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# Predictive Intelligence for Drug Release Behavior Across Advanced Controlled Delivery Platforms

**Harish Asifiqbal Jardawala[1], Nirav chandravadanbhai kansara[2], Khant shilpaben kishorsinh[3], Vijay Bharatbhai vasaiya[4], Akshar Hiteshbhai Brahmbhatt[5], Mande Ashmita Sunil[6]**

[1]Assistant Professor, Department of Computer Engineering, Parul Polytechnic Institute, Parul University.
Email : harishjarda23@gmail.com
[2]Assistant Professor, Department of Computer Engineering, Parul Polytechnic Institute, Parul University.
Email : kansara.nirav1234@gmail.com
[3]Assistant Professor, Department of Computer Engineering, Parul Polytechnic Institute, Parul University.
Email : khantshilpa7027@gmail.com
[4]Assistant Professor, Department of Computer Engineering, Parul Polytechnic Institute, Parul University.
Email : vizvasaiya5@gmail.com
[5]Assistant Professor, Department of Computer Engineering, Parul Polytechnic Institute, Parul University.
Email : aksharbrahmbhatt862@gmail.com
[6]Assistant Professor, Department of Computer Engineering, Parul Polytechnic Institute, Parul University.
Email : mandeashmita11@gmail.com

**Abstract**
The precise control and prediction of drug release kinetics remains a fundamental challenge in the design and optimization of controlled drug delivery systems. Conventional empirical and mechanistic modeling approaches, while informative, are often limited by their inability to capture the complex, nonlinear interactions among formulation variables, polymer matrices, and physiological conditions. This study presents a machine learning (ML)-based predictive intelligence framework capable of accurately forecasting drug release behavior across a diverse range of advanced controlled delivery platforms, including hydrogels, nanoparticles, microspheres, and polymeric implants.
A comprehensive dataset encompassing physicochemical drug properties, carrier material characteristics, processing parameters, and in vitro release profiles was curated and employed to train and validate multiple ML algorithms, including Random Forest, Gradient Boosting, Support Vector Regression, and Artificial Neural Networks. Feature importance analysis revealed that polymer molecular weight, drug-polymer interaction parameters, particle size distribution, and pH conditions were among the most influential determinants of release kinetics. The optimized ML models demonstrated superior predictive accuracy, achieving $R^2$ values exceeding 0.95 and significantly outperforming traditional mathematical models such as Korsmeyer-Peppas and Higuchi.
Furthermore, the proposed framework enables rapid in silico screening of formulation candidates, substantially reducing experimental burden and accelerating the development pipeline. This work underscores the transformative potential of predictive intelligence in pharmaceutical sciences, offering a robust, data-driven strategy for the rational design of next-generation controlled drug delivery systems.
**Keywords**: Drug release, Machine Learning, Drug Release Kinetics, Controlled Drug Delivery, Predictive Modeling, Formulation Optimization, Nanoparticles, Polymer Matrix
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## INTRODUCTION

The development of controlled drug delivery systems (CDDS) has revolutionized modern pharmacotherapy by enabling the sustained, targeted, and programmable release of therapeutic agents at predefined rates and sites of action. Unlike conventional dosage forms, advanced delivery platforms — encompassing polymeric nanoparticles, hydrogels, microspheres, liposomes, and implantable devices — offer significant clinical advantages, including reduced dosing frequency, minimized systemic side effects, improved patient compliance, and enhanced therapeutic efficacy. Despite these remarkable advances, the rational design and optimization of such systems remain inherently complex, owing to the multifaceted interplay among drug physicochemical properties, carrier material characteristics, manufacturing parameters, and the dynamic physiological microenvironment. Drug release kinetics, which describes the rate and mechanism by which an active pharmaceutical ingredient (API) is liberated from its delivery matrix, serves as a critical quality attribute governing the overall therapeutic performance of a controlled delivery platform. Traditionally,

drug release behavior has been described using mathematical models such as the zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models. While these mechanistic frameworks provide valuable mechanistic insights, they are often constrained by oversimplified assumptions, limited generalizability across diverse formulation types, and an inability to account for the high-dimensional, nonlinear relationships that govern real-world drug release phenomena.

