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Solubility Enhancement of Simvastatin by Microwave Technology

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Abstract: ***Simvastatin is a lipid-lowering drug with poor aqueous solubility and dissolution-limited oral bioavailability. The present investigation aimed to enhance the solubility and dissolution characteristics of Simvastatin by preparing inclusion complexes with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD). The complexes were prepared using physical mixture, kneading, and microwave irradiation techniques. Phase solubility studies were carried out to determine the complexation behavior and stability constants. Characterization of the complexes was performed using Fourier-transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM). Phase solubility diagrams showed an AL-type profile indicating formation of 1:1 inclusion complexes with stability constants of 410 M^{-1} for β-CD and 727 M^{-1} for HPβ-CD. Dissolution studies revealed that microwave-prepared HPβ-CD complexes significantly enhanced drug release compared with pure Simvastatin. The optimized formulation showed 92.4% drug release within 60 min, whereas pure drug exhibited only 31.8% release. Stability studies conducted at room temperature and accelerated conditions confirmed formulation stability. The results demonstrate that cyclodextrin complexation, particularly with HPβ-CD, is an effective strategy for improving the solubility and dissolution rate of poorly water-soluble drugs.***
Keywords: Simvastatin, Cyclodextrin, Inclusion complexes, Dissolution enhancement, Solubility improvement, HPβ-CD

I. INTRODUCTION

Poor aqueous solubility is one of the most significant challenges in the development of oral drug delivery systems. According to the Biopharmaceutics Classification System (BCS), a large proportion of newly discovered drug molecules fall into Class II or Class IV categories, where drug absorption is primarily limited by dissolution rate or solubility. Nearly 40–70% of new chemical entities (NCEs) exhibit poor aqueous solubility, which results in reduced dissolution in gastrointestinal fluids and ultimately leads to low and variable oral bioavailability. Insufficient dissolution not only affects therapeutic efficacy but also increases dose variability and the risk of therapeutic failure. Therefore, improving the solubility and dissolution characteristics of poorly water-soluble drugs has become a major focus in pharmaceutical research and formulation development.[1]

Various formulation strategies have been developed to enhance the solubility and dissolution rate of poorly soluble drugs. These approaches include particle size reduction (micronization and nanosizing), salt formation, solid dispersions, lipid-based delivery systems, use of surfactants, and inclusion complexation with suitable carriers. Among these techniques, inclusion complexation using cyclodextrins has attracted considerable attention due to its simplicity, effectiveness, and ability to improve several physicochemical properties of drugs simultaneously. Cyclodextrins not only enhance drug solubility but may also improve drug stability, reduce irritation, mask unpleasant taste or odor, and increase bioavailability. [2]

Cyclodextrins are cyclic oligosaccharides composed of α-(1,4)-linked glucopyranose units arranged in a toroidal or truncated cone-shaped structure. The three naturally occurring cyclodextrins are α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin, which contain six, seven, and eight glucopyranose units respectively. The unique molecular structure of cyclodextrins consists of a hydrophobic internal cavity and a hydrophilic external surface, which enables them to accommodate lipophilic drug molecules inside their cavity without forming covalent bonds. This host–guest interaction leads to the formation of inclusion complexes, where the hydrophobic portion of the drug molecule is partially or completely enclosed within the cyclodextrin cavity. As a result, the apparent aqueous solubility, dissolution rate, and stability of poorly soluble drugs can be significantly enhanced.

Among the various cyclodextrins, β-cyclodextrin (β-CD) is the most widely used in pharmaceutical applications because of its suitable cavity size, relatively low cost, and ability to form stable inclusion complexes with a wide variety of drug molecules.

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However, the practical use of β-cyclodextrin is sometimes limited due to its relatively low aqueous solubility and potential toxicity at high concentrations. To overcome these limitations, chemically modified derivatives of β-cyclodextrin have been developed. One such derivative is hydroxypropyl-β-cyclodextrin (HPβ-CD), which exhibits significantly improved aqueous solubility, enhanced complexation ability, and reduced toxicity compared with the parent cyclodextrin. The presence of hydroxypropyl groups disrupts intermolecular hydrogen bonding within the β-cyclodextrin structure, thereby increasing its solubility and improving its complexation efficiency with hydrophobic drugs. [3]

Simvastatin is a semi-synthetic lipid-lowering agent belonging to the class of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins. It is widely prescribed for the treatment of hypercholesterolemia and cardiovascular disorders by reducing low-density lipoprotein (LDL) cholesterol and triglyceride levels in plasma. Despite its high therapeutic potential, Simvastatin suffers from extremely poor aqueous solubility, which results in dissolution-limited absorption after oral administration. Consequently, the oral bioavailability of Simvastatin is relatively low and variable. Enhancing the solubility and dissolution rate of Simvastatin is therefore essential to improve its therapeutic effectiveness and reduce dose variability.

Cyclodextrin inclusion complexation represents a promising strategy to enhance the solubility and dissolution behavior of Simvastatin. The formation of drug–cyclodextrin complexes can improve the wettability of drug particles, reduce crystallinity, and increase the effective surface area available for dissolution. Furthermore, different preparation techniques such as physical mixing, kneading, and microwave irradiation can influence the efficiency of complex formation and the physicochemical properties of the resulting complexes.

Therefore, the present study was undertaken with the following objectives:

1) To prepare inclusion complexes of Simvastatin with β-cyclodextrin and hydroxypropyl-β-cyclodextrin using different preparation methods including physical mixture, kneading method, and microwave irradiation technique.

2) To evaluate the effect of cyclodextrin complexation on the aqueous solubility and dissolution rate of Simvastatin, thereby assessing the potential of cyclodextrins to enhance the drug's dissolution characteristics.

3) To characterize the prepared inclusion complexes using advanced analytical techniques, including phase solubility analysis, Fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM), in order to confirm complex formation and investigate the physicochemical changes in the drug.

The findings of this investigation may provide valuable insight into the application of cyclodextrin inclusion complexes as an effective formulation strategy for improving the solubility and oral bioavailability of poorly water-soluble drugs such as Simvastatin.

