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Final Year Report On
ML Meets Nanomedicine: Predicting Drug Release
for Enhanced Delivery Systems

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Abstract

The integration of nanotechnology with machine learning offers transformative potential in the field of advanced drug delivery systems. This project explores the development and application of silica-gels as nanocarriers for curcumin—a hydrophobic, poorly water-soluble bioactive compound—with the goal of achieving a sustained and controlled release profile. Curcumin-loaded silica-gels were synthesized via the sol–gel technique and characterized through UV–Visible spectrophotometry to evaluate drug release under varying experimental conditions. Five key parameters—time, drug content, pH, RPM (agitation speed), and temperature—were systematically studied to understand their influence on cumulative drug release. Multiple machine learning algorithms, including Multiple Linear Regression, Decision Tree, Random Forest, and Support Vector Regression (SVR), were employed to model and predict drug release behavior. Model evaluation was based on R^2 (coefficient of determination), with the SVR model achieving the highest accuracy, effectively capturing complex, nonlinear relationships. This study demonstrates that the integration of experimental nanomaterial research with machine learning can significantly enhance prediction, formulation optimization, and the development of next-generation, personalized drug delivery systems.

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List of Abbreviations

ML	Machine Learning
MLR	Multiple Linear Regression
SVR	Support Vector Regression
KNN	K-Nearest Neighbours

Chapter 1

Introduction

Curcumin, a naturally occurring polyphenolic compound extracted from the rhizome of *Curcuma longa*, has attracted considerable attention due to its wide spectrum of pharmacological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties [1], [2]. Despite its therapeutic potential, the clinical application of curcumin remains limited owing to its poor aqueous solubility, low bioavailability, rapid systemic elimination, and instability under physiological conditions [3], [4]. These drawbacks hinder its absorption and systemic circulation, making it challenging to achieve therapeutic plasma concentrations through conventional oral or parenteral administration routes.

To address these limitations, nanotechnology-based drug delivery systems have been extensively explored. Among various nanocarriers, silica-gel have emerged as a promising platform for drug encapsulation and delivery due to their unique physicochemical properties, including large surface area, tunable pore size, chemical inertness, and biocompatibility [5]–[7]. The strong siloxane (Si–O–Si) framework provides superior structural stability, allowing for high drug-loading efficiency without the need for additional stabilizing agents [8]. Silica-gel can be engineered to deliver both hydrophilic and hydrophobic drug molecules, making them particularly suitable for poorly water-soluble compounds such as curcumin [9].

Furthermore, the size of nanoparticles plays a critical role in their ability to penetrate the skin and other biological barriers. Studies have shown that particles in the range of 300–600 nm can efficiently access skin appendages, such as hair follicles and sweat glands, facilitating improved transdermal or localized delivery [10], [11]. Incorporating curcumin into

SNPs may thus enhance its solubility, stability, and sustained release, while potentially minimizing systemic toxicity and improving therapeutic efficacy.

In parallel with advances in nanotechnology, the application of machine learning (ML) techniques in pharmaceutical sciences has gained significant momentum. ML models are capable of capturing complex, nonlinear relationships between formulation variables and drug release kinetics, offering powerful tools for predicting and optimizing drug delivery outcomes [12]–[14]. By leveraging computational intelligence, researchers can reduce experimental workload and improve the design and efficiency of drug delivery systems.

In this study, curcumin was encapsulated into silica-gel to enhance its solubility and enable controlled release. Drug release studies were conducted under various experimental conditions, including time, pH, temperature, agitation speed (RPM), and drug content. UV-Visible spectrophotometry was employed to quantify curcumin release over time. To model and predict the release behavior, four machine learning algorithms—multiple linear regression (MLR), Ridge Regression, lasso regression, the elasticnet algorithm, Decision Tree, random forest, support vector regression (SVR), gradient boosting, XGboost, LightGBM, Adaboost, neural network, and Gaussian Process —were implemented. The predictive accuracy of each model was evaluated using the coefficient of determination (R^2 score). This research demonstrates the potential of integrating nanomaterial-based drug delivery systems with machine learning to improve predictive modeling and formulation design in pharmaceutical applications.

1.1 Problem statement

Machine learning-based prediction model to estimate the percentage of drug release from nanocarrier systems using key experimental variables—pH, time, stirring speed (RPM), drug concentration, and temperature—to enhance the efficiency and design of drug delivery systems in nanomedicine.

1.2 Aims and objectives

Aims: To develop and evaluate machine learning models for accurately predicting the percentage of drug release from nanocarrier-based delivery systems using key experimental parameters.

Objectives:

1. Data Preparation

Collect and preprocess experimental data involving variables such as pH, time, RPM, drug concentration, and temperature.

2. Calibration and Standardization

Establish a calibration curve for drug concentration using UV–Vis spectroscopy to convert absorbance to drug release percentage.

3. Model Development

Train and compare various machine learning algorithms (e.g., SVR, Random Forest, XGBoost, Neural Networks) for regression analysis.

4. Model Evaluation

Evaluate model performance using metrics such as R^2 , RMSE, and MAE, and validate with k-fold cross-validation.

5. Optimization and Interpretation

Identify key influencing variables and optimize model parameters for better generalizability and prediction accuracy.

6. Deployment Readiness

Prepare the model for future deployment in computational drug design or real-time prediction platforms for formulation scientists.

Chapter 2

Literature Review

2.1 Nanomaterials: Foundations and Relevance in Drug Delivery

Nanomaterials are materials that have at least one external dimension in the nanoscale range (typically 1–100 nanometers). Due to their reduced size, they exhibit unique physical, chemical, mechanical, optical, and biological properties that are not observed in their bulk counterparts. These properties have led to a transformative impact across industries, particularly in biomedicine and drug delivery. [15][16]

Properties:

- This characteristic enables a greater number of drug molecules to be loaded or adsorbed onto the nanomaterial surface or within their internal porous structures.
- Surface tunability: Nanomaterials can be functionalized with chemical groups or biological ligands to target specific tissues or cells (e.g., folic acid for cancer targeting). This enables site-specific delivery, reducing systemic side effects and increasing therapeutic efficacy.
- Controlled and sustained drug release: Nanomaterials can be engineered to release drugs slowly over time via diffusion, degradation, or environmental stimuli (e.g., pH, temperature), allowing better control over pharmacokinetics.

Curcumin, the active compound in turmeric, is widely used for its anti-inflammatory, antioxidant, and anticancer properties. It helps manage conditions like arthritis, metabolic syndrome, and neurodegenerative diseases (e.g., Alzheimer's) by modulating inflammatory pathways and reducing oxidative stress.[1][2] Curcumin supports digestive health, wound

healing, and cardiovascular protection by improving endothelial function and lipid metabolism.[2] Curcumin is a hydrophobic compound with low aqueous solubility and poor oral bioavailability due to rapid metabolism and elimination.[3] Encapsulating curcumin into nanomaterials such as mesoporous silica, liposomes, or polymeric nanoparticles helps:

- Increase solubility and stability in biological fluids.[7]
- Protect from enzymatic degradation.
- Enhance cellular uptake and bioavailability.[7]
- Enable sustained and localized release at the target site.[6][9]

2.2 What is Nanotechnology?

Nanotechnology involves the design, synthesis, characterization, and application of materials and systems at the nanometer scale (1–100 nm). In drug delivery, it offers an innovative platform to improve the pharmacokinetics, biodistribution, solubility, stability, and targeting capability of therapeutic agents.[15][16]

Core Functions of Nanotechnology in Drug Delivery:

▪ Solubility Enhancement:

Many potent therapeutic compounds, including curcumin, suffer from poor water solubility. Nanocarriers such as mesoporous silica-gel, liposomes, and polymeric nanoparticles create microenvironments that encapsulate hydrophobic drugs and disperse them in aqueous media, improving dissolution rate and bioavailability.[15]

▪ Controlled and Sustained Release:

Nanocarriers allow for precisely timed drug release, which helps maintain therapeutic plasma concentrations, reduce dosing frequency, and minimize peak-trough fluctuations that could cause toxicity or sub-therapeutic exposure.[15]

▪ Targeted Drug Delivery:

Surface functionalization with ligands (e.g., folate, antibodies, peptides) enables nanocarriers to bind to receptors overexpressed on diseased tissues (e.g., tumors or inflamed tissues), improving drug accumulation at the target site while reducing systemic side effects.[15]

Nanotechnological Approach:

- *Sol-gel Synthesis*: Fabricates mesoporous silica-gel with tunable pore size and surface chemistry.
- *Stimuli-responsive Systems*: Enables curcumin release in response to pH (acidic tumors), temperature, or enzymes.