In recent years, the advent of artificial intelligence (AI) and machine learning (ML) has opened transformative new avenues for predictive modeling in pharmaceutical sciences. By leveraging large, multidimensional datasets, ML algorithms are capable of identifying complex patterns and nonlinear dependencies that are beyond the reach of conventional statistical and mechanistic approaches. Techniques such as Random Forest, Gradient Boosting Machines, Support Vector Regression, and Deep Neural Networks have demonstrated remarkable success across a spectrum of pharmaceutical applications, including drug solubility prediction, formulation optimization, toxicity screening, and pharmacokinetic modeling.

However, the systematic application of ML methodologies to predict drug release kinetics across diverse and advanced controlled delivery platforms remains insufficiently explored. Most existing studies are narrowly focused on specific drug-polymer combinations or single delivery system archetypes, limiting their broader applicability and translational relevance. There exists, therefore, a compelling need for a unified, data-driven predictive intelligence framework capable of generalizing across multiple delivery platform types, drug classes, and experimental conditions.

The present work addresses this gap by developing and validating a comprehensive ML-based predictive model for drug release behavior across a wide array of advanced controlled delivery platforms. By integrating diverse formulation descriptors, material properties, and process parameters into a robust modeling pipeline, this study aims to establish a reliable, scalable, and interpretable framework that can accelerate formulation development, reduce experimental workload, and ultimately contribute to the rational design of next-generation drug delivery systems.

## LITERATURE REVIEW

### 2.1 Evolution of Controlled Drug Delivery Systems

The concept of controlled drug delivery has evolved significantly over the past five decades, transitioning from simple sustained-release oral tablets to sophisticated nanotechnology-based platforms capable of site-specific and stimuli-responsive drug liberation. Early contributions by Langer and Folkman (1976) demonstrated the feasibility of sustained macromolecule release from polymeric matrices, laying the groundwork for an entirely new field of pharmaceutical engineering. Subsequently, the development of biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and chitosan enabled the fabrication of biocompatible nanoparticles, microspheres, and implants with tunable degradation and release profiles. Today, advanced delivery platforms encompass a broad spectrum of architectures, including stimuli-responsive hydrogels, lipid-based nanocarriers, dendrimers, and electrospun nanofiber scaffolds, each presenting unique release mechanisms and kinetic behaviors.

### 2.2 Mathematical Modeling of Drug Release Kinetics

The quantitative description of drug release kinetics has historically relied on a series of empirical and semi-mechanistic mathematical models. The zero-order model describes systems wherein drug release proceeds at a constant rate independent of drug concentration, while the first-order model accounts for concentration-dependent release phenomena. The Higuchi model, originally developed for matrix systems, relates cumulative drug release to the square root of time, reflecting diffusion-controlled mechanisms. The Korsmeyer-Peppas power law model has been widely adopted to elucidate the dominant release mechanism — Fickian diffusion, anomalous transport, or Case-II relaxation — through the exponent n. More recently, the Weibull, Hopfenberg, and Peppas-Sahlin models have been proposed to capture more complex, multiphasic release profiles. Despite their widespread utility, these models are inherently limited by their reliance on idealized geometric assumptions, single-mechanism frameworks, and the inability to simultaneously accommodate the influence of multiple formulation and process variables.

### 2.3 Machine Learning in Pharmaceutical Sciences

The integration of machine learning into pharmaceutical research has gained substantial momentum over the past decade, driven by the exponential growth of experimental data, advances in computational infrastructure, and the development of powerful open-source ML libraries. Supervised learning algorithms, including Random Forest (RF), Gradient Boosting Machines (GBM), Support Vector Machines (SVM), and Artificial Neural Networks (ANN), have been successfully applied to diverse pharmaceutical challenges. Lusci et al. (2013) demonstrated the utility of deep learning for aqueous solubility prediction, while Reker et al. (2015) employed active learning strategies to optimize drug-target interaction screening. In the domain of formulation science, Aksu et al. (2012) utilized artificial neural networks to optimize tablet formulations, and Pereira et al. (2020) applied ML models to predict nanoparticle size and encapsulation efficiency. These studies collectively underscore the capacity of ML to uncover hidden structure-property relationships within high-dimensional pharmaceutical datasets.

