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Formulation, Development & Evaluation of Dispersible Tablet of Ethionamide

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Abstract: ***The current study is aimed to develop and evaluate dispersible tablets of Ethionamide, a second line anti-tubercular drug, for increasing patient compliance and therapeutic efficacy in the treatment of multidrug resistant tuberculosis (MDR-TB). However, ethionamide is not well tolerated due to adverse gastrointestinal effects and bioavailability problems. Accordingly, dispersible tablet formulations with different concentration of excipients such as Crospovidone (as superdisintegrant), PVP K-30, Maize starch and Microcrystalline cellulose were formulated by the direct compression method to achieve its quick disintegration and uniform drug dissolution.***

The prepared batches (F1–F7) were analyzed for weight variation, hardness, friability, thickness, drug content, disintegration time, dissolution test and stability studies. Furthermore, F6 had the best results from all prepared formulae with disintegration time of 45 ± 2 s, friability of only 0.763 ± 0.096% drug content of 99.75 ± 0.74%, and cumulative amount released within first 15 min to be (98.74%). Drug release kinetics was found to fit a Higuchi model (R^2 = 0.994) and the drug exhibited close to zero-order pattern of release (R^2 = 0.989), suggesting diffusion-controlled pattern of drug release. Stability studies as per ICH guidelines indicated that the optimized batch lost its physical and chemical integrity under accelerated conditions (40°C/75% RH) for 3 months.The study reveals that the optimized Formulation F6 of Ethionamide dispersible tablet is a fast disintegrating, stable and effective dosage form, which can be a potential way to improve patient compliance, especially in pediatric and geriatric patients who have difficulty in swallowing.

Keywords: Ethionamide, Dispersible Tablets, Fast Disintegrating drugs, Anti-tubercular drugs

I. INTRODUCTION

The patient convenience and compliance-driven pharmaceutical research has resulted in the emergence of safer and better drug delivery systems[1]. Among these advances, Fast Dissolving Drug Delivery Systems (FDDSs) or Dispersible tablets have been gaining attention because they can disintegrate or dissolve within a short period when placed in the oral cavity and hence eliminate the need for water or chewing to facilitate self-administration[2]. Dispersible tablets have gained popularity as patient-friendly dosage forms owing to their advantages of improved patient compliance and convenience. These formulations are useful in addressing the problems of conventional oral solid dosages, particularly for patients with difficulty swallowing such as pediatric, geriatric or bedridden populations[3].

As one of the most common and dangerous bacterial infectious diseases, tuberculosis (TB) is still widespread worldwide and is primarily caused by Mycobacterium tuberculosis. The disease is a major worldwide health problem in the face of drug-resistant strains arising from partially treated, discontinuation of therapy and poor patient compliance. While TB is mainly a pulmonary disease, it can be systemic and involve other organs[4]. Once thought to be a disease of the poor, it has re-emerged even in developed countries as immune systems have been weakened by HIV/AIDS, drug use and immunosuppressive drugs. Although there is pharmacotherapy available for more than five decades, the long duration of treatment and high pill burden remain obstacles to patient's adherence leading to decrease efficacy of the treatment[5].

Ethionamide is one of the most effective and commonly used second-line anti-tubercular drugs that are being administered for treatment of MDR-TB. Doses ranging from 0.5–1 g/day are commonly used as conventional tablets. However, ethionamide has been clinically associated with poor tolerability because of gastrointestinal irritation and to diminished oral bioavailability as consequence of the first pass metabolism. Enteric-coated preparations have been made to protect against gastric intolerance, but many are no more effective in minimizing gastrointestinal adverse side effects[6,7].

Hence, in this current study formulation design and evaluation of dispersible tablets for Ethionamide by direct compression method has been studied. The research aims to improve patient compliance due to faster disintegration and dissolution of the drug and consequently increased therapeutic efficacy and bioavailability. Formulation with different concentrations of diluents were prepared and altogether compared for their physicochemical characteristics and in-vitro drug releaser profiles, to identify the best composition to offer rapid and effective Ethionamide delivery.

II. MATERIAL AND METHOD

A. *Material requirements*

The formulation was prepared using the ingredients mentioned in table 2.1.