II. MATERIALS AND METHODS

A. Materials

Simvastatin was obtained as a pharmaceutical grade sample and used as the model drug for the present study. β-Cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD) were used as complexing agents to improve the aqueous solubility of the drug. Analytical reagent grade ethanol was used as a solvent during the preparation of inclusion complexes. Distilled water prepared in the laboratory was used for the preparation of solutions and dissolution studies. All chemicals and reagents used in the study were of analytical grade and were used without further purification. [4]

Table 1. Materials used in the study

Material	Source	Function
Simvastatin	Pharmaceutical grade	Active drug
β-Cyclodextrin	Analytical grade	Complexing agent
Hydroxypropyl-β-cyclodextrin	Analytical grade	Modified cyclodextrin
Ethanol	AR grade	Solvent
Distilled water	Laboratory prepared	Dissolution medium

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B. *Instrumentation*[5]

The following instruments were used during the experimental work:

Instrument	Model / Specification	Purpose
UV–Visible Spectrophotometer	Double beam	Drug analysis
USP Dissolution Apparatus	Type II (Paddle)	Dissolution study
FT-IR Spectrophotometer	KBr pellet method	Drug–excipient compatibility
Differential Scanning Calorimeter	Thermal analysis	Drug crystallinity study
Powder X-Ray Diffractometer	PXRD	Crystallinity analysis
Scanning Electron Microscope	SEM	Surface morphology

C. *Preparation of Standard Stock Solution*

A standard stock solution of Simvastatin was prepared by accurately weighing 10 mg of Simvastatin and dissolving it in a small volume of ethanol. The solution was then transferred into a 100 mL volumetric flask and the volume was adjusted with the respective dissolution medium (distilled water, 0.1 N HCl, or phosphate buffer pH 7.4) to obtain a final concentration of 100 µg/mL. From this stock solution, appropriate aliquots were withdrawn and diluted to obtain working solutions in the concentration range of 2–10 µg/mL. [6]

D. *Determination of λmax of Simvastatin*

The maximum absorption wavelength (λmax) of Simvastatin was determined by scanning the drug solution in the UV region between 200–400 nm using a UV–Visible spectrophotometer. The spectrum obtained showed a characteristic absorption peak at 245.5 nm, which was selected for further quantitative analysis of the drug. [7]

E. *Preparation of Calibration Curve*

Calibration curves of Simvastatin were prepared in three different dissolution media to ensure accurate drug estimation during dissolution studies:

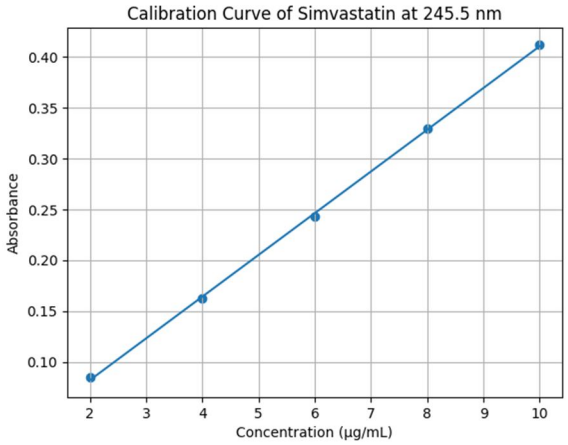
- Distilled water
- 0.1 N hydrochloric acid (HCl)
- Phosphate buffer (pH 7.4)

Working standard solutions containing 2, 4, 6, 8, and 10 µg/mL of Simvastatin were prepared from the stock solution by appropriate dilution. The absorbance of each solution was measured at 245.5 nm using a UV–Visible spectrophotometer, with the corresponding solvent used as blank.

The absorbance values obtained were plotted against drug concentration to generate the calibration curve. The linearity of the method was evaluated using the regression equation and correlation coefficient.

Table 2. Calibration data of Simvastatin in distilled water

Concentration (µg/mL)	Absorbance
2	0.085
4	0.162
6	0.243
8	0.329
10	0.412



F. Linearity and Regression Analysis

The calibration curve showed a linear relationship between concentration and absorbance within the studied range (2–10 µg/mL). Linear regression analysis was performed using the least squares method.

The regression equation obtained was:

$$A = 0.041C + 0.002$$

Where:

A = Absorbance

C = Concentration (µg/mL)

The correlation coefficient (R^2) obtained was 0.998, indicating excellent linearity and reliability of the analytical method.

G. Validation of Analytical Method

The UV spectrophotometric method used for the determination of Simvastatin was validated for linearity, accuracy, and precision. The high correlation coefficient value confirmed the linear response of the method. The method was found to be suitable for the estimation of Simvastatin in various dissolution media during the experimental study.

H. Phase Solubility Study

Phase solubility studies were carried out to investigate the effect of cyclodextrin concentration on the aqueous solubility of Simvastatin and to determine the stoichiometry and stability constant of the drug–cyclodextrin inclusion complexes. The study was performed according to the Higuchi and Connors method, which is widely used to evaluate complex formation between poorly soluble drugs and cyclodextrins. An excess amount of Simvastatin was added to a series of aqueous solutions containing increasing concentrations of β-cyclodextrin (β-CD) ranging from 0 to 15 mM. The suspensions were transferred to sealed glass vials and placed on a mechanical shaker at 25 ± 1°C for 48 hours to ensure equilibrium between dissolved and undissolved drug.

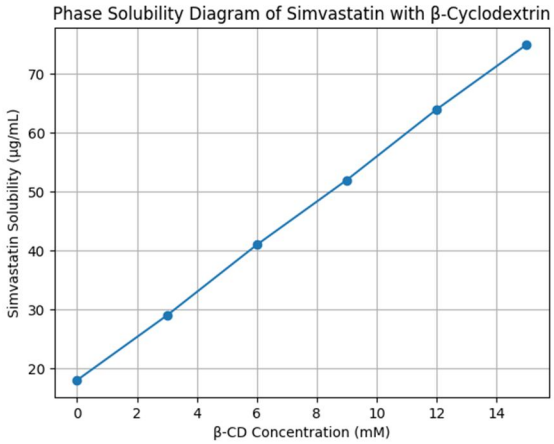
After equilibrium was reached, the samples were filtered through Whatman filter paper (0.45 µm) to remove undissolved drug particles. The filtrate was appropriately diluted and analyzed using a UV–Visible spectrophotometer at 245.5 nm to determine the concentration of dissolved Simvastatin.