### 2.4 Machine Learning for Drug Release Prediction

Despite the broader success of ML in pharmaceutical sciences, its application to drug release kinetics prediction remains a relatively nascent and fragmented area of investigation. pioneering work by Goh et al. (2019) demonstrated that artificial neural networks could accurately predict in vitro drug release profiles from polymeric microspheres based on formulation composition and process parameters. Similarly, Medarević et al. (2020) employed ML algorithms to model drug release from immediate-release

tablets, identifying critical material attributes influencing dissolution behavior. More recently, deep learning architectures, including Long Short-Term Memory (LSTM) networks and Convolutional Neural Networks (CNNs), have been explored for the prediction of time-series drug release profiles, offering improved capacity to capture temporal dynamics. However, the majority of existing ML-based studies are constrained to narrow drug-polymer combinations, single delivery platform types, or limited dataset sizes, restricting their generalizability and translational applicability across the broader landscape of controlled drug delivery.

### 2.5 Research Gaps and Motivation

A critical review of the existing literature reveals several important gaps that motivate the present study. First, there is an absence of unified ML frameworks capable of predicting drug release behavior across heterogeneous delivery platforms, including nanoparticles, hydrogels, microspheres, and implants, within a single modeling architecture. Second, the systematic evaluation and comparison of multiple ML algorithms for drug release prediction — coupled with rigorous feature importance analysis — remains underexplored. Third, the interpretability of ML models in this context, a crucial prerequisite for regulatory acceptance and mechanistic understanding, has received limited attention. The present study is designed to address these gaps by developing a comprehensive, interpretable, and generalizable ML-based predictive framework for drug release kinetics across advanced controlled delivery platforms.

## METHOD

### 3.1 Dataset Collection and Curation

A comprehensive dataset was assembled from peer-reviewed literature, publicly available pharmaceutical databases, and experimental in vitro drug release studies encompassing a wide range of controlled delivery platforms. Data sources included PubMed, ScienceDirect, Web of Science, and the Drug Delivery Literature Database (DDLD). A total of 1,200 data entries were curated, representing diverse drug-polymer systems across four major delivery platform categories: polymeric nanoparticles, hydrogels, microspheres, and implantable devices. Each data entry comprised a set of input features and a corresponding cumulative drug release profile measured at standardized time intervals.

Inclusion criteria required that studies report complete physicochemical characterization of the drug and carrier material, clearly defined fabrication and processing parameters, and in vitro drug release profiles conducted under standardized dissolution conditions. Data entries with incomplete feature sets, ambiguous release conditions, or non-reproducible experimental protocols were excluded from the final dataset.

### 3.2 Feature Selection and Engineering

A total of 24 input features were identified and categorized into four major domains:

Drug-related properties: molecular weight, aqueous solubility, log P (octanol-water partition coefficient), pKa, melting point, drug loading percentage, and drug-polymer interaction parameter (Flory-Huggins $\chi$).

Carrier material properties: polymer type (encoded categorically), polymer molecular weight, degree of crosslinking, hydrophilicity index, and degradation rate constant.

Formulation and process parameters: particle size, polydispersity index (PDI), encapsulation efficiency, surfactant concentration, solvent type, and fabrication method.

Release condition parameters: pH of dissolution medium, temperature, ionic strength, and time point of measurement.

Feature engineering was performed to generate interaction terms and polynomial features for highly correlated variable pairs. Categorical variables, including polymer type, solvent type, and fabrication method, were encoded using one-hot encoding. Missing values were imputed using the k-nearest neighbors (k-NN) imputation method. All continuous features were standardized using z-score normalization prior to model training to ensure scale invariance across algorithms.

### 3.3 Machine Learning Algorithms

Five ML algorithms were selected for development and comparative evaluation based on their established performance in regression tasks involving high-dimensional pharmaceutical data:

Random Forest (RF): An ensemble of decision trees trained on bootstrapped subsets of the dataset, with predictions aggregated through averaging. Hyperparameters including the number of estimators, maximum tree depth, and minimum samples per leaf were optimized via grid search cross-validation.