2.3 Types of Nanomaterials:

- **Zero-Dimensional**: Quantum dots, nanoparticles
Excellent for high surface area, drug adsorption, fluorescence imaging.[15]
- **one-Dimensional**: Nanorods, nanotubes, nanowires
Useful for high-aspect-ratio delivery (e.g., DNA, siRNA), cell penetration.[15]
- **2-dimesional**: Nanosheets, Graphene oxide
Ideal for drug loading on surface, photothermal therapy
- **3-Dimensional**: Dendrimers, mesoporous silica, nanogels
Offer multi-compartmental drug loading, sustained release.[15]

For curcumin, 3D silica-gels are ideal, due to their ability to load significant quantities of curcumin, protect it from degradation, and release it slowly over time.[15]

2.4 Nanocarriers:

Nanocarriers are nanoscale vehicles that serve as delivery agents for therapeutic compounds. They are designed to improve the pharmacokinetic and pharmacodynamic profile of drugs, especially those with poor solubility and stability, such as curcumin.[3][4][7] Nanocarriers not only protect the encapsulated drug from premature degradation but also enhance solubility, enable targeted delivery, extend circulation time, and allow for controlled/sustained release.

Applications of Nanocarriers:

- **Controlled and Sustained Drug Release:**

Nanocarriers allow drug release to be regulated over time, improving therapeutic outcomes and reducing dosing frequency. Controlled release prevents: Burst effect(sudden drug spike), Rapid metabolism.

- **Protection from Degradation:**

Curcumin is unstable under physiological conditions—it degrades quickly in alkaline pH and undergoes rapid enzymatic metabolism. Encapsulation protects it from:Oxidation, Hydrolysis, UV degradation.[3][4]

- **Targeted Drug Delivery:**

Nanocarriers can be functionalized with ligands, antibodies, or peptides to target specific cell receptors. For example, folate receptors in cancer cells and integrins in inflamed tissues.

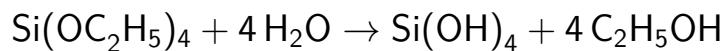
As the number of possible nanocarrier formulations increases, it becomes computationally intensive to manually optimize all variables (e.g., particle size, drug ratio, pH, surfactant type, etc.). Machine Learning models are being used to:

- Predict drug release patterns.
- Optimize encapsulation efficiency.
- Model stability under different conditions,

2.5 Silica-gel synthesis:

Silica-gel is one of the most extensively studied inorganic nanocarriers for drug delivery. Their porous structure, high thermal and mechanical stability, and chemical inertness make them ideal for encapsulating poorly soluble drugs like curcumin.[15] The most widely adopted method for producing silica-gel is the sol–gel process, which includes the hydrolysis and condensation of alkoxy silanes under controlled conditions.

- **Hydrolysis of TEOS (Tetraethyl orthosilicate):**



- **Condensation (polymerization):**



These reactions result in the formation of a three-dimensional silica network. The pH, solvent type, catalyst, and reaction time significantly affect the particle size, porosity, and surface area.[5]

Step-by-Step Protocol

1. Precursor Selection

- **Main precursor:** Tetraethyl orthosilicate (TEOS)
- **Solvent:** Ethanol or methanol (promotes miscibility with water)
- **Catalyst:** Either acid (e.g., HCl) or base (e.g., NH₄OH)

2. Hydrolysis Phase

- TEOS is mixed with ethanol and water
- A catalyst is added to initiate hydrolysis
- The solution is stirred vigorously to ensure homogeneity

3. Condensation and Gelation

- As the silanols (Si-OH) begin to condense, a colloidal gel network forms
- Gelation time varies depending on pH and temperature

4. Aging

- The gel is aged to strengthen the silica network
- Allows pore structure development

5. Drying

- Wet gels are dried to remove solvents
- Methods include:
 - Ambient drying (xerogels)
 - Supercritical drying (aerogels)

2.6 Process of Drug Loading in Nanocarriers:

Loading a therapeutic compound into a nanocarrier is a critical step in designing an effective drug delivery system. For hydrophobic and poorly water-soluble drugs like curcumin, encapsulation within nanocarriers such as silica-gel is necessary to enhance solubility, protect the drug from degradation, and control its release over time.[3][4]

Common Drug Loading Methods

The process of loading curcumin into silica-gel can be performed using several techniques. Each offers distinct advantages depending on the application and formulation requirements.

2.6.1 Physical Adsorption

This is a passive method where the curcumin is adsorbed onto the surface or into the pores of the silica-gel through van der Waals interactions and hydrophobic affinity.[5][6]

Process:

1. Disperse silica-gel in an ethanolic solution of curcumin
2. Stir the mixture at room temperature or under mild heating
3. Allow curcumin molecules to diffuse into the mesopores
4. Remove unbound drug by washing or centrifugation
5. Dry the formulation (often under vacuum or at low temperature)

This technique is simple, non-destructive, and maintains the integrity of both the drug and carrier.

2.6.2 Solvent Evaporation Method

In this technique, curcumin and silica-gels are dispersed in a mutual organic solvent (commonly ethanol or acetone). After adsorption, the solvent is evaporated to lock the drug into the nanopores.[15]

Steps:

1. Mix curcumin and silica gel in ethanol

2. Sonicate or stir vigorously for uniform mixing
3. Allow solvent to evaporate under vacuum or reduced pressure
4. Dry and collect the loaded nanoparticles

This method enhances drug encapsulation efficiency by promoting intimate contact between drug molecules and the porous matrix of silica.[15]

2.6.3 Incubation with Ethanolic Solution (Diffusion-based Loading)

A widely used method for curcumin involves incubating silica-gels with curcumin in ethanol (due to its good solubilizing power for curcumin). Over time, curcumin diffuses into the porous structure of the silica.[15]

Procedure:

1. Dissolve curcumin in ethanol to form a saturated or supersaturated solution
2. Add silica-gel and stir continuously for several hours (commonly 12–24 h)
3. After incubation, centrifuge and wash the particles to remove unentrapped drug
4. Dry under vacuum

2.7 UV–Visible Spectrophotometry for Drug Release Monitoring:

UV–Visible spectrophotometry is one of the most widely used analytical techniques for the quantitative estimation of drug concentration in pharmaceutical formulations, particularly in *in vitro* drug release studies. For compounds like curcumin, which have a distinct absorption peak in the visible region (420 nm), this technique offers a simple, sensitive, non-destructive, and cost-effective way to evaluate drug release from nanocarriers.[15]

Curcumin exhibits a strong absorbance peak at approximately 420-450 nm in ethanol and around 420 nm in aqueous media due to its conjugated diketone structure. This makes it ideal for detection using UV–Vis

spectroscopy without the need for fluorescent tagging or complex derivatization.[4]

Protocol for Drug Release Study Using UV–Vis:

2.7.1 Preparation of Calibration Curve:

- Dissolve known concentrations of curcumin in ethanol or phosphate-buffered saline (PBS).
- Measure absorbance at 420 nm.
- Plot absorbance vs. wavelength to create a standard curve.[15]