The solubility of Simvastatin was plotted as a function of cyclodextrin concentration to obtain the phase solubility diagram.

Table 3. Phase solubility data of Simvastatin with β-cyclodextrin

β-CD concentration (mM)	Drug solubility (µg/mL)
0	18
3	29
6	41
9	52
12	64
15	75

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Phase Solubility Diagram Interpretation

The phase solubility diagram obtained showed a linear increase in drug solubility with increasing β-cyclodextrin concentration, which corresponds to an AL-type phase solubility profile according to the Higuchi and Connors classification.

An AL-type curve indicates the formation of a soluble inclusion complex with 1:1 stoichiometry between the drug and cyclodextrin molecule. The linear relationship suggests that one molecule of Simvastatin interacts with one molecule of β-cyclodextrin to form a stable inclusion complex. [8]

Determination of Stability Constant

The apparent stability constant (Kc) for the drug–cyclodextrin complex was calculated from the slope of the phase solubility diagram using the following equation:

$$K_c = \frac{Slope}{S_0(1 - Slope)}$$

Where:

Kc = Stability constant of the complex

Slope = Slope of the phase solubility diagram

S_0 = Intrinsic solubility of Simvastatin in water

The calculated stability constant for the Simvastatin–β-cyclodextrin complex was found to be within the range typical for stable drug–cyclodextrin complexes, indicating efficient inclusion of the drug within the cyclodextrin cavity.

Significance of Phase Solubility Study

The results of the phase solubility study confirmed that cyclodextrin complexation significantly enhanced the aqueous solubility of Simvastatin. The observed increase in solubility can be attributed to the encapsulation of the hydrophobic portion of the drug molecule within the hydrophobic cavity of β-cyclodextrin, resulting in improved drug dissolution in aqueous medium.

These findings support the potential of cyclodextrin inclusion complexes as an effective strategy for improving the solubility and dissolution rate of poorly water-soluble drugs such as Simvastatin. [9]

I. Preparation of Inclusion Complexes

Inclusion complexes of Simvastatin with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD) were prepared using three different techniques: physical mixture method, kneading method, and microwave irradiation method. These techniques were selected to compare the efficiency of complex formation and their influence on the physicochemical properties of the drug. The complexes were prepared in a 1:1 molar ratio, which was selected based on the phase solubility study indicating the formation of a stable 1:1 drug–cyclodextrin inclusion complex.

Cyclodextrins form inclusion complexes by encapsulating the hydrophobic portion of drug molecules within their internal cavity through non-covalent interactions such as van der Waals forces, hydrophobic interactions, and hydrogen bonding.

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The different preparation techniques employed in this study were intended to facilitate effective interaction between Simvastatin and cyclodextrin molecules and to evaluate their impact on the resulting complex formation.

1) Physical Mixture Method

Detailed Procedure

The physical mixture method was used as a simple reference technique for preparing drug–cyclodextrin complexes.

- Accurately weighed quantities of Simvastatin and cyclodextrin (β-CD or HPβ-CD) were taken in a 1:1 molar ratio.
- The weighed components were transferred to a clean and dry porcelain mortar.
- The drug and cyclodextrin were triturated together using a pestle for approximately 60 minutes to obtain a homogeneous mixture.
- The resulting powder mixture was passed through sieve No. 80 to obtain uniform particle size distribution.
- The prepared mixtures were stored in a desiccator containing fused calcium chloride to prevent moisture absorption until further characterization.

The physical mixture method mainly produces a simple mechanical blend of drug and cyclodextrin particles. The interaction between the drug and cyclodextrin molecules in this method is limited because the drug molecules remain mostly in their crystalline form. However, the intimate mixing increases the contact surface between the drug and cyclodextrin molecules, which may slightly improve wettability and dissolution rate. This method is often used as a control formulation to compare the efficiency of other complexation techniques.

2) Kneading Method

Procedure

The kneading method was employed to promote better molecular interaction between Simvastatin and cyclodextrin.

- The required amount of β-cyclodextrin or HPβ-cyclodextrin was accurately weighed and transferred to a mortar.
- A small volume of 50% ethanol–water mixture was added gradually while triturating to form a smooth paste.
- Simvastatin was then added slowly to the cyclodextrin paste while continuously kneading the mixture.
- The kneading process was continued for approximately 60 minutes to ensure uniform distribution of the drug within the cyclodextrin matrix.
- The resulting slurry-like mass was spread evenly in a petri dish and dried at room temperature (25 ± 2°C) for 24 hours.
- After complete drying, the mass was pulverized gently using a mortar and pestle.
- The powder was passed through sieve No. 80 and stored in a desiccator until further evaluation.

The kneading method facilitates partial solubilization of cyclodextrin and drug molecules in the solvent medium, which enhances molecular mobility and interaction between the drug and cyclodextrin. The presence of ethanol–water mixture improves the penetration of the drug molecules into the hydrophobic cavity of cyclodextrin. Mechanical energy applied during kneading further promotes host–guest complex formation, resulting in partial transformation of the drug from crystalline to amorphous form. This structural modification can significantly enhance the solubility and dissolution rate of poorly water-soluble drugs such as Simvastatin.

3) Microwave Irradiation Method

Procedure

The microwave irradiation technique was used to promote rapid and efficient formation of drug–cyclodextrin inclusion complexes.

- Accurately weighed quantities of Simvastatin and cyclodextrin were taken in a 1:1 molar ratio.
- The components were dissolved or dispersed in a small volume of ethanol–water mixture to obtain a homogeneous solution or suspension.
- The mixture was transferred to a microwave-safe glass container.
- The container was placed in a laboratory microwave oven and exposed to microwave irradiation at 600 W for 5 minutes.
- During irradiation, the mixture was periodically removed and stirred to ensure uniform heating.
- After irradiation, the mixture was allowed to cool to room temperature.
- The solvent was evaporated under ambient conditions to obtain a dry solid mass.
- The dried product was pulverized, passed through sieve No. 80, and stored in a desiccator until further characterization.