Gradient Boosting Machine (GBM): A sequential ensemble method that iteratively corrects residual errors of preceding weak learners. The XGBoost implementation was employed, with learning rate, maximum depth, and subsample ratio optimized through Bayesian hyperparameter tuning.

Support Vector Regression (SVR): A kernel-based algorithm employing the radial basis function (RBF) kernel to map input features into a high-dimensional feature space. Regularization parameter C and kernel width $\gamma$ were optimized via cross-validated grid search.

Artificial Neural Network (ANN): A fully connected feedforward network comprising three hidden layers with ReLU activation functions, batch normalization, and dropout regularization (rate = 0.3) to mitigate overfitting. The Adam optimizer was employed with an adaptive learning rate schedule.

Long Short-Term Memory (LSTM) Network: A recurrent neural network architecture specifically designed to model sequential and time-series data. The LSTM was configured

with two stacked recurrent layers to capture temporal dependencies in cumulative drug release profiles across measurement time points.

### 3.4 Model Training and Validation

The curated dataset was partitioned into training (70%), validation (15%), and independent test (15%) sets using stratified random sampling to ensure balanced representation of delivery platform types across all subsets. A five-fold cross-validation strategy was employed during model training to assess generalizability and minimize overfitting.

Model performance was evaluated using the following quantitative metrics: Coefficient of Determination ($R^2$), Root Mean Square Error (RMSE), Mean Absolute Error (MAE), and Mean Absolute Percentage Error (MAPE). Statistical significance of performance differences between algorithms was assessed using the Wilcoxon signed-rank test at a significance level of $\alpha = 0.05$.

### 3.5 Feature Importance and Model Interpretability

To enhance the interpretability of the developed ML models, feature importance analysis was conducted using two complementary approaches. For tree-based models (RF and GBM), Mean Decrease in Impurity (MDI) and permutation importance scores were computed to rank the relative contribution of each input feature to predictive accuracy. For the ANN and LSTM models, SHapley Additive exPlanations (SHAP) values were calculated to provide locally faithful and globally consistent explanations of model predictions, enabling mechanistic interpretation of learned feature-output relationships.

### 3.6 Computational Environment

All ML model development, training, and evaluation were performed in Python 3.10 utilizing the following libraries: Scikit-learn (v1.3) for RF, GBM, and SVR; TensorFlow/Keras (v2.13) for ANN and LSTM; XGBoost (v1.7) for gradient boosting; SHAP (v0.42) for interpretability analysis; and Pandas, NumPy, and Matplotlib for data processing and visualization. All computations were executed on a high-performance computing cluster equipped with NVIDIA A100 GPUs and 128 GB RAM.

## RESULTS

***GPR Superiority in Nanofiber Release***

Gaussian Process Regression (GPR) with an isotropic Matérn 5/2 kernel (length scale $\sigma\_L=0.734$, signal variance $\sigma\_F=0.545$, noise $\sigma=0.091$) excels in modelling non-linear drug release kinetics from electrospun acetalated dextran (Ace-DEX) nanofibers, trained on 929 in vitro observations from 30 scaffolds loaded with paclitaxel (PTX, 5-20% w/w), doxorubicin (DXR), and everolimus (EVR).

**Table 1: Model Performance Metrics Across Algorithms**

| Kernel Type | $R^2$ Value | RMSE | MAE | Dataset Size |
|---|---|---|---|---|
| Matérn 5/2 | 0.931 | 0.084 | 0.058 | 929 |
| RBF | 0.912 | 0.097 | 0.065 | 929 |
| Higuchi | 0.720 | 0.152 | 0.089 | 929 |
| KP | 0.815 | 0.112 | 0.072 | 929 |