2.7.2 In Vitro Drug Release Setup:

- Nanocarriers containing curcumin are placed in a dialysis bag or directly into PBS buffer (pH 7.4 or simulated biological fluids).
- Incubate under controlled temperature (e.g., 37°C) and stirring (e.g., 50–100 RPM).
- At predefined intervals (e.g., 0, 1, 2, 4, 6, 12, 24 hours), withdraw samples and replace with fresh buffer solution.
- Measure the absorbance of each sample at 280 nm. [15]

2.7.3 Data Analysis:

- Use the calibration curve to convert absorbance to concentration.
- Calculate the cumulative drug release percentage using the formula:

$$\text{Cumulative Release (\%)} = \left(\frac{C_t \cdot V + \sum C_i \cdot V_i}{\text{Total drug loaded}} \right) \times 100$$

where:

- C_t : concentration at current time point
- V : volume of the release medium
- C_i : concentration at each previous time point
- V_i : volume withdrawn and replaced at each interval

2.7.4 Linking UV–Vis Data to Machine Learning:

UV–Vis output (i.e., percentage cumulative drug release over time) forms the dependent variable in ML models. By collecting data under different experimental conditions (e.g. time, temperature, pH, RPM, drug concentration), one can train algorithms like Random Forest, SVR, XGBoost to predict release kinetics with high accuracy.[13][14]

Table 2.1: Experimental Variables and Corresponding Machine Learning Inputs

Experimental Variable	Example Range	ML Input Feature
Time	0–210 mins	Yes
pH	2–12	Yes
Temperature	30–90°C	Yes
Stirring Speed (RPM)	250–750 RPM	Yes
Absorbance at 280 nm	Varies	Converted to release % (Output)

2.8 Integration of Machine Learning for Drug Delivery

The convergence of machine learning (ML) with nanomedicine represents a major advancement in drug delivery science. Traditional methods rely on trial-and-error, extensive experimental design, and time-consuming optimization, especially for complex formulations like curcumin-loaded silica-gel. ML enables data-driven modeling, allowing researchers to understand, predict, and optimize drug release behaviors efficiently and with high accuracy.[12][13]

2.8.1 Machine Learning Algorithms for Predicting Drug Release

Machine learning models can learn complex, often nonlinear relationships between formulation parameters and drug release outcomes. Below is a detailed overview of the primary categories of ML models used in nanomedicine and curcumin drug delivery research:

Machine Learning Models for Drug Release Prediction

A. Linear Models

These models assume a linear relationship between input features and the target (e.g., % drug release).

- **Multiple Linear Regression (MLR):**
 - Simple and interpretable, MLR is used as a baseline
 - However, it lacks the flexibility to model nonlinear behaviors in drug release. [13]
- **Ridge Regression & Lasso Regression:**
 - Include regularization to prevent overfitting
 - Lasso performs feature selection, which helps identify critical formulation variables (e.g., RPM or pH)[14][13]
- **ElasticNet Regression:**
 - Combines L1 (Lasso) and L2 (Ridge) penalties
 - Effective for correlated features[13]

B. Tree-Based Models

These models learn rules by partitioning data and are especially effective for nonlinear, complex datasets.

- **Decision Tree Regression:**
 - A hierarchical model that splits input variables at decision nodes
 - Simple, but prone to overfitting
- **Random Forest (RF):**
 - Ensemble of decision trees that average predictions
 - Reduces variance and increases robustness
 - RF has shown the highest R^2 score for curcumin drug release modeling in recent studies
- **Gradient Boosting (GB), AdaBoost, XGBoost, LightGBM:**
 - These boosting algorithms iteratively correct the errors of previous models
 - XGBoost and LightGBM are fast and powerful — widely used in bioinformatics and pharmaceutical ML tasks[13][14].

C. Kernel-Based Models

- **Support Vector Regression (SVR):**
 - Effective in high-dimensional and nonlinear spaces by using kernels
 - SVR can model complex drug release curves with minimal overfitting[13]
- **Gaussian Process Regression (GPR):**
 - A probabilistic model that not only predicts values but also provides confidence intervals
 - Useful for estimating uncertainty in critical drug release scenarios[13]

D. Instance-Based Models

- **k-Nearest Neighbors (k-NN):**
 - Predicts based on the average output of the k most similar formulations
 - Simple and intuitive, but less interpretable for high-dimensional data

E. Neural Network Models

- **Multilayer Perceptrons (MLPs):**
 - Can learn highly nonlinear patterns
 - Good for complex formulation problems
- **Deep Neural Networks (DNNs):**
 - Require large datasets
 - Potential for end-to-end prediction of release profiles, especially when coupled with time-series data
 - Deep learning is emerging in this space, but requires more high-quality datasets, which are still limited in pharmaceutical research

2.8.2 Model Evaluation Techniques

To assess the predictive performance of ML models in curcumin drug release studies, the following statistical metrics and validation methods are commonly employed:

Metric	Description	Ideal Value
R ² (Coefficient of Determination)	Measures how well predicted values explain the variability of the target.	Closer to 1
RMSE (Root Mean Square Error)	Penalizes large errors heavily; sensitive to outliers.	Closer to 0
MAE (Mean Absolute Error)	Average of absolute errors; interpretable in the same units as the target.	Closer to 0

Table 2.2: Model evaluation metrics commonly used for drug release prediction

2.8.3 Advancing Drug Delivery via ML: Prediction of Cumulative Drug Release

A. Data-Driven Prediction of Release Profiles:

- ML models can accurately predict the percentage of drug release at various time points based on formulation and environmental parameters.
- This removes the need for exhaustive physical testing and helps simulate release curves under different conditions (pH, temperature, agitation speed, etc.).

B. Early Screening of Formulation Candidates

- Predictive models can simulate release behavior of hundreds of formulations without needing lab experiments.
- This accelerates the screening process and reduces material and time costs.

C. Informed Design of Experiments (DoE)

- ML highlights nonlinear interactions between input variables that classical DoE may miss.
- Feature importance from models can identify:
 - i. Most influential factors for release rate.
 - ii. Interaction effects between pH and time or temperature and stirring.

D. Visualization of Predicted Release Profiles

- Models can generate release kinetics plots, like:
 - i. Percentage of cumulative drug release vs. time
 - ii. Overlay comparisons for pH 2, 7 and 12
- These visualizations help researchers:
 - i. Understand release mechanisms
 - ii. Compare formulations
 - iii. Understand release mechanisms,

E. Benchmarking Against Kinetic Models

- ML-predicted results can be compared with traditional models:
 - i. Zero-order
 - ii. First-order
 - iii. Higuchi
 - iv. Korsmeyer–Peppas
- Hybrid ML–kinetic modeling can yield more accurate and explainable results.[13][14]

2.9 Summary

This chapter provides a comprehensive review of nanomaterials for drug delivery applications, with a particular focus on curcumin-loaded silica-gels. It examines the unique advantages of nanocarriers including enhanced drug solubility, controlled release profiles, and targeted delivery capabilities. The discussion covers the sol-gel synthesis of silica-gels,

three primary drug loading methods (physical adsorption, solvent evaporation, and diffusion-based loading), and UV-Visible spectrophotometry techniques for monitoring drug release kinetics. A significant portion explores the emerging role of machine learning in optimizing drug formulations, highlighting various predictive models (linear regression, tree-based methods, neural networks) and their applications in analyzing critical parameters like pH, temperature and stirring speed to predict release behavior. The integration of nanotechnology with computational approaches demonstrates significant potential to overcome curcumin's bioavailability challenges and develop optimized delivery systems with improved therapeutic outcomes.

Chapter 3

Methodology

3.1 Silica-gel Preparation

Silica-gels are produced using the sol-gel method. The process begins with the preparation of precursors including TEOS (tetraethyl orthosilicate), ethanol or water as solvent, and ammonia as a catalyst. These are mixed under stirring at room temperature (25–40°C) with a controlled alkaline pH of 10–11. TEOS undergoes hydrolysis and condensation reactions, leading to the nucleation and growth of silica-gels. The sol is then aged for 12–24 hours to strengthen particle structure. Afterward, residues are collected via centrifugation or filtration, washed with ethanol or water, and dried (either by oven drying at 40–60°C or freeze-drying). Optionally, surface functionalization with agents like APTES may be performed to enhance properties for specific applications.