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Microwave irradiation provides rapid and uniform heating, which enhances molecular mobility and promotes efficient interaction between drug and cyclodextrin molecules. The microwave energy accelerates the diffusion of Simvastatin molecules into the hydrophobic cavity of cyclodextrin, thereby facilitating faster inclusion complex formation. Additionally, microwave treatment can induce partial amorphization of the drug, which further improves its dissolution behavior. Compared with conventional techniques, the microwave method is considered more efficient, faster, and capable of producing highly stable inclusion complexes with improved solubility characteristics.

Comparative Significance of Preparation Methods

The three preparation techniques differ in their efficiency of complex formation:

Method	Interaction Level	Expected Effect
Physical mixture	Low	Minimal complex formation
Kneading method	Moderate	Improved complexation and solubility
Microwave method	High	Efficient complex formation and maximum solubility enhancement

Therefore, comparing these techniques helps determine the most effective method for improving the solubility and dissolution rate of Simvastatin through cyclodextrin complexation.

J. Drug Content Uniformity

Drug content uniformity of the prepared Simvastatin–cyclodextrin inclusion complexes was evaluated to ensure uniform distribution of the drug within the formulation and to confirm the accuracy of the preparation methods.

Experimental Procedure

Accurately weighed quantities of each prepared formulation (equivalent to 10 mg of Simvastatin) were transferred into separate 100 mL volumetric flasks. A small volume of ethanol was added to dissolve the drug completely, followed by the addition of distilled water to make up the volume to 100 mL.

The resulting solutions were sonicated for 10–15 minutes to ensure complete extraction of the drug from the cyclodextrin matrix. The solutions were then filtered using Whatman filter paper (0.45 µm) to remove any undissolved particles.

An appropriate aliquot of the filtrate was further diluted with distilled water to obtain a solution within the calibration range. The absorbance of the diluted sample was measured at 245.5 nm using a UV–Visible spectrophotometer. [10]

The drug content was calculated using the previously obtained calibration curve regression equation.

Calculation of Drug Content

The percentage drug content was calculated using the following equation:

$$Drug\ Content\ (\%) = \frac{Actual\ amount\ of\ drug\ present}{Theoretical\ amount\ of\ drug} \times 100$$

Table 4. Drug content uniformity of Simvastatin inclusion complexes

Formulation	Drug Content (%)
F1	97.8
F2	98.6
F3	99.1
F4	98.4
F5	99.2

The results indicate that all formulations exhibited high drug content uniformity, ranging from 97.8% to 99.2%, which falls within acceptable pharmaceutical limits. The slight variation in drug content may be attributed to minor losses during processing or handling. The high drug content values confirm that the preparation methods used for the inclusion complexes resulted in uniform distribution of Simvastatin within the cyclodextrin matrix. These results also demonstrate the reproducibility and reliability of the preparation techniques used in the study.

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Significance

Drug content uniformity is an important parameter in pharmaceutical formulation development as it ensures that each prepared formulation contains the desired amount of active drug, thereby guaranteeing consistent therapeutic efficacy and dosage accuracy.

K. Aqueous Solubility Study

The aqueous solubility study was carried out to evaluate the effect of cyclodextrin complexation on the solubility of Simvastatin. Since Simvastatin is a poorly water-soluble drug, improving its solubility is essential for enhancing its dissolution rate and oral bioavailability.

Procedure

The solubility of pure Simvastatin and its inclusion complexes with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD) was determined using the shake flask method, which is widely employed for solubility determination of pharmaceutical compounds.

An excess amount of pure drug or the prepared inclusion complex was added to 10 mL of distilled water in separate stoppered conical flasks. The flasks were placed in a mechanical shaker maintained at 25 ± 1°C and agitated continuously for 48 hours to achieve equilibrium.

After reaching equilibrium, the suspensions were filtered through Whatman filter paper (0.45 µm) to remove undissolved drug particles. The filtrate was appropriately diluted with distilled water and analyzed using a UV–Visible spectrophotometer at 245.5 nm to determine the amount of dissolved Simvastatin. [11]

The solubility of the drug in each sample was calculated using the previously established calibration curve.

Table 5. Solubility enhancement of Simvastatin inclusion complexes

Sample	Solubility (µg/mL)
Pure Simvastatin	18
β-CD complex	52
HPβ-CD complex	75

The results demonstrate a significant increase in the aqueous solubility of Simvastatin after complexation with cyclodextrins. The solubility of the pure drug was found to be 18 µg/mL, indicating its poor aqueous solubility. However, the solubility increased to 52 µg/mL when complexed with β-cyclodextrin and further increased to 75 µg/mL with hydroxypropyl-β-cyclodextrin. The HPβ-CD complex exhibited approximately 4.1-fold enhancement in solubility compared with the pure drug. This improved solubility can be attributed to the ability of cyclodextrin molecules to form inclusion complexes with the hydrophobic drug molecules. The hydrophobic cavity of cyclodextrin encapsulates the lipophilic portion of Simvastatin, while the hydrophilic outer surface of cyclodextrin interacts with the aqueous medium, thereby improving the apparent solubility of the drug. The higher solubility enhancement observed with HPβ-CD compared with β-CD can be explained by its greater aqueous solubility and improved complexation efficiency. The presence of hydroxypropyl groups in HPβ-CD disrupts intermolecular hydrogen bonding within the cyclodextrin structure, which increases its solubility and enhances its ability to form stable inclusion complexes with hydrophobic drugs. Improving the aqueous solubility of Simvastatin is expected to enhance its dissolution rate, which may subsequently lead to improved oral bioavailability and therapeutic efficacy. The results of the solubility study therefore confirm that cyclodextrin complexation, particularly with HPβ-CD, is an effective strategy for enhancing the solubility of poorly water-soluble drugs.