Table 2.1: Material requirements and their use in formulation

S. No.	Name of the Material	Category/Use
1	Ethionamide	Anti-tubercular API
2	Microcrystalline cellulose	Diluent
3	Sucralose	Sweetener
4	Maize starch	Binder
5	Povidone	Binder
6	Crospovidone	Super disintegrant
7	Hydroxy propyl cellulose	Binder
8	Peppermint flavor	Flavor
9	Aspartame	Sweetener
10	Sodium chloride	Taste masking
11	Menthol	flavor
12	Aerosil	Glident
13	Magnesium sterate	Lubricant

B. *Preparation of Formulations*

The formulation of dispersible tablets of Ethionamide was carried out in four main stages: dry mixing, granulation, pre-lubrication, and lubrication.

1) Dry Mixing- Ethionamide, Microcrystalline Cellulose (MCC PH 101), and Crospovidone were accurately weighed and passed through a #40 mesh sieve to ensure uniform particle size. The sieved materials were then transferred into a Rapid Mixer Granulator (RMG) and mixed thoroughly for 7 minutes to obtain a homogeneous blend.

2) Granulation- First the binder solution was prepared followed by wet granulation.

a) Preparation of Binder Solution: The total quantity of water required was divided into three equal portions.Maize starch was dispersed in the first portion of water.The second portion was boiled, and the starch dispersion was added gradually under continuous stirring until a transparent starch paste was formed. The paste was then allowed to cool to room temperature.PVP K-30 was dissolved in the remaining portion of water and added to the cooled starch paste under stirring to obtain a uniform binder solution.

b) *Wet Granulation: The prepared binder solution was slowly added to the dry-mixed powders in the RMG under slow impeller speed until smooth and uniform granules were formed. The wet granules were dried in a Fluidized Bed Dryer (FBD) at 60°C for 30 minutes. The dried granules were then passed through a #40 mesh sieve to achieve uniform particle size distribution.*

3) Pre-Lubrication- The dried granules were blended with MCC PH 102, Crospovidone, Acacia, Sodium chloride, Menthol, Aspartame, Peppermint flavour, L-HPC LH 11, Talc, and Aerosil. All excipients were previously passed through a #40 mesh sieve to ensure uniformity. The mixture was transferred to a blender and mixed for 10 minutes to ensure proper distribution of all ingredients.

4) Lubrication- Magnesium stearate was sifted through a #60 mesh sieve and added to the pre-lubricated blend. The mixture was then transferred to blender and mixed for 3 minutes to obtain a uniform lubricated blend. The final blend was collected in a clean polybag and compressed into tablets

Table 2.2: Formulation of different formulations of ethionamide prepared

Ingredients	F1	F2	F3	F4	F5	F6	F7
Dry mix							
Ethionamide	125	125	125	125	125	125	125
Crospovidone	5	7	10	10	10	15	16
MCC PH 101	70	64	57	57	57	52	48
Sucralose	1.5	3	4	4	4	4	4
Granulation							
Maize starch	–	–	5	15	10	10	12
PVP K-30	4	4	5	5	10	10	12
Purified water	QS	QS	QS	QS	QS	QS	QS
Pre-lubrication							
Crospovidone	10	13	12	12	12	16	17
MCC PH 102	23	19	5	5	5	19	17
Acacia	0.5	1	–	–	–	–	–
Sodium chloride	2	3	4	4	4	4	4
Aspartame	1.5	3	4	4	4	4	4
Menthol	1	2	2	2	2	2	2
Peppermint flavour	1.5	3	4	4	4	4	4
L-HPC LH 11	–	–	–	–	–	2	2
Talc	2	–	–	–	–	–	–
Aerosil	1	1	1	1	1	1	1
Lubrication							
Magnesium stearate	2	2	2	2	2	2	2
Total weight (mg)	250	250	250	250	250	270	270

III.EVALUATION STUDIES

As per pharmacopeial standards, all batches of Ethionamide dispersible tablets were evaluated for various physical and mechanical parameters, including weight variation, thickness, hardness, friability, disintegration time, fineness of dispersion, drug content (assay), dissolution, and stability studies.

1) Weight Variation: Twenty tablets were randomly selected from each batch and weighed individually using a calibrated digital balance. The average weight was calculated, and each individual tablet weight was compared with the mean value. The formulation passes the USP test for weight variation if not more than two tablets deviate from the percentage limits and none deviate by more than twice the percentage limit.

Table 3.1: Acceptance Criteria for Tablet Weight Variation

Average Weight of Tablet (mg)	Percentage Difference Allowed
80 mg or less	±10%
80 mg to 250 mg	±7.5%
More than 250 mg	±5%

2) Thickness- Tablet thickness was measured using a Vernier caliper to ensure uniformity of size among different batches. Ten tablets were randomly selected, and their thickness recorded in millimeters (mm).