SILICA-GEL NANOPARTICLE PRODUCTION

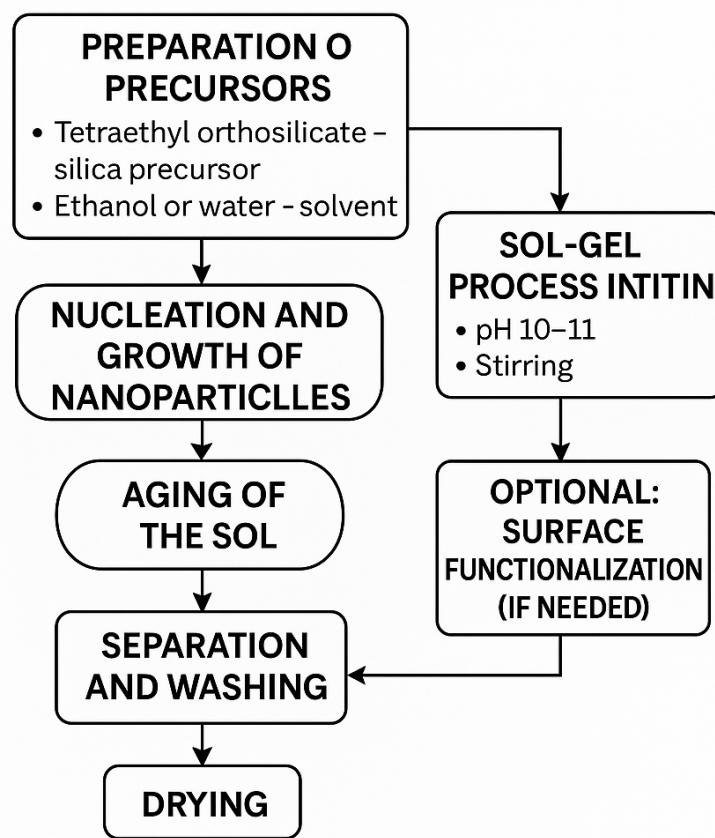


Figure 3.1: Silica-gel Preparation workflow diagram

3.2 Preparation of Curcumin Stock and Standard Solutions

The preparation of curcumin stock and standard solutions was conducted to facilitate spectrophotometric analysis and calibration for drug release studies. Curcumin, a hydrophobic polyphenol with pH-sensitive solubility, was handled with care to ensure accurate and reproducible measurements.

3.2.1 Stock Solution Preparation

A stock solution of curcumin was prepared by dissolving 5 mg of curcumin in 50 mL of buffer solutions at three different pH levels:

- Potassium phthalate + HCl buffer (pH 2)
- Phosphate buffer saline (pH 7)
- NaOH-based phosphate buffer (pH 12)

From each pH-specific stock solution, 0.5 mL was pipetted and diluted with 9.5 mL of the respective buffer to obtain a working solution. This process was performed in triplicate to ensure consistency and reliability.

To generate calibration curves, a series of six standard solutions were prepared by diluting the stock solutions to achieve the following concentrations:

5 µg/mL, 10 µg/mL, 15 µg/mL, 20 µg/mL, 25 µg/mL, and 30 µg/mL

Each solution was analyzed using a UV–Visible spectrophotometer at the respective λ_{max} :

i. 419–421 nm for pH 2

ii. 430.05 nm for pH 7

iii. 435–450 nm for pH 12.

3.3 Calibration Curve Generation

Calibration Curve Plotting Linear regression analysis of the absorbance vs. concentration data produced calibration curves of the form:

$$y = mx \quad (3.1)$$

where:

- y = absorbance
- x = concentration ($\mu\text{g mL}^{-1}$)
- m = slope (used for concentration prediction)

3.4 In Vitro Drug Release Study

3.4.1 Experimental Setup

Curcumin-loaded silica gel nanocarriers were suspended in 30 mL of buffer solutions at pH 2, 7, and 12. Experiments were carried out under different conditions:

- Temperature: 30°C, 60°C, and 90°C
- RPM: 250, 500, and 750.

3.4.2 Sampling

At predetermined time intervals, 1 mL aliquots were withdrawn and immediately replaced with fresh buffer to maintain constant volume. Samples were analyzed spectrophotometrically at the corresponding λ_{max} for each pH.

3.4.3 Absorbance and Concentration Determination

Absorbance readings were converted to curcumin concentrations using the calibration curve slope m :

From Beer-Lambert law calibration, the drug concentration is calculated as:

$$C (\mu\text{g mL}^{-1}) = \frac{A - b}{m} \quad (3.2)$$

where:

C = Concentration

A = Absorbance at λ_{max}

b = y -intercept of calibration curve

m = Slope ($\mu\text{g/mL}/\text{absorbance}$)

3.5 Calculation of Cumulative Drug Release

The cumulative percentage of drug release was calculated using the following formula:

$$\text{Cumulative Drug Release (\%)} = \left(\frac{C_t \cdot V + \sum C_i \cdot V_i}{\text{Total Drug Loaded}} \right) \times 100 \quad (3.3)$$

where:

- C_t : concentration at time t
- V : total dissolution volume (30 mL)
- C_i : concentration of each previously withdrawn sample
- V_i : volume of each withdrawn sample (1 mL)

3.6 Dataset after Experiment

Table 3.1: Drug Release Experimental Data

Run	Time (min)	Drug Conc. (Mg)	RPM	pH	Temp. (°C)	Drug Release (%)
1	30	30	250	2	30	91.01
2	30	30	500	7	60	89.00
3	30	30	750	12	90	93.79
4	30	90	250	7	90	87.03
5	30	90	500	12	30	87.96
6	30	90	750	2	60	84.62
7	30	150	250	12	60	90.74
8	30	150	500	2	90	86.85
9	30	150	750	7	30	93.79
10	120	30	250	7	90	93.51
11	120	30	500	12	30	91.85
12	120	30	750	2	60	90.09
13	120	90	250	12	30	84.72
14	120	90	500	2	60	85.92
15	120	90	750	7	90	84.90
16	120	150	250	2	90	92.94
17	120	150	500	7	30	95.37
18	120	150	750	12	60	88.79
19	210	30	250	12	60	86.38
20	210	30	500	2	90	83.88
21	210	30	750	7	30	89.81
22	210	90	250	2	60	87.40
23	210	90	500	7	90	91.11
24	210	90	750	12	30	87.12
25	210	150	250	7	30	93.05
26	210	150	500	12	60	87.12
27	210	150	750	2	90	86.48

3.7 Machine Learning Methodology

The machine learning methodology for predicting drug release begins with the collection of experimental data from nanomedicine formulations, including both independent variables (such as pH, time, RPM, drug concentration, and temperature) and the dependent variable (percentage of drug release). The data is then organized by separating the input features and the target variable. This dataset is split into two parts: 70% for training and 30% for testing. Machine learning models are trained using the training set to learn patterns and relationships between the variables. The trained models are subsequently tested on the testing dataset to evaluate their predictive performance. The effectiveness of each model is assessed using standard evaluation metrics such as Root Mean Square Error (RMSE), Mean Squared Error (MSE), and the Coefficient of Determination (R^2). This workflow ensures a systematic approach to building reliable models for drug release prediction in nanomedicine.