L. In-vitro Dissolution Study

The in-vitro dissolution study was carried out to evaluate the effect of cyclodextrin complexation on the dissolution behavior of Simvastatin. Dissolution testing is an important parameter for poorly water-soluble drugs because the rate of dissolution directly influences the drug's absorption and bioavailability.

Procedure

The dissolution studies of pure Simvastatin and its inclusion complexes with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD) were performed using a USP Dissolution Apparatus Type II (Paddle method).

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The dissolution conditions were maintained as follows:

- Rotation speed: 50 rpm
- Temperature: 37 ± 0.5°C
- Dissolution medium: 900 mL of distilled water

Accurately weighed quantities of pure Simvastatin or inclusion complexes equivalent to 10 mg of Simvastatin were introduced into the dissolution vessel containing the dissolution medium.

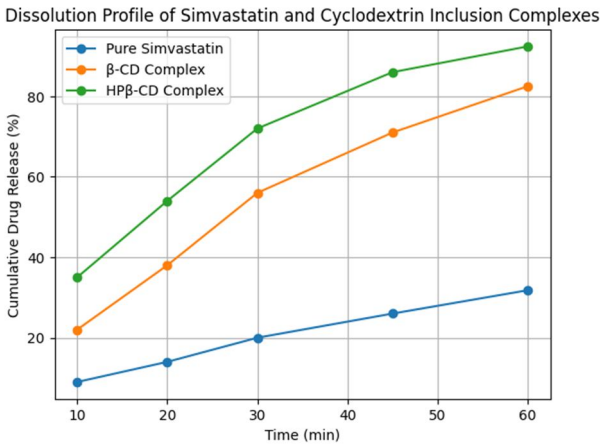
At predetermined time intervals (10, 20, 30, 45, and 60 minutes), 5 mL samples were withdrawn from the dissolution medium using a syringe fitted with a membrane filter to remove any undissolved particles. An equal volume of fresh dissolution medium maintained at the same temperature was replaced immediately after each sampling to maintain constant volume and sink conditions.

The withdrawn samples were suitably diluted and analyzed spectrophotometrically at 245.5 nm using a UV–Visible spectrophotometer to determine the amount of drug released.

The cumulative percentage of drug released was calculated and plotted against time to obtain the dissolution profiles of the pure drug and inclusion complexes.

Table 6. Dissolution profile of Simvastatin and its inclusion complexes

Time (min)	Pure Drug (%)	β-CD Complex (%)	HPβ-CD Complex (%)
10	9.0	22.0	35.0
20	14.0	38.0	54.0
30	20.0	56.0	72.0
45	26.0	71.0	86.0
60	31.8	82.5	92.4



The dissolution study results clearly indicate that cyclodextrin complexation significantly improved the dissolution rate of Simvastatin.

The pure drug exhibited a slow dissolution rate, with only 31.8% drug release after 60 minutes, which confirms the poor aqueous solubility of Simvastatin. In contrast, the inclusion complexes demonstrated a remarkable improvement in drug release.

The β-cyclodextrin complex showed enhanced dissolution, reaching 82.5% drug release within 60 minutes, which represents more than a 2.5-fold increase compared with the pure drug.

The HPβ-cyclodextrin complex exhibited the highest dissolution enhancement, achieving 92.4% drug release within 60 minutes. This superior performance can be attributed to the higher aqueous solubility and better complexation efficiency of HPβ-CD. [12]

The improved dissolution behavior of the inclusion complexes can be explained by several factors:

- Improved wettability of the drug particles due to the hydrophilic outer surface of cyclodextrins.
- Reduction in drug crystallinity and possible transformation into an amorphous form during complex formation.
- Molecular encapsulation of the drug within the cyclodextrin cavity, which increases the apparent solubility of the drug.
- Increased surface area available for dissolution due to improved dispersion of the drug within the cyclodextrin matrix.

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Among the tested formulations, the HPβ-CD inclusion complex demonstrated the highest dissolution efficiency, indicating that it is the most effective formulation for enhancing the dissolution rate of Simvastatin.

Enhancing the dissolution rate of poorly soluble drugs is a critical step in improving their oral bioavailability. The results obtained in this study suggest that cyclodextrin complexation, particularly with HPβ-cyclodextrin, is an effective strategy for improving the dissolution characteristics of Simvastatin and may lead to improved therapeutic performance.

III. CHARACTERIZATION OF INCLUSION COMPLEXES

Characterization studies were performed to confirm the formation of inclusion complexes between Simvastatin and cyclodextrins and to evaluate the physicochemical changes in the drug after complexation. Various analytical techniques such as Fourier Transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM) were employed.

A. Fourier Transform Infrared Spectroscopy (FT-IR)

FT-IR spectroscopy was used to investigate possible drug–excipient interactions and to confirm the compatibility of Simvastatin with the cyclodextrin carriers.

Experimental Procedure

FT-IR spectra of pure Simvastatin, β-cyclodextrin, HPβ-cyclodextrin, and the prepared inclusion complexes were recorded using an FT-IR spectrophotometer employing the KBr pellet method.

Approximately 1–2 mg of sample was mixed with 100 mg of dry potassium bromide (KBr) and compressed into a transparent pellet using a hydraulic press. The spectra were recorded over a wavelength range of 4000–400 cm^{-1}.

Characteristic FT-IR Peaks of Simvastatin

The FT-IR spectrum of pure Simvastatin showed several characteristic absorption peaks corresponding to its functional groups.

Functional Group	Wavenumber (cm^{-1})
O–H stretching	3540
C=O stretching (lactone group)	1697
C–O stretching	1160

These characteristic peaks represent the functional groups present in the Simvastatin molecule.

The FT-IR spectra of the Simvastatin–cyclodextrin inclusion complexes showed no significant shift, disappearance, or appearance of new peaks when compared with the spectrum of pure Simvastatin.

The characteristic peaks corresponding to the functional groups of Simvastatin remained almost unchanged in the complexes, indicating that no chemical interaction or degradation occurred during the complexation process.

However, slight variations in peak intensity and broadening of some absorption bands were observed in the complexes, which may be attributed to weak intermolecular interactions such as hydrogen bonding and van der Waals forces between the drug and cyclodextrin molecules.