3) Hardness (Crushing Strength)- The mechanical strength of tablets was determined using a Hardness Tester. Hardness was expressed in kg/cm² or N, and ten tablets were evaluated from each batch. Variations in hardness may affect both disintegration and dissolution characteristics.

4) Friability Test- Friability testing evaluates a tablet's ability to resist mechanical abrasion during handling and transportation. The test was performed using a Roche Friabilator. A sample of tablets equivalent to a total weight of 6.5 g was accurately weighed (W_1) and placed in the drum. The apparatus was rotated 100 times at 25 rpm, after which tablets were dedusted and reweighed (W_2). The percentage friability was calculated.

5) Disintegration Test- The disintegration time was evaluated using a USP disintegration apparatus. Six tablets were tested in 900 mL of distilled water maintained at 37 ± 0.5°C. The time taken for complete disintegration and passage of all particles through the screen was recorded. For dispersible tablets, the disintegration time should be less than 3 minutes.

6) Fineness of Dispersion- This qualitative test, as per European Pharmacopoeia (EP), evaluates the smoothness and particle size uniformity of the tablet dispersion. Two tablets were placed in 100 mL of water and gently stirred until completely disintegrated. The resulting dispersion was passed through a 710 µm sieve, and the formulation was considered to comply if no residue remained on the sieve mesh.

7) Assay (Drug Content Uniformity)- Twenty tablets were weighed, powdered, and an amount equivalent to 100 mg of Ethionamide was transferred into a 250 mL volumetric flask. The sample was extracted with 100 mL of mobile phase, sonicated, and filtered. A 5mL aliquot of this filtrate was further diluted to 200 mL with methanol and mixed thoroughly. The absorbance was measured using a UV–Visible spectrophotometer, and the drug content was calculated from the calibration curve.

8) In Vitro Dissolution Test- The dissolution test determines the rate and extent of drug release from the tablet under standardized conditions. The study was carried out using a USP Type I (Basket) Apparatus under the following conditions:

Table 3.2: In vitro Dissolution parameters

Dissolution Parameter	Condition
Medium	0.1 N HCl
Volume	900 mL
Temperature	37 ± 0.5°C
Rotation Speed	50 rpm
Sampling Intervals	15, 30, and ∞ minutes

Samples were withdrawn at specified time intervals, filtered, suitably diluted with dissolution medium, and analyzed spectrophotometrically at the predetermined wavelength.

9) Stability Studies- Stability studies were performed to assess the effect of environmental factors such as temperature and humidity on the quality of the dispersible tablets.

The studies were conducted according to ICH guidelines (Q1A R2) for long-term, intermediate, and accelerated conditions. The parameters evaluated included appearance, hardness, assay, disintegration time, and dissolution profile.

Table 3.3: Stability Study Conditions and Duration

Study Type	Storage Condition	Minimum Time Period
Long-term	25 ± 2°C / 60 ± 5% RH or 30 ± 2°C / 65 ± 5% RH	12 months
Intermediate	30 ± 2°C / 65 ± 5% RH	6 months
Accelerated	40 ± 2°C / 75 ± 5% RH	6 months

A significant change during accelerated testing is indicated by:

- ≥5% change in assay from the initial value,
- failure to meet acceptance criteria for dissolution, pH, or degradation products,
- visible physical changes (e.g., discoloration, phase separation, softening).

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IV. RESULTS AND DISCUSSION

The Ethionamide dispersible tablet formulations (F1–F7) were evaluated to assess their physical characteristics and compliance with pharmacopeial standards. The results are summarized in Table 4.1.

The hardness of the formulations ranged from 3.2 ± 0.3 kg/cm² (F5) to 3.5 ± 0.2 kg/cm² (F2), indicating that all formulations exhibited adequate mechanical strength to withstand handling, transportation, and packaging stress. The uniformity in hardness values suggests consistent compression force and homogeneity of the granule blends during tablet manufacturing.

The friability values of all formulations were within the acceptable limit of less than 1%, ranging between 0.658 ± 0.025% (F1) and 0.856 ± 0.014% (F3). These low friability values demonstrate that the prepared tablets possess excellent resistance to abrasion and mechanical shock.

The weight variation results ranged from 247 ± 4 mg (F5) to 255 ± 7 mg (F2), confirming the uniform distribution of powder blend during compression. All formulations complied with the USP limits for weight variation, ensuring dosage uniformity.