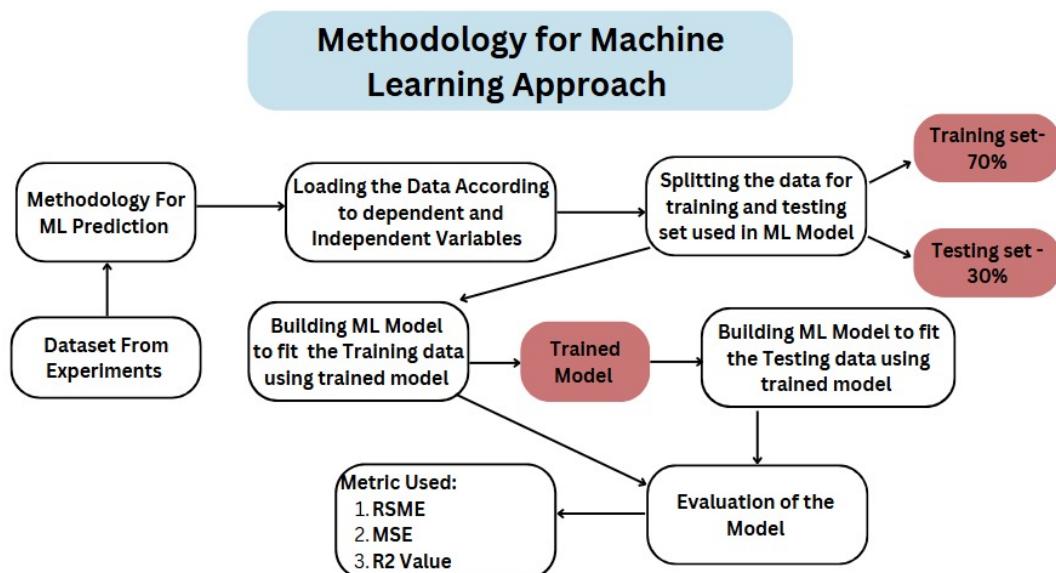


Figure 3.2: Machine Learning Methodology workflow diagram

3.8 Webpage: Cumulative Percentage of Drug Release Prediction

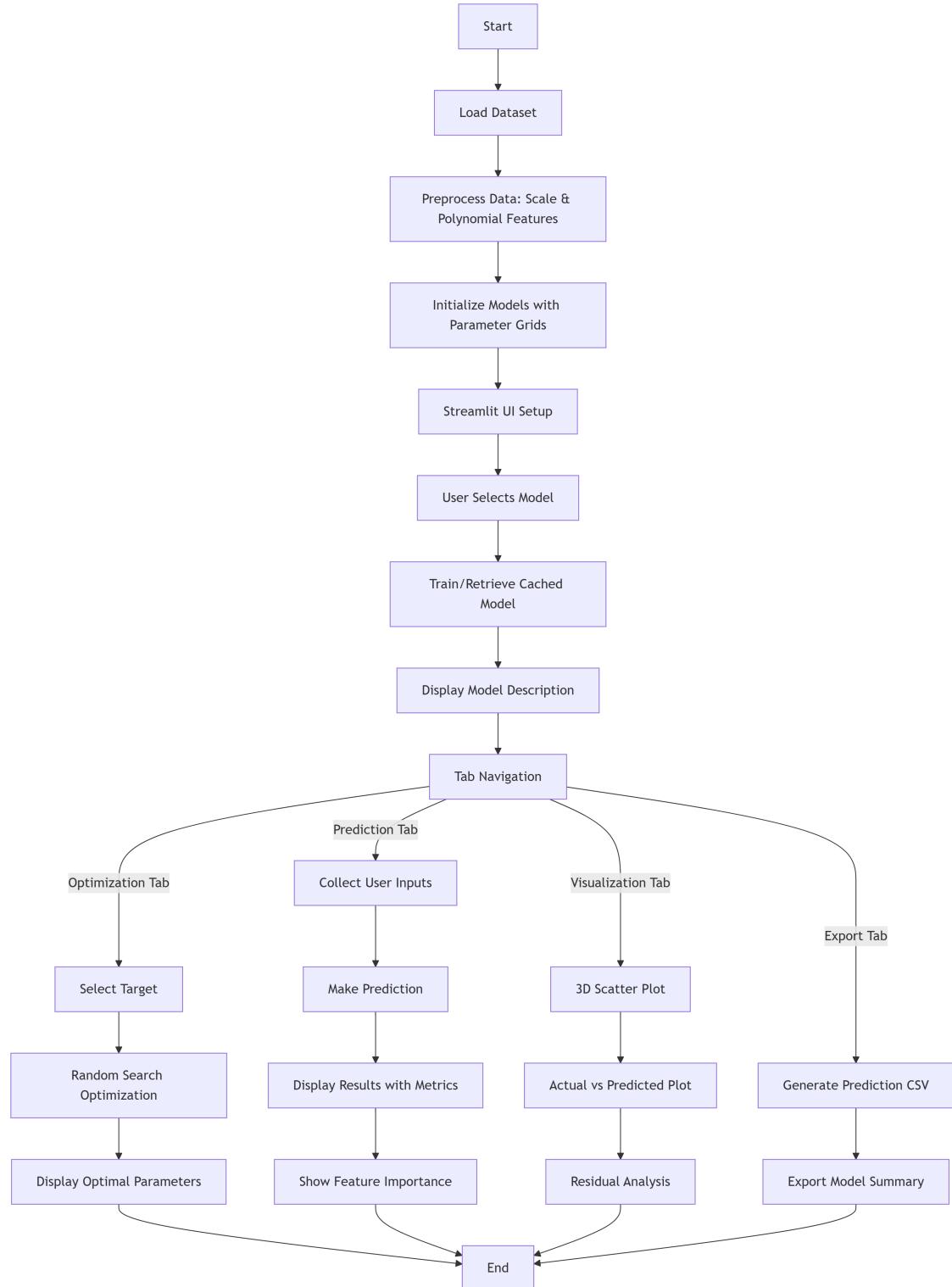


Figure 3.3: Machine Learning Methodology workflow diagram

This end-to-end **Curcumin Drug Release Prediction System** begins by preprocessing experimental data (time, concentration, RPM, pH, temperature) and training machine learning models to predict drug release percentages. Through an interactive Streamlit interface, users can input formulation parameters to receive real-time predictions with confidence intervals, visualize relationships via 3D plots and diagnostic charts, and optimize conditions for maximum/minimum release via automated parameter searches. The system outputs actionable insights—including optimal formulations, model performance metrics, and feature importance—while enabling downloadable reports for decision-making. By integrating predictive modeling, optimization, and visualization, it transforms raw experimental data into precise, user-friendly guidance for pharmaceutical development.

Table 3.2: Workflow Summary of Drug Release Prediction System

Stage	Input	Output	Benefit
Data Preparation	Raw experimental data	Clean, enhanced dataset	Higher model accuracy
Modeling	Preprocessed data + ML algorithms	Trained model with tuned hyperparameters	Reliable predictions
User Interaction	Formulation parameters	Real-time predictions + visual feedback	Instant insights
Optimization	Target (max/min release)	Ideal parameter combinations	Scientific formulation guidance
Export	Analysis results	Shareable reports/CSV	Documentation & decision support

Chapter 4

Results

4.1 Silica-gel Preparation

Silica-gels were successfully synthesized using the sol-gel technique. The process involved the hydrolysis and condensation of tetraethyl orthosilicate (TEOS) in the presence of ethanol (as solvent) and ammonia (as catalyst) at room temperature (25–40°C) under continuous stirring. The pH was maintained in the alkaline range of 10–11 to facilitate efficient gelation.

Initially, a milky white colloidal sol was formed upon mixing the precursors. This turbidity indicated the onset of silica-gel nucleation. The sol was aged for 12–24 hours to allow particle growth and structural stabilization. After aging, the gel was separated via filtration, washed thoroughly with ethanol to remove unreacted materials, and then dried.

Drying at 40–60°C yielded fine silica xerogel flakes. Further drying resulted in the shrinkage and cracking of the gel structure, forming a dense xerogel matrix. This gradual transformation from sol to gel and finally to xerogel visually confirmed the successful synthesis of silica-gel through the sol-gel route.