The FT-IR results confirm that the inclusion complex formation between Simvastatin and cyclodextrin occurs primarily through non-covalent interactions rather than chemical bonding. This is consistent with the mechanism of cyclodextrin complexation, where the drug molecule is physically encapsulated within the hydrophobic cavity of the cyclodextrin molecule.

Therefore, FT-IR analysis demonstrated that Simvastatin is compatible with β-cyclodextrin and HPβ-cyclodextrin, and the complexation process does not alter the chemical structure of the drug.

B. Powder X-Ray Diffraction (PXRD)

Powder X-ray diffraction analysis was performed to investigate the crystalline nature of Simvastatin and the structural changes occurring after complexation with cyclodextrins.

Experimental Procedure

The PXRD patterns of pure Simvastatin, β-cyclodextrin, HPβ-cyclodextrin, and the prepared inclusion complexes were recorded using a powder X-ray diffractometer equipped with Cu-Kα radiation (λ = 1.5406 Å).

The samples were scanned over a 2θ range of 5°–50° at a scanning speed of 2° per minute. The diffraction patterns obtained were analyzed to determine the degree of crystallinity and possible structural modifications of the drug after complex formation.

PXRD Pattern of Pure Drug

The PXRD pattern of pure Simvastatin showed distinct sharp diffraction peaks, confirming its highly crystalline nature. The major characteristic peaks were observed at the following diffraction angles:

Diffraction Angle (2θ)	Interpretation
17.3°	Characteristic crystalline peak
22.8°	Strong diffraction peak
25.6°	Prominent crystalline reflection

These sharp and intense peaks indicate that Simvastatin exists predominantly in a crystalline form.

PXRD Pattern of Inclusion Complexes

In contrast, the PXRD patterns of the Simvastatin–cyclodextrin inclusion complexes exhibited a significant reduction in the intensity of the characteristic crystalline peaks of Simvastatin. Some peaks were broadened or partially disappeared in the diffractograms.

The reduction in peak intensity indicates a loss of crystallinity and partial transformation of the drug from crystalline to amorphous form after complexation with cyclodextrin molecules.

The observed decrease in crystallinity suggests that Simvastatin molecules were molecularly dispersed within the cyclodextrin matrix, resulting in amorphization of the drug. Amorphous forms generally exhibit higher solubility and faster dissolution rates compared with their crystalline counterparts. Therefore, the PXRD results support the improved dissolution behavior observed in the inclusion complexes.

C. Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry was performed to evaluate the thermal behavior of Simvastatin and to confirm the formation of inclusion complexes with cyclodextrins.

Procedure

Thermal analysis of pure Simvastatin, β-cyclodextrin, HPβ-cyclodextrin, and the prepared inclusion complexes was carried out using a differential scanning calorimeter (DSC).

Approximately 5–10 mg of sample was accurately weighed and placed in a sealed aluminum pan. The samples were heated at a constant rate of 10°C per minute in a temperature range of 30°C to 300°C under a nitrogen atmosphere to prevent oxidative degradation.

Thermal Behavior of Pure Simvastatin

The DSC thermogram of pure Simvastatin showed a sharp endothermic peak at approximately 139°C, corresponding to the melting point of the drug. This sharp melting peak confirms the crystalline nature and purity of Simvastatin.

Thermal Behavior of Inclusion Complexes

In the DSC thermograms of the Simvastatin–cyclodextrin inclusion complexes, the characteristic melting peak of Simvastatin at 139°C was either significantly reduced or completely absent.

The disappearance of the melting endotherm indicates that the drug was no longer present in its crystalline form but was molecularly dispersed within the cyclodextrin cavity.

The absence of the characteristic melting peak of Simvastatin in the inclusion complexes confirms the successful formation of drug–cyclodextrin inclusion complexes. The disappearance of the melting endotherm suggests that Simvastatin molecules were incorporated into the cyclodextrin cavity and converted into an amorphous or molecularly dispersed state.

The transformation of the drug into an amorphous state contributes to the enhanced solubility and dissolution rate observed in the prepared inclusion complexes.

D. Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) was employed to examine the surface morphology and particle characteristics of pure Simvastatin and the prepared inclusion complexes with cyclodextrins. SEM analysis provides valuable information about the physical appearance, surface texture, and structural changes occurring during complex formation.

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Experimental Procedure

The surface morphology of pure Simvastatin, β-cyclodextrin complex, and HPβ-cyclodextrin complex was analyzed using a scanning electron microscope.

A small quantity of each sample was mounted on a metallic stub using double-sided adhesive carbon tape. The samples were then coated with a thin layer of gold using a sputter coater to improve electrical conductivity and obtain clear images.

The coated samples were examined under the scanning electron microscope at suitable magnification levels (typically 500× to 5000×) and the micrographs were recorded.

SEM Observations

The SEM images revealed significant differences in the morphology of the pure drug and the prepared inclusion complexes.

Sample	Observed Morphology
Pure Simvastatin	Well-defined crystalline particles
β-Cyclodextrin complex	Irregular aggregated particles
HPβ-Cyclodextrin complex	Amorphous and porous structure

Interpretation of SEM Results

The SEM micrograph of pure Simvastatin showed distinct crystalline particles with smooth surfaces, confirming the crystalline nature of the drug.

In contrast, the β-cyclodextrin inclusion complex exhibited irregular aggregated particles, indicating partial disruption of the crystalline structure of the drug due to interaction with cyclodextrin molecules.

The HPβ-cyclodextrin complex displayed a highly amorphous and porous morphology, which suggests that the drug was molecularly dispersed within the cyclodextrin matrix. The disappearance of the typical crystalline structure of Simvastatin in the HPβ-CD complex indicates successful inclusion complex formation.

The morphological transformation from crystalline particles to amorphous aggregates observed in the SEM micrographs supports the results obtained from PXRD and DSC studies, confirming the formation of drug–cyclodextrin inclusion complexes.

The amorphous structure of the HPβ-CD complex is expected to improve drug wettability, solubility, and dissolution rate, which explains the enhanced dissolution behavior observed during in-vitro dissolution studies.

