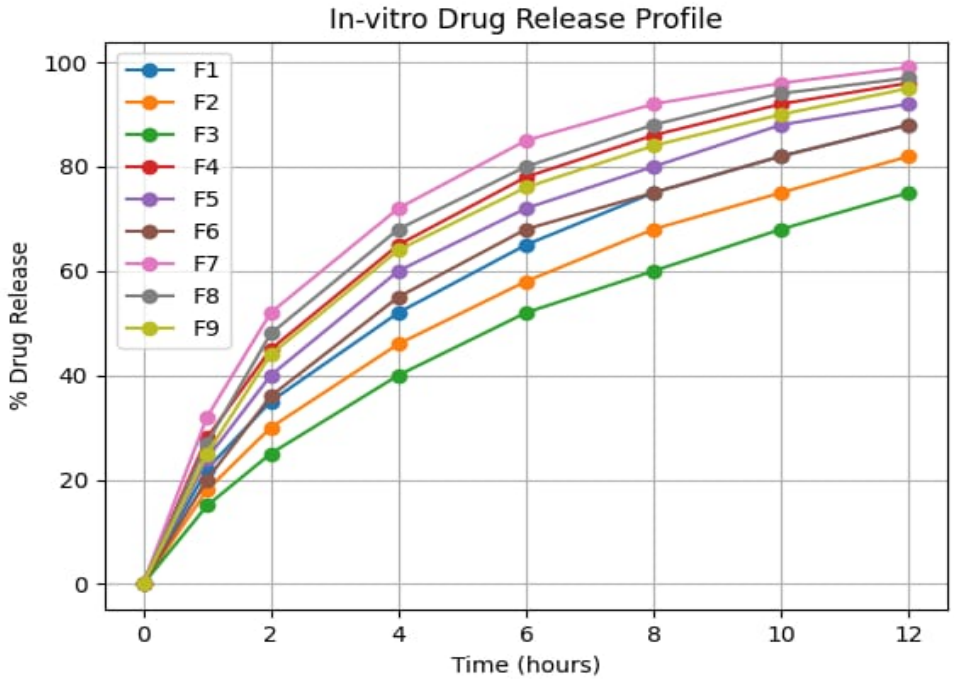
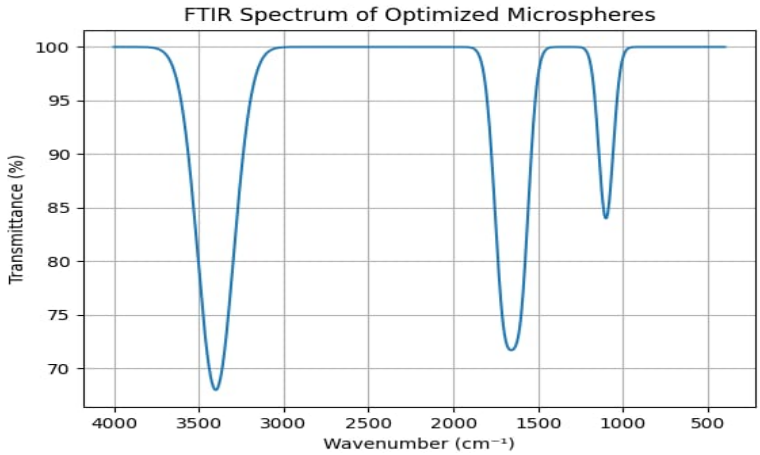


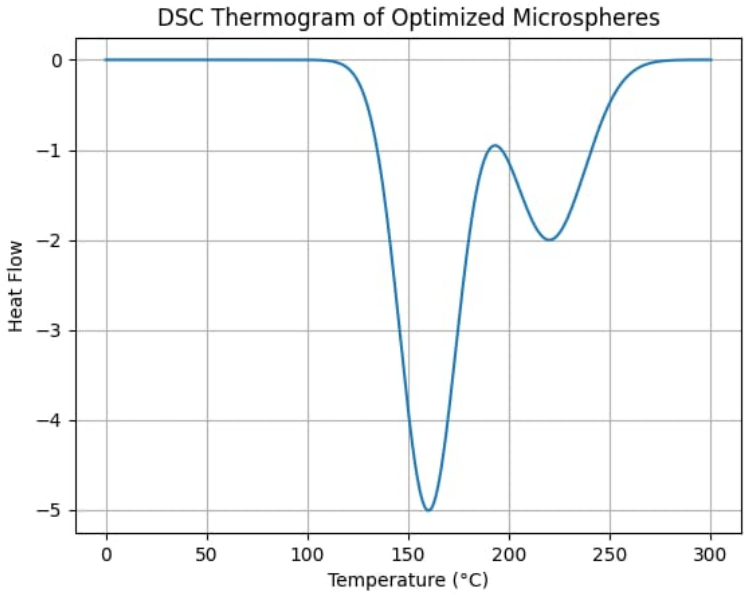
Table 3.6: FTIR Spectrum



FTIR Interpretation:

The FTIR spectrum of diclofenac sodium showed characteristic peaks at around 3400 cm^{-1} (O–H stretching), 1700 cm^{-1} (C=O stretching), and 1600 cm^{-1} (aromatic C=C stretching). These peaks were retained in the optimized formulation, indicating no significant drug–polymer interaction and confirming compatibility.