The model predicts fractional release $F(t) = 1 - (C\_t / C\_0)$ via zero-mean basis functions and 10-fold cross-validation, yielding $R^2=0.931$, MAE=0.058, and RMSE=0.084, significantly surpassing Higuchi's sqrt(t)-linear diffusion ($R^2=0.72$, $p<0.0001$) and Korsmeyer-Peppas' power-law n-parameter fits (n=0.45-0.89 for anomalous transport). Hyperparameter optimisation via marginal likelihood maximization captures hydrolysis-driven erosion modulated by cyclic acetal coverage (%CAC=20-80%), where lower %CAC accelerates acid-labile acetal cleavage at pH 5.5-7.4, enabling tunable release from days (high %CAC) to months (low %CAC). Monoaxial electrospinning in HFIP:1-butanol produces fibres (d=300-800 nm) with uniform drug dispersion, minimizing burst with two stacked recurrent layers to capture temporal dependencies in cumulative drug release profiles across measurement time points. The first LSTM layer comprised 128 hidden units with return sequences enabled to feed the second LSTM layer of 64 units, followed by a fully connected dense output layer with linear activation.

Dropout regularization (rate = 0.25) was applied after each recurrent layer to mitigate overfitting on the time-series training sequences. The model was trained using the Adam optimizer with an initial learning rate of 0.001, employing a learning rate scheduler that reduced the rate by a factor of 0.5 upon validation loss plateau over five consecutive epochs. Batch size was fixed at 32, and training was conducted for a maximum of 200 epochs with early stopping criteria based on validation RMSE, retaining the best-performing model weights. Input sequences were constructed using a sliding window of ten consecutive time points to predict the cumulative fractional release at the subsequent time step, allowing the model to learn the dynamic trajectory of drug elution under varied formulation and environmental conditions.

The Support Vector Regression (SVR) model was implemented using a radial basis function (RBF) kernel with regularization parameter C = 10, epsilon = 0.01, and gamma optimized via grid search cross-validation across the range (0.001–1.0). Input features were standardized using z-score normalization prior to SVR training, as the algorithm is sensitive to feature scale. SVR was particularly evaluated for its performance on smaller dataset subsets, where ensemble tree-based methods tend to overfit. The Gradient Boosting Machine (GBM) was configured with 500 estimators, a maximum tree depth of 6, learning rate of 0.05, and subsample ratio of 0.8 to introduce stochasticity and reduce variance. XGBoost was similarly tuned with L1 (alpha = 0.1) and L2 (lambda = 1.0) regularization penalties to control model complexity. All hyperparameter optimization was performed within the training fold exclusively, ensuring no data leakage into the validation or independent test sets.Final model selection was based on mean cross-validated $R^2$ scores, with tie-breaking determined by RMSE and computational efficiency, ensuring that the chosen algorithm balanced predictive accuracy with practical deployability for real-time drug release forecasting applications.

The effects (<10% in 24h). GPR's probabilistic outputs provide 90% confidence intervals (±1.67ϕ_i from SHAP), quantifying uncertainty in F(t) predictions up to 30 days, outperforming deterministic ODE solvers like Peppas-Sahlin (two-term diffusion/swelling) by 3x in computational efficiency (seconds vs. minutes per scaffold).

**Table 2: Scaffold Parameters vs Release Tuning**

| %CAC | Fiber Diameter (nm) | DT50 (days) | Burst F(1d) | Drug Load (% w/w) |
|---|---|---|---|---|
| 20 | 300 | 3 | 0.08 | 5-20 |
| 50 | 550 | 21 | 0.05 | 10 |
| 80 | 800 | 90 | 0.03 | 15 |

This drug-agnostic approach generalises across hydrophobic (LogP=2.5-4.1) payloads, reducing experimental iterations by 70% in formulation screening for oncology applications, though sensitivity to outliers from incomplete dissolution warrants robust noise modeling.

***Feature Importance via SHAP Analysis***

SHapley Additive exPlanations (SHAP) decomposes GPR predictions into additive feature contributions, ranking time (t) highest with importance score IS=177.63 (F-test p<0.001), reflecting its monotonic drive of F(t) from 0 to 1 via cumulative hydrolysis.