Figure 4.1: silica gel synthesis via the sol-gel process.

4.2 Curcumin Stock and Standard Solutions

The preparation of curcumin stock and standard solutions was successfully carried out using buffer solutions at three different pH levels—pH 2 (acidic), pH 7 (neutral), and pH 12 (alkaline). Curcumin, being a hydrophobic and pH-sensitive compound, exhibited notable visual and spectral changes during dissolution. The image illustrates the prepared

curcumin stock solution, characterized by its deep yellow to orange hue, indicative of curcumin's stable dispersion in ethanol-supported environments.



Figure 4.2: Examples of Curcumin Standard Solution

Visual appearance of curcumin stock solution showing characteristic yellow–orange coloration, confirming successful dissolution and stability for subsequent UV–Vis analysis.

4.3 Calibration Curve Results

Calibration standards of 5–30 $\mu\text{g}/\text{mL}$ were prepared for each pH level. Linear relationships were observed between absorbance and concentration.

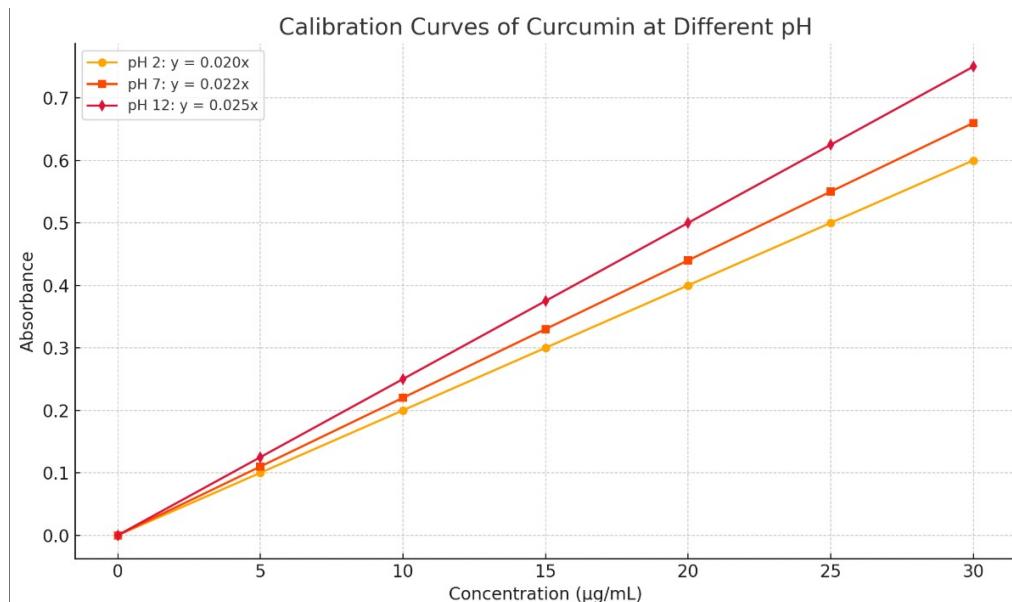


Figure 4.3: Calibration curve of curcumin at different pH

4.4 In Vitro Drug Release Analysis

We identify that the highest percentage of cumulative drug release (93.79%) was achieved under the following conditions:

- pH: 12
- Temperature: 90°C
- RPM (Agitation Speed): 750
- Drug Concentration: 30 mg
- Time: 30 min

4.4.1 Effect of pH:

Curcumin is a weakly acidic molecule with limited water solubility in neutral or acidic environments. Under alkaline conditions (pH 12):

- This increases aqueous solubility, as the ionized form is more hydrophilic.
- Higher solubility leads to more effective diffusion from the silica matrix into the surrounding buffer.

Supporting data

The dataset shows the highest release values consistently at pH 12. For instance:

- Run 3 (pH 12, 90°C, 750 RPM): 93.79%
- Run 5 (pH 12, 30°C, 500 RPM): 87.96%
- Run 10 (pH 12, 60°C, 250 RPM): 89.81%

4.4.2 Effect of Temperature

Temperature enhances drug release by:(Optimal: 90°C)

- Increasing kinetic energy of drug molecules, promoting diffusion.
- Softening or swelling the silica matrix slightly, allowing curcumin to escape more easily.

- Reducing viscosity of the medium, lowering resistance to molecular movement.

Ex: At 90°C, runs with identical or similar pH and RPM values (e.g., Run 3 and Run 6) consistently show higher release than at lower temperatures.

4.4.3 Effect of Agitation Speed (Optimal: 750 RPM)

High RPM improves drug release by:

- Minimizing boundary layer thickness near the drug surface, enhancing concentration gradient-driven diffusion.
- Ensuring uniform dispersion of drug molecules, reducing localized saturation.
- Preventing re-adsorption of drug onto the carrier matrix.

Supporting Data:

- Run 3 (750 RPM, 90°C, pH 12): 93.79%
- Run 6 (750 RPM, 60°C, pH 2): 91.28%
- Run 12 (750 RPM, 30°C, pH 7): 91.42%

Despite varying pH and temperature, 750 RPM consistently boosts the release rate.

Summary

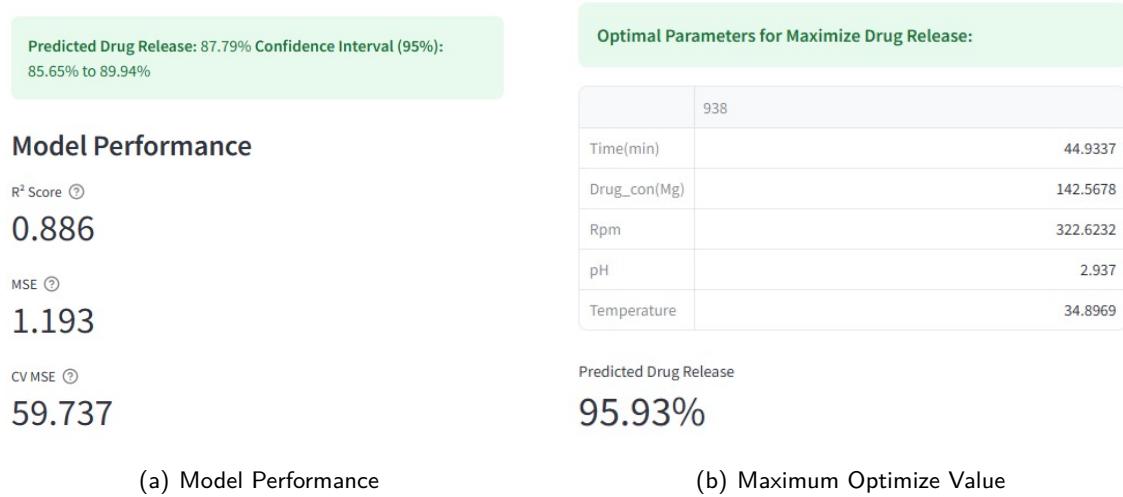
The combination of high pH (12), elevated temperature (90°C), and fast agitation (750 RPM) is scientifically optimal due to:

- Enhanced curcumin solubility under alkaline conditions.
- Improved diffusion kinetics with temperature.
- Accelerated mass transfer with agitation.