The thickness of the tablets varied slightly between 1.32 ± 0.03 mm (F4) and 1.37 ± 0.02 mm (F3), indicating consistent die fill and uniformity in tablet size across the formulations.

The drug content ranged from 96.45 ± 0.63% (F7) to 99.75 ± 0.74% (F6), confirming precise and uniform incorporation of Ethionamide in all batches. The drug content results were within the acceptable range (95–105%) specified by official standards.

Overall, all the formulations exhibited satisfactory post-compression characteristics. Among them, Formulation F6 demonstrated optimal parameters, with balanced hardness (3.4 ± 0.5 kg/cm²), minimal friability (0.763 ± 0.096%), acceptable weight uniformity (251 ± 8 mg), consistent thickness (1.36 ± 0.05 mm), and the highest drug content (99.75 ± 0.74%), suggesting its suitability for further evaluation in dissolution and stability studies.

Table 4.1 :Evaluation All Formulations

F. Code	Hardness test (kg/cm²)	Friability (%)	Weight variation (mg)	Thickness (mm)	Drug content (%)
F1	3.4 ± 0.3	0.658 ± 0.025	254 ± 6	1.35 ± 0.08	98.12 ± 0.15
F2	3.5 ± 0.2	0.745 ± 0.023	255 ± 7	1.32 ± 0.06	96.85 ± 0.32
F3	3.4 ± 0.3	0.856 ± 0.014	248 ± 5	1.37 ± 0.02	97.85 ± 0.14
F4	3.3 ± 0.4	0.775 ± 0.056	250 ± 3	1.32 ± 0.03	98.12 ± 0.52
F5	3.2 ± 0.3	0.658 ± 0.087	247 ± 4	1.35 ± 0.08	98.08 ± 0.65
F6	3.4 ± 0.5	0.763 ± 0.096	251 ± 8	1.36 ± 0.05	99.75 ± 0.74
F7	3.3 ± 0.4	0.748 ± 0.045	253 ± 9	1.32 ± 0.07	96.45 0.63

A. Results of Disintegration Time Parameters of All Formulations

The disintegration time results for the Ethionamide dispersible tablet formulations (F1–F7) demonstrated notable variation among the different batches, as shown in Table 4.2. The disintegration time is a critical parameter for dispersible tablets, as it directly influences the rate and extent of drug release and, consequently, the onset of therapeutic action.

Among all formulations, Formulation F6 exhibited the shortest disintegration time of 45 ± 2 seconds, signifying its superior capability to rapidly disperse and release the active drug under physiological conditions. This rapid disintegration may be attributed to the optimal concentration and synergistic effect of super disintegrants, appropriate binder levels, and efficient granule characteristics achieved during formulation.

The other formulations showed disintegration times ranging from 65 ± 5 seconds (F7) to 95 ± 3 seconds (F1), indicating acceptable but relatively slower breakdown compared to F6. The consistent and lower disintegration time of F6 highlights its potential as the most optimized formulation, combining both mechanical integrity and rapid dispersion properties.

Therefore, Formulation F6 was identified as the best-performing batch based on the criterion of rapid tablet breakdown, making it a promising candidate for achieving faster therapeutic onset in dispersible tablet dosage form development.

Table 4.2: Results of Disintegration Time Parameters of All Formulations

Formulation Code	Disintegration Time (Sec)
F1	95 ± 3
F2	82 ± 2
F3	73 ± 4
F4	87 ± 5
F5	80 ± 3
F6	45 ± 2
F7	65 ± 5

Table 4.3: In-vitro Drug Release Data for Optimized Formulation F6

Time (min)	Square Root of Time (h)$^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	1.00	0.000	42.36	1.627	57.64	1.761
5	2.24	0.698	63.32	1.802	36.68	1.564
10	3.16	1.000	82.25	1.915	17.75	1.249
15	3.87	1.176	98.74	1.994	1.26	0.100