IV. STABILITY STUDIES

Stability studies were carried out to evaluate the physical and chemical stability of the optimized Simvastatin–cyclodextrin inclusion complex formulation during storage. Stability testing is an important parameter in pharmaceutical development as it ensures that the formulation maintains its quality, safety, and therapeutic efficacy throughout its shelf life.

The stability study was conducted in accordance with the International Council for Harmonisation (ICH) guidelines (ICH Q1A(R2)) for stability testing of pharmaceutical products.

A. Procedure

The optimized formulation of the Simvastatin inclusion complex (showing maximum dissolution performance) was placed in airtight glass containers and stored under two different environmental conditions:

- Room temperature (25 ± 2°C)
- Accelerated stability conditions (40°C ± 2°C / 75% ± 5% relative humidity)

The samples were stored for a period of six weeks. At predetermined intervals, the formulations were withdrawn and evaluated for drug release behavior using in-vitro dissolution studies under the previously established dissolution conditions.

The percentage of drug released was determined spectrophotometrically using a UV–Visible spectrophotometer at 245.5 nm.

Table 7. Stability results of optimized Simvastatin inclusion complex

Storage Condition	Drug Release (%) after 6 weeks
Room temperature	91.3
40°C / 75% RH	89.7

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The results obtained from the stability study showed no significant change in the dissolution profile of the optimized formulation during the storage period.

The formulation stored at room temperature exhibited 91.3% drug release, while the formulation stored under accelerated conditions (40°C / 75% RH) showed 89.7% drug release after six weeks. The slight reduction in drug release under accelerated conditions may be attributed to minor environmental effects such as humidity and temperature.

However, the observed variation was minimal and remained within acceptable pharmaceutical limits. These results indicate that the Simvastatin–cyclodextrin inclusion complex formulation maintained its stability during the storage period.

Significance of Stability Study

The stability study confirms that the optimized formulation is physically and chemically stable under both normal and accelerated storage conditions. The inclusion complex remained intact and retained its enhanced dissolution characteristics throughout the study period.

This stability may be attributed to the protective encapsulation of Simvastatin within the cyclodextrin cavity, which can protect the drug molecule from environmental degradation such as hydrolysis and oxidation.

V. DISCUSSION

The present study aimed to enhance the aqueous solubility and dissolution behavior of Simvastatin through the formation of cyclodextrin inclusion complexes using β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HPβ-CD). The results obtained from the various physicochemical and analytical studies clearly demonstrated that cyclodextrin complexation significantly improved the solubility and dissolution characteristics of Simvastatin.

The phase solubility studies revealed a linear increase in the solubility of Simvastatin with increasing concentrations of cyclodextrin, producing an AL-type phase solubility diagram according to the Higuchi–Connors classification. This type of profile indicates the formation of 1:1 drug–cyclodextrin inclusion complexes. The calculated stability constant values suggested that the complex formed with HPβ-CD was more stable than that formed with β-CD. The higher stability constant observed with HPβ-CD may be attributed to its greater aqueous solubility and enhanced complexation efficiency, which facilitates stronger host–guest interactions with the hydrophobic Simvastatin molecule.

The aqueous solubility study further confirmed the effectiveness of cyclodextrin complexation in improving drug solubility. Pure Simvastatin exhibited very low aqueous solubility due to its hydrophobic nature and crystalline structure. However, complexation with β-CD and HPβ-CD resulted in a significant increase in solubility, with HPβ-CD showing the highest solubility enhancement. The improved solubility can be explained by the encapsulation of the hydrophobic portion of the drug molecule within the hydrophobic cavity of cyclodextrin, while the hydrophilic outer surface of the cyclodextrin molecule interacts with the surrounding aqueous environment.

The in-vitro dissolution studies demonstrated a remarkable improvement in the dissolution rate of Simvastatin following cyclodextrin complexation. The pure drug showed a slow dissolution rate due to its poor aqueous solubility and crystalline nature. In contrast, the inclusion complexes exhibited significantly enhanced dissolution profiles. Among the formulations studied, the HPβ-CD complex prepared using the microwave irradiation technique showed the highest dissolution rate, reaching more than 90% drug release within 60 minutes. This improvement can be attributed to several factors, including enhanced wettability of the drug particles, reduction in crystallinity, improved dispersion of the drug within the cyclodextrin matrix, and increased surface area available for dissolution.

The microwave irradiation technique proved to be the most efficient method for the preparation of inclusion complexes. Microwave energy promotes rapid and uniform heating, which enhances molecular mobility and facilitates effective interaction between drug and cyclodextrin molecules. As a result, the drug molecules can more readily penetrate the hydrophobic cavity of the cyclodextrin structure, leading to efficient inclusion complex formation and improved physicochemical properties.

The characterization studies provided further evidence supporting the formation of inclusion complexes. FT-IR analysis showed that the characteristic functional group peaks of Simvastatin remained largely unchanged in the complexes, indicating the absence of chemical interactions between the drug and cyclodextrin molecules. This confirms that the complexation process occurs through non-covalent interactions such as hydrogen bonding, hydrophobic interactions, and van der Waals forces.

PXRD analysis revealed a significant reduction in the intensity of the characteristic crystalline peaks of Simvastatin in the inclusion complexes, indicating a loss of crystallinity and transformation of the drug into a partially amorphous form. Similarly, DSC thermograms showed the disappearance or significant reduction of the characteristic melting endotherm of Simvastatin at approximately 139°C, further confirming the molecular dispersion of the drug within the cyclodextrin matrix.

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SEM analysis also supported these findings by demonstrating substantial morphological changes after complex formation. Pure Simvastatin exhibited well-defined crystalline particles, whereas the inclusion complexes showed irregular and amorphous structures. The disappearance of the characteristic crystalline morphology indicates successful encapsulation of the drug within the cyclodextrin cavity.

The stability studies performed under both room temperature and accelerated storage conditions demonstrated that the optimized formulation remained stable during the storage period. The minimal change in drug release behavior suggests that the inclusion complex protects the drug from environmental factors such as temperature and humidity, thereby maintaining its stability.