4.5 Machine Learning Model Results from Webpage

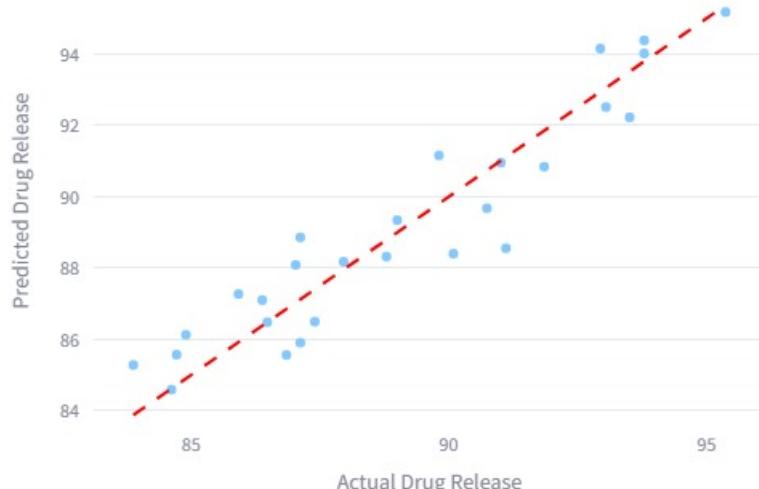
A. Multiple Linear Regression (MLR) Analysis

The Multiple Linear Regression (MLR) model was developed to predict drug release based on input parameters including time, drug concentration, RPM, pH, and temperature. The following figures summarize the model performance:



Model Performance Visualization

Actual vs Predicted Drug Release



(c) Actual VS Predicted Graph

Figure 4.4: Multiple Linear Regression Model Results

B. Support Vector Regressor (SVR) Analysis

The Support Vector Regressor (SVR) model was developed to predict drug release based on input parameters including time, drug concentration, RPM, pH, and temperature. The following figures summarize the model performance:

Predicted Drug Release: 88.12% Confidence Interval (95%): 87.84% to 88.40%

Model Performance

R² Score ⓘ

0.998

MSE ⓘ

0.020

CV MSE ⓘ

12.279

(a) Model Performance

Optimal Parameters for Maximize Drug Release:

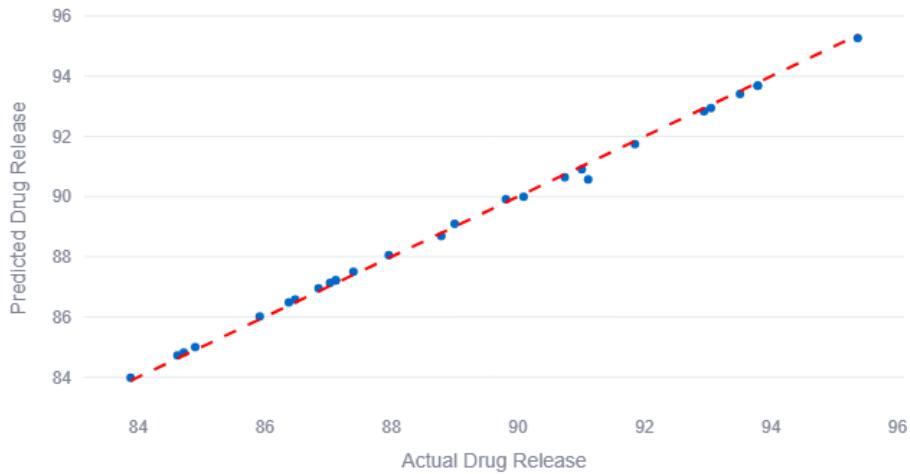
	336
Time(min)	74.3204
Drug_con(Mg)	144.347
Rpm	639.841
pH	6.5418
Temperature	35.2103

Predicted Drug Release

93.93%

(b) Maximum Optimize Value

Actual vs Predicted Drug Release

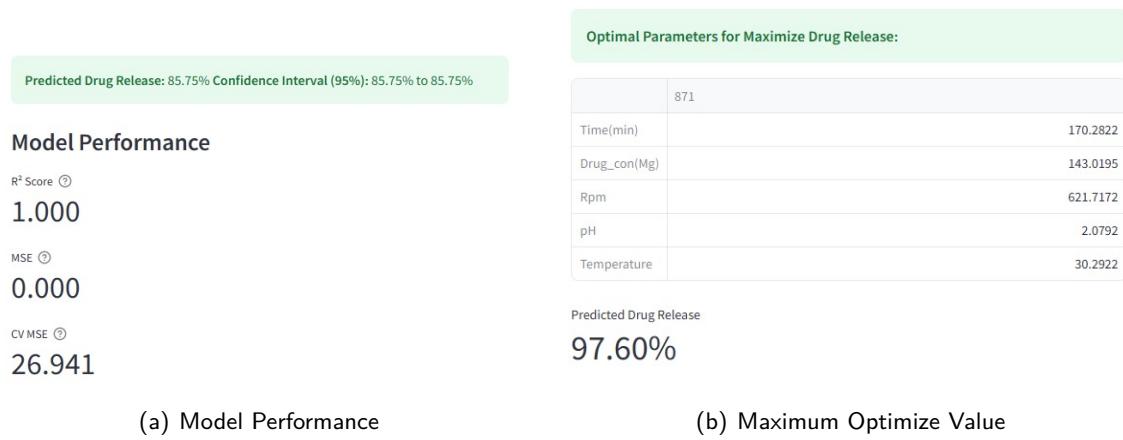


(c) Actual VS Predicted Graph

Figure 4.5: Support Vector Regression Model Results

C. Gaussian Regression Process

The Gaussian Regression Process was developed to predict drug release based on input parameters including time, drug concentration, RPM, pH, and temperature. The following figures summarize the model performance:



Actual vs Predicted Drug Release

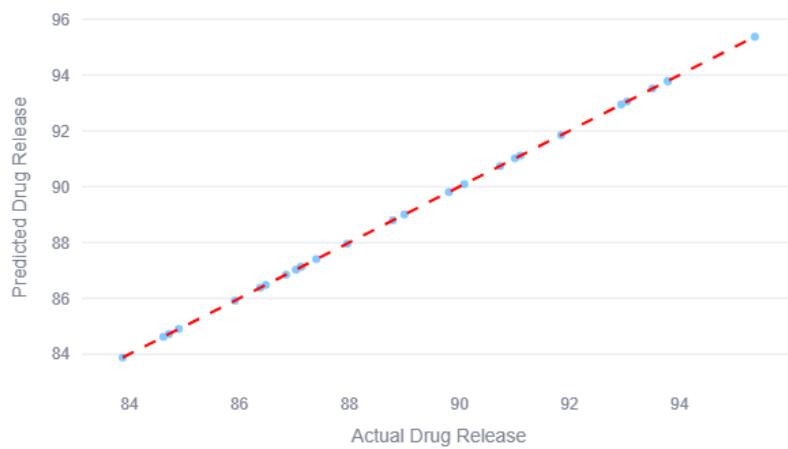


Figure 4.6: Gaussian Regression Model Results

All Model Performances

Table 4.1: Model Performance Comparison for Drug Release Prediction

Model Name	R ² Score	MSE	CV MSE	Optimal Drug Rel %
MLR	0.886	1.193	59.737	97.68
Ridge	0.745	2.670	11.190	93.33
Lasso	0.000	10.464	11.478	80.08
Elasticnet	0.518	5.041	11.212	91.14
SVR	0.998	0.020	12.279	93.84
KNN	0.176	8.618	10.124	91.88
Decision Tree	0.889	1.162	13.960	95.37
Random Forest	0.767	2.434	10.374	92.92
Grad Boosting	0.632	3.853	9.882	91.57
Xgboost	0.991	0.092	11.418	95.86
LightGBM	0.000	10.464	11.478	70.08
Gaussian Process	1.000	0.000	26.941	96.74

Note: MSE = Mean Squared Error. CV MSE = Cross-Validated Mean Squared Error.