Zero order release kinetics of formulation F6

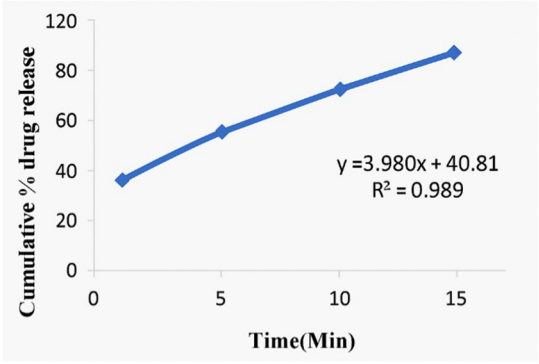

Figure 4.1 Graph of zero order release Kinetics of formulation F6

First order release Kinetics of formulation F6

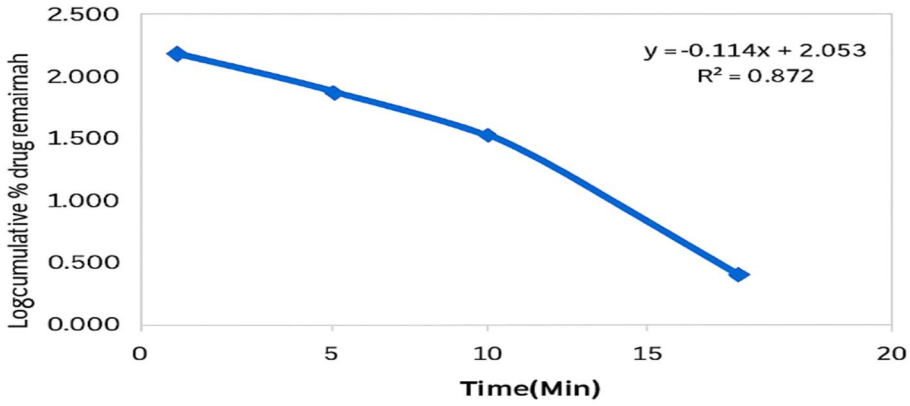

Figure 4.2 Graph of first order release Kinetics of formulation F6

Higuchi release Kinetics of formulation F6

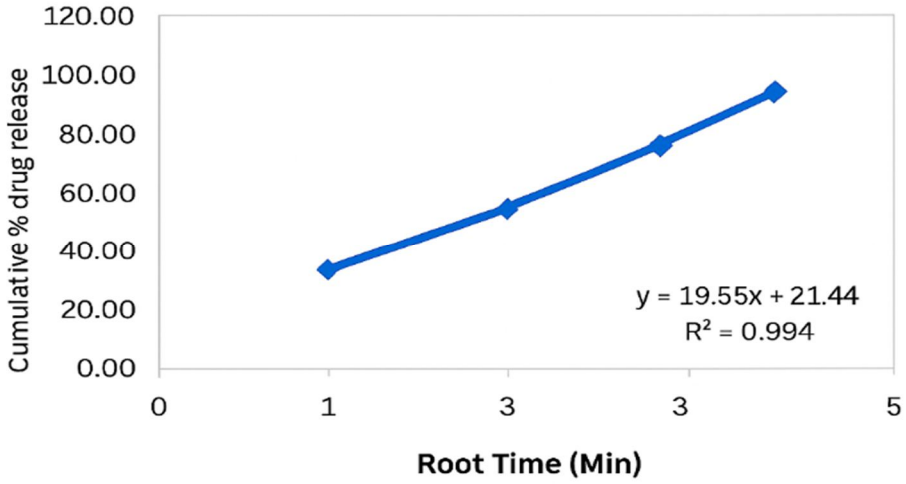

Figure 4.3 Graph of Higuchi release Kinetics of formulation F6

B. Regression analysis data

Table 4.4 : Regression analysis data

Batch	Zero Order (r^2)	First Order (r^2)	Higuchi (r^2)
F6	0.989	0.872	0.994

C. Stability Studies

Physical parameters of the optimized formulation after 3 months of stability (25°C/60% RH, 40°C/75%RH) in the Alu-Alu strip pack.

Table 4.5: Physical parameters of optimized formulation in Alu-Alu strip pack

Parameters	Alu-Alu strip pack	
	25°C/60% RH	40°C/75% RH
Thickness ± SD*	1.35 ± 0.05	1.38 ± 0.30
Hardness ± SD*	3.2 ± 0.2	3.4 ± 0.3
DT ± SD**	47 ± 2	45 ± 1

* Represents average value ± SD (n=5)

** Represents average value ± SD (n=6)

V. CONCLUSION

The current study confirmed that it could successfully design and evaluate dispersible tablet of Ethionamide to enhance bioavailability and patient compliance. All formulated formulations were found to comply with the pharmacopeial standards in regard to their physicochemical characteristics. Formulation F6 of the seven batches proved to be superior in terms of hardness, friability, drug content, rapid disintegration, and dissolution performance.