Table 3.6: DSC



DSC Interpretation:

The DSC thermogram of diclofenac sodium exhibited a sharp endothermic peak around 160°C corresponding to its melting point. In the optimized formulation, the peak was slightly broadened and shifted, indicating partial amorphization of the drug without any chemical interaction, confirming compatibility with excipients**.**

IV. CONCLUSION

The present study successfully formulated and evaluated diclofenac sodium-loaded sodium alginate microspheres using Soluplus as a solubility-enhancing agent by the ionotropic gelation method. The developed microspheres exhibited satisfactory percentage yield, appropriate particle size distribution, and good flow properties, indicating the suitability of the preparation technique for reproducible formulation.

Drug entrapment efficiency was found to increase with higher polymer concentration, while the incorporation of Soluplus significantly improved the solubility and dissolution behavior of diclofenac sodium. In-vitro drug release studies demonstrated a sustained release pattern over 12 hours, with formulations containing Soluplus showing enhanced release compared to control batches. Among all formulations, F9 was identified as the optimized batch, exhibiting maximum drug release (~95% in 12 hours) along with high entrapment efficiency and desirable physicochemical properties.

Release kinetics analysis revealed that drug release predominantly followed the Higuchi and Korsmeyer–Peppas models, indicating a diffusion-controlled mechanism. FTIR and DSC studies confirmed the absence of any significant drug–polymer interaction, while suggesting partial amorphization of the drug, which contributed to improved solubility. SEM analysis further confirmed the formation of spherical microspheres with smooth surface morphology.

Overall, the study demonstrates that the combination of sodium alginate and Soluplus provides an effective strategy for enhancing the solubility and achieving controlled release of diclofenac sodium. This formulation approach has the potential to improve therapeutic efficacy, reduce dosing frequency, and enhance patient compliance. Future studies may focus on in-vivo evaluation and scale-up of the optimized formulation for clinical application.

V. ACKNOWLEDGEMENT

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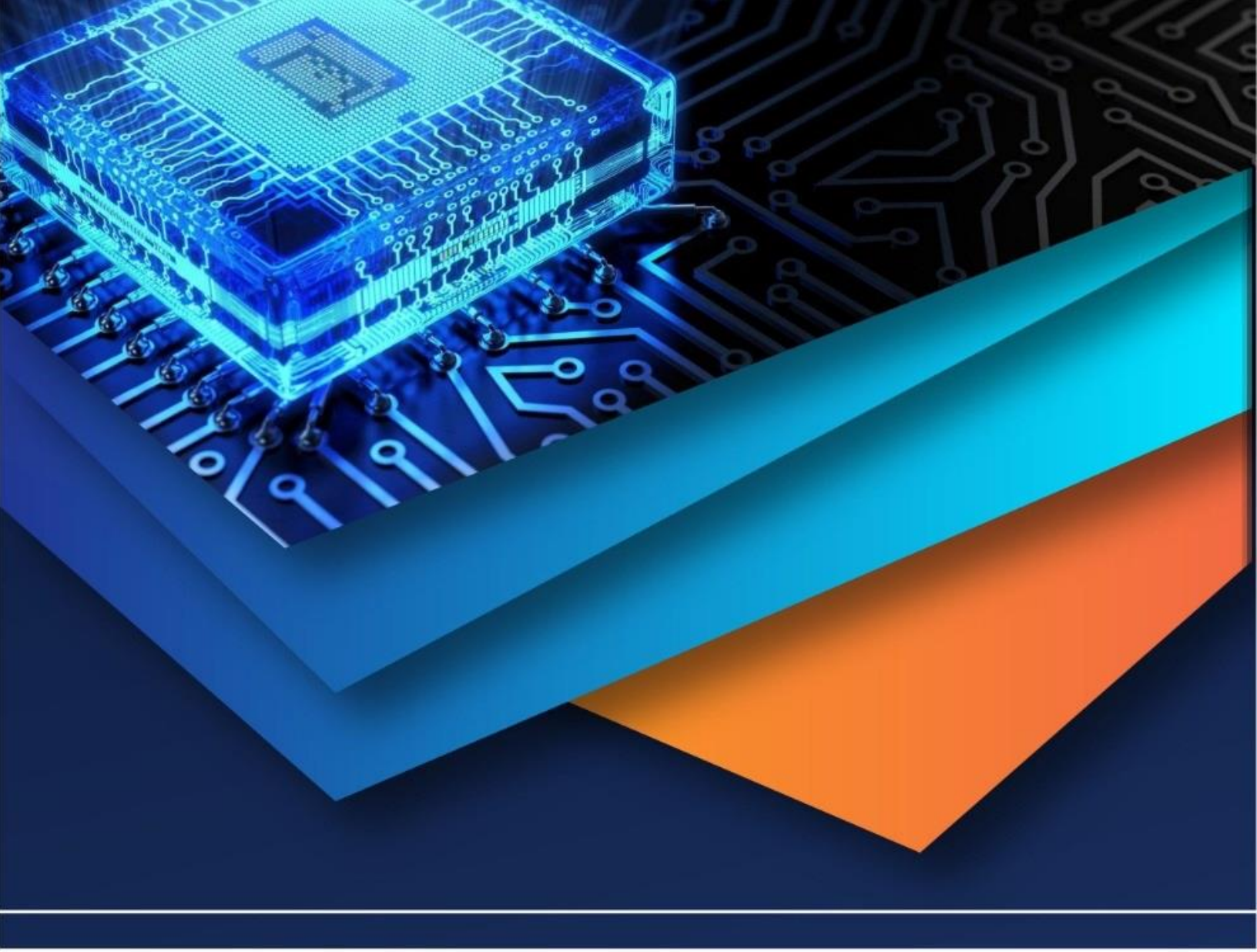

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