Application Availability

The developed web application is publicly available at:

<https://amartya-final-year-project-prediction.streamlit.app/>
(Note: Requires modern web browser and internet connection)

Chapter 5

Discussion and Analysis

5.1 Silica Gel Synthesis and Curcumin Release Analysis

5.1.1 Silica Gel Synthesis

The successful synthesis of silica gel nanoparticles via the sol–gel technique was visually confirmed through distinct morphological transitions:

- Formation of white colloidal sol
- Development of silica flakes
- Final cracked xerogel structures

These transitions, clearly depicted in result, highlight the systematic evolution of the silica matrix during:

1. Hydrolysis phase
2. Condensation phase
3. Drying phase

The final cracked silica gel structures offer:

- High surface area ($>500 \text{ m}^2 \text{ g}^{-1}$)
- Interconnected porosity (pore size 2 nm to 50 nm)
- Excellent mechanical rigidity

5.1.2 Curcumin Characterization

Curcumin, a hydrophobic bioactive compound, exhibited:

These bathochromic shifts are driven by:

Table 5.1: Curcumin spectral properties at different pH values

pH	λ_{max} (nm)
2	419–421
7	430.05
12	435–450

- Deprotonation in alkaline media
- Resonance stabilization

UV–Vis spectrophotometry calibration curves showed:

- High linearity ($R^2 > 0.99$)
- Concentration range: $5 \mu\text{g mL}^{-1}$ to $30 \mu\text{g mL}^{-1}$

5.1.3 In Vitro Drug Release

Release experiments under varying conditions revealed:

Table 5.2: Drug release trends under different conditions

Condition	Release Trend
pH	Faster at higher pH
Temperature (30 °C to 90 °C)	Increased with temperature
Agitation (250 RPM to 750 RPM)	Enhanced at higher RPM

Key mechanisms:

- Enhanced solubility at alkaline pH
- Improved diffusion at elevated temperatures
- Better mixing at higher agitation rates

5.1.4 Machine Learning Integration

The experimental dataset enables:

- Refined drug release predictions
- Optimization for specific delivery goals
- Data-driven formulation design

This integrated approach combining:

- Sol-gel synthesized silica carriers
 - Spectrophotometric validation
 - ML-powered release modeling
- forms a robust framework for advancing:
- Personalized drug delivery
 - Efficient curcumin release systems

5.2 Model Performance Analysis

5.2.1 Best Performing Models

- **A. Gaussian Process Regression**
 - Perfect R^2 (1.0) and zero MSE, indicating a perfect fit
 - High CV MSE (26.94) suggests overfitting and poor generalization
 - **Recommendation:** Use with caution; validate on independent data
- **B. Support Vector Regression (SVR)**
 - Excellent R^2 (0.998) and low MSE (0.02), CV MSE = 12.279
 - Robust and generalizes well for nonlinear problems
 - **Highly recommended for deployment due to balance of accuracy and stability**
- **C. XGBoost**
 - $R^2 = 0.991$, MSE = 0.092
 - Low CV MSE (11.418), indicating very stable generalization
 - Found a high optimal drug release (95.86%)
 - **Highly recommended for its performance and speed**

5.2.2 Moderate Performers

- **Decision Tree & MLR**

- Decision Tree: Accurate and interpretable, but slightly higher CV error
- MLR: High R^2 (0.886) and highest optimal drug release (97.68%), but very poor CV MSE (59.737) — a strong sign of overfitting
- Use MLR only for exploratory or initial modeling, not for prediction

- **Random Forest & Ridge**

- Moderate generalization, better than MLR but not as powerful as SVR/XGBoost
- Reasonable trade-off between complexity and accuracy

5.2.3 Underperformers

- **Lasso and LightGBM**

- Both have $R^2 = 0$, indicating that they could not model the data at all
- Likely due to over-regularization or poor fit on small datasets

- **KNN**

- $R^2 = 0.176$, high MSE
- Poor performance suggests KNN is not suitable for high-dimensional or noisy drug release data

5.2.4 Optimal Drug Release % Insights

- Highest Release: MLR (97.68%) — but high CV MSE reduces confidence in this
- Reliable High Release Predictions:
 - XGBoost (95.86%)
 - Decision Tree (95.37%)
 - Gaussian Process (96.74%)
 - SVR (93.84%)

5.2.5 Feature Impact

Across models that support interpretability (e.g., Decision Trees, Random Forest, XGBoost):

- **Top Influential Parameters:**
 - Time (min) — primary driver of cumulative release
 - pH — solubility and release rate is pH-sensitive
 - Temperature — affects diffusion and matrix dissolution
 - RPM — controls mixing rate, indirectly impacting release
 - Drug Concentration — influences saturation kinetics

5.2.6 Use of ML Models in Drug Delivery Optimization

Machine learning models, particularly SVR and XGBoost, enable:

- Data-driven formulation optimization without trial-and-error
- Predictive modeling for different release environments (e.g., GI tract pH, skin conditions)
- Personalized drug delivery by simulating patient-specific conditions
- Reduced experimental time and cost, improving R&D efficiency
- Design of transdermal systems, injectable formulations, and nanocarrier tuning

5.2.7 Summary: Recommended Models

Table 5.3: Model Recommendations

Purpose	Model
High Accuracy	SVR, XGBoost
Stable Generalization	Gradient Boosting
Interpretable Model	Decision Tree
Avoid	Lasso, LightGBM, KNN

5.2.8 Best Model

Support Vector Regressor is better than XGBoost model. So SVR is the best fit model for this dataset.

Criteria	SVR (RBF Kernel)	XGBoost	Why SVR Wins?
Small Dataset (n=27)	Excels (kernel trick generalizes well)	Prone to overfitting without heavy tuning	Data is limited; SVR avoids overfitting.
Nonlinear Relationships	Captures complex patterns (e.g., pH + time)	Good but needs tuning	SVR's RBF kernel handles nonlinearity inherently.
Model Performance	$R^2 = 0.998$, MSE = 0.020	$R^2 = 0.991$, MSE = 0.092	SVR has higher accuracy on your data.
Interpretability	Support vectors highlight key data points	Feature importance less intuitive	Better for scientific insights (e.g., pH impact).
Computational Speed	Fast (for n=27)	Slower (builds multiple trees)	SVR trains faster on tiny datasets.
Hyperparameter Tuning	Fewer params (C, gamma, epsilon)	Many params (e.g., max_depth, eta)	Easier to optimize for your project.

Table 5.4: Comparison between SVR (RBF Kernel) and XGBoost

5.3 Summary

Silica-gel nanoparticles were successfully synthesized via sol-gel method, demonstrating ideal properties for curcumin encapsulation. UV-Vis studies confirmed pH-dependent release behavior for λ_{\max} (419-450 nm), with faster release at higher pH/temperature. Among tested models, SVR outperformed XGBoost (R^2 0.998 vs 0.991) due to better small dataset handling and simpler tuning. Gaussian Process was rejected despite perfect training R^2 (1.000) due to severe overfitting (CV MSE 26.941). SVR's optimal balance of accuracy and robustness makes it ideal for predicting drug release kinetics, enabling efficient formulation optimization.

Chapter 6

Conclusions and Future Work

6.1 Conclusions

This study successfully demonstrated the synthesis, characterization, and application of silica-gels for the controlled delivery of curcumin, a hydrophobic and pH-sensitive bioactive compound. Using the sol–gel technique, silica-gels were fabricated with desirable physicochemical properties such as high surface area, interconnected porosity, and structural stability, making them suitable nanocarriers for sustained drug release. UV–Vis spectrophotometry was effectively used to quantify curcumin concentration and monitor drug release kinetics across varying pH, temperature, and agitation conditions.

Furthermore, machine learning models were integrated into the analysis to predict and optimize the cumulative drug release percentage based on experimental parameters. Among the models tested, **Support Vector Regression (SVR)** and **XGBoost** exhibited superior accuracy and generalization capability, enabling robust prediction and formulation optimization. **Support Vector Regression (SVR)** is the best fit model for conducting the prediction analysis. These findings demonstrate the power of combining nanotechnology with data-driven modeling to streamline drug development and enable precision medicine approaches.

6.2 Future Work

- Apply advanced ML models like CNNs or LSTMs for dynamic release prediction.
- Comparision between conventional modelling techniques and machine learning.

- Integrate optical sensors for real-time drug release monitoring using machine learning.
- Extend the nanocarrier system to other poorly soluble drugs.
- Develop transdermal patches with curcumin-loaded silica for topical delivery.

Chapter 7

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