Overall, the results obtained from phase solubility studies, solubility analysis, dissolution testing, and various characterization techniques consistently confirmed the successful formation of Simvastatin–cyclodextrin inclusion complexes. Among the cyclodextrins evaluated, HPβ-CD showed superior performance in improving solubility and dissolution rate due to its higher aqueous solubility and enhanced complexation ability.

These findings indicate that cyclodextrin complexation, particularly with HPβ-cyclodextrin prepared using microwave irradiation, represents an effective formulation strategy for enhancing the solubility and dissolution rate of poorly water-soluble drugs such as Simvastatin.

VI. CONCLUSION

The present study successfully demonstrated that cyclodextrin inclusion complexation is an effective strategy for improving the aqueous solubility and dissolution characteristics of poorly water-soluble drugs such as Simvastatin. Inclusion complexes of Simvastatin were prepared using β-cyclodextrin and hydroxypropyl-β-cyclodextrin through different preparation techniques including physical mixture, kneading method, and microwave irradiation method.

Phase solubility studies confirmed the formation of 1:1 drug–cyclodextrin inclusion complexes, indicating effective molecular interaction between Simvastatin and the cyclodextrin carriers. The aqueous solubility and dissolution studies revealed a significant enhancement in drug solubility and dissolution rate following complexation, particularly in the case of the HPβ-CD complexes.

Among the different preparation methods evaluated, the microwave irradiation technique proved to be the most efficient method, producing inclusion complexes with superior solubility and dissolution performance. The improved dissolution behavior observed in the microwave-prepared complexes may be attributed to enhanced molecular interaction between the drug and cyclodextrin molecules, reduction in drug crystallinity, and improved wettability of the drug particles.

Characterization studies including FT-IR spectroscopy, powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) confirmed the successful formation of stable inclusion complexes and indicated partial transformation of the drug from a crystalline to an amorphous state. Stability studies conducted under both normal and accelerated conditions further demonstrated that the optimized formulation remained stable during storage.

Overall, the results of the present investigation indicate that hydroxypropyl-β-cyclodextrin inclusion complexes prepared by microwave irradiation offer a promising formulation approach for enhancing the solubility and dissolution rate of Simvastatin. This strategy may ultimately lead to improved oral bioavailability and therapeutic efficacy of poorly water-soluble drugs.

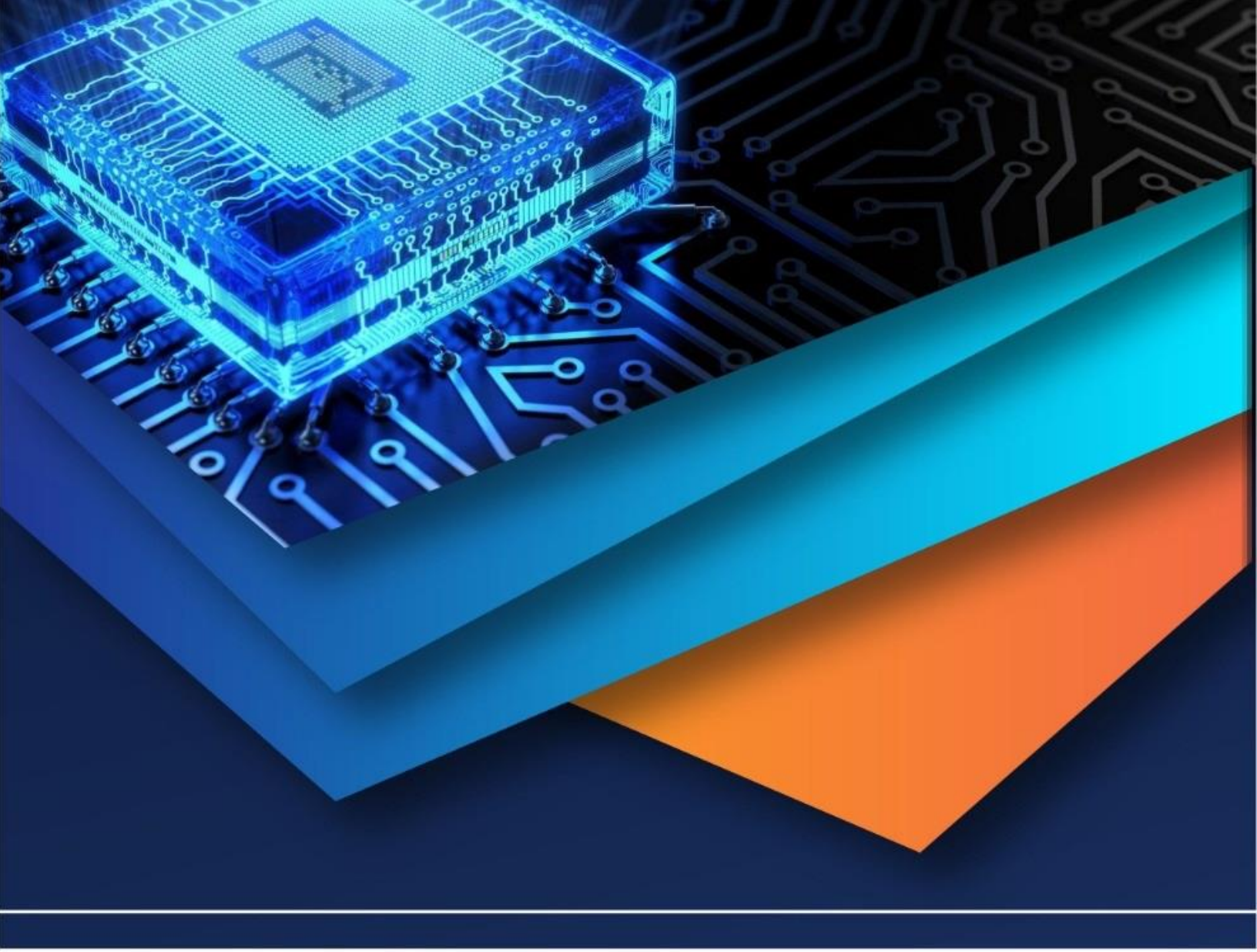
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