The optimized formulation demonstrated a minimum disintegration time of 45 s and cumulative drug release of up to 98.74% in 15 min after tracer, based on Higuchi diffusion kinetics with the correlation coefficient $R^2 = 0.994$). The stability study demonstrated that F6 was stable at the accelerated and long-term storage conditions.

Thus, it may be summarized that ethionamide dispersible tablets; in particular, formulation F6 can be employed as a potential patient friendly alternative to the conventional market preparation of ET, leading faster onset of action and improved compliance for managing MDR TB. This method is capable of minimizing treatment load, which means it might be useful for pediatric, geriatric and dysphagic patients.

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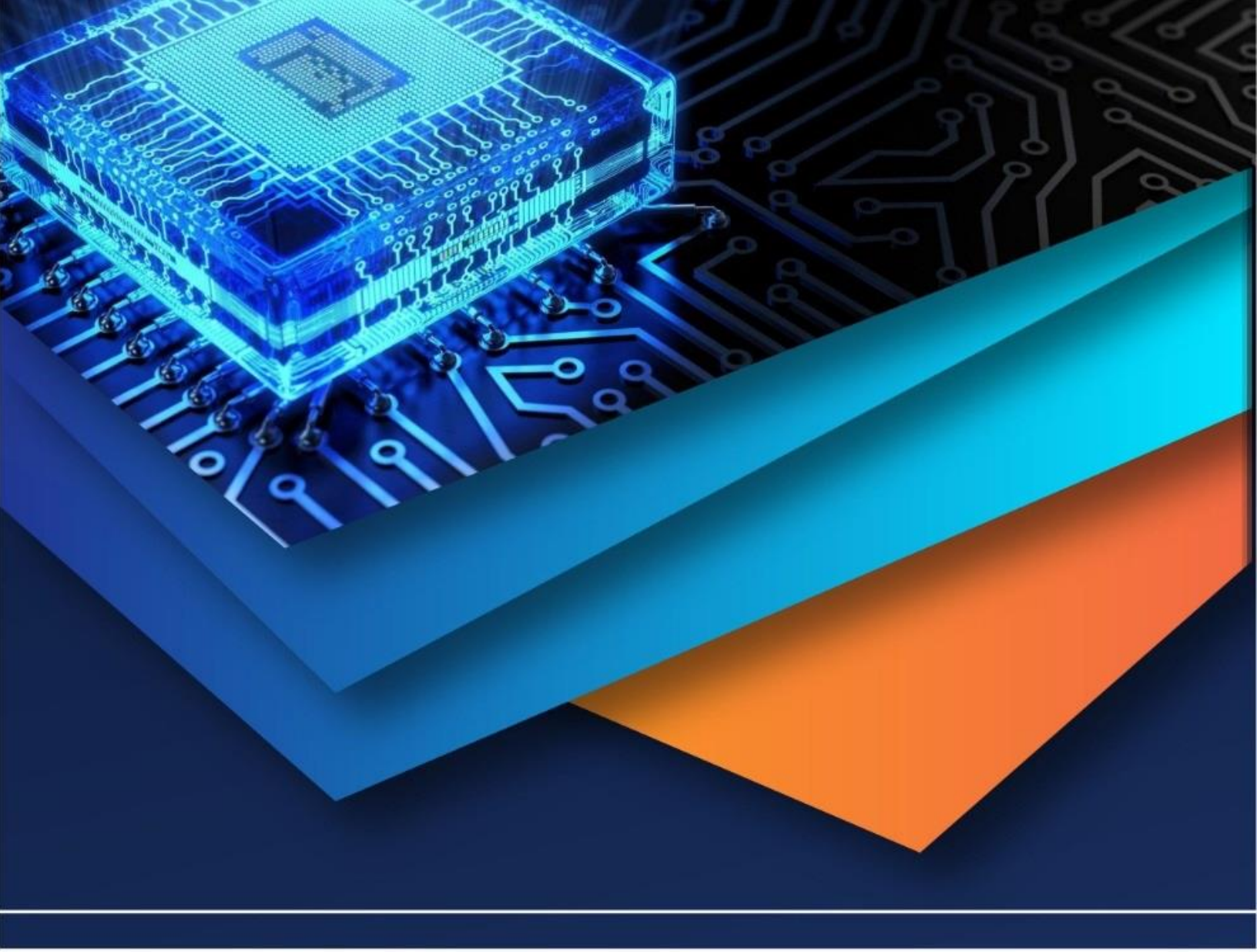

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