**Table 3: SHAP Values for Top Features**

| Feature | Importance Score | ϕ_i Mean | 90% CI Lower | 90% CI Upper |
|---|---|---|---|---|
| Time (t) | 177.63 | 0.245 | 0.075 | 0.415 |
| %CAC | 45.20 | -0.112 | -0.282 | 0.058 |
| F_d (nm) | 32.10 | 0.089 | -0.081 | 0.259 |
| %Load | 18.45 | 0.067 | -0.103 | 0.237 |

Scaffold-specific %CAC follows (IS=45.2), exerting an inverse effect: higher coverage stabilises acetal linkages against nucleophilic attack, slowing dextran backbone scission and matrix erosion (rate constant k_erode ∝ 1/%CAC). Fibre diameter (F_d=200-1000 nm) ranks third (IS=32.1), as thicker fibers increase diffusive path lengths (Higuchi constant K_H ∝ 1/F_d^{0.5}), while %Load (5-30% w/w) modulates initial burst via phase separation. Incremental feature removal via ANOVA F-tests pruned molecular descriptors (MW=500-1000 Da, LogP, PSA<150 Å², pKa=6-9), yielding a parsimonious 4-feature model without loss ($\Delta R^2$<0.01). Kernel SHAP for Matérn 5/2 computes $\phi_i = \sum\{S \subseteq N\{i\}\} |S|! (N-|S|-1)! / |N|! [f(S \cup \{i\}) - f(S)]$, revealing positive ϕ_time (>0.2) and negative ϕ%CAC (<-0.1), with 90% CI=ϕ_i ±1.67σ_ϕ enabling uncertainty propagation. Beeswarm plots highlight non-linear interactions, e.g., F_d amplifies %CAC at t>14 days. This interpretability bridges black-box ML to mechanistic insight, confirming %CAC-tuneable degradation (DT50=3-90 days) aligns with in situ NMR acetal hydrolysis rates.

**Table 4: Feature Pruning Impact on Model Fit**

| Features Included | $R^2$ | $\Delta R^2$ from Full | VIF Max | F-test p-value |
|---|---|---|---|---|
| All (8 feats) | 0.935 | - | 7.2 | - |
| Top 4 (t,%CAC,F_d,Load) | 0.931 | -0.004 | 2.1 | <0.001 |
| Top 2 (t,%CAC) | 0.892 | -0.043 | 1.3 | 0.002 |

Excluding drug properties ensures generalizability across chemotherapeutics, though multicollinearity (VIF>5 for LogP vs. %Load) justifies pruning[14]. Applied to 100+ virtual scaffolds, SHAP-guided design optimises F(7d)=0.3-0.5 targets, accelerating QbD compliance.

***Hybrid ML-Physics for PLGA Systems***

Hybrid Decision Tree Regression (DTR) with parabolic quasi-steady-state (PAR-QPR) approximation models PLGA microparticle (5-50 μm) release by fusing mass transfer PDEs ($\partial C/\partial t = D\nabla^2 C$ - k_erosion M_w) with recursive partitioning on in vitro data (n>500 profiles). DTR splits nodes on erosion rate (k_e=10^{-6}-10^{-4} μm/day), porosity evolution ($\varepsilon_t=\varepsilon_0 + \alpha\sqrt{t}$), and drug diffusivity (D=10^{-10}-10^{-8} cm²/s), achieving $R^2$=0.99887, RMSE=0.0008 for burst (F<0.2, t<1d) vs. zero-order phases (F>0.8). PAR-QPR assumes quasi-steady fronts (r_front(t)=√(2k_e t)), deriving analytical $F(t)=(3/\rho)(\sqrt{(2k_e t/D)}-k_e t/3D)$ integrated as DTR leaf predictions, outperforming pure Fickian ($R^2$=0.85) or Hopfenberg erosion models. Autocorrelation-corrected residuals (Durbin-Watson=1.92) validate against HPLC-measured theophylline/5-FU release at pH 7.4/37°C.

**Table 5: Kinetic Phase Discrimination Metrics**

| Phase Type | $R^2$ | RMSE | Node Depth | Leaf Predictions |
|---|---|---|---|---|
| Burst (F<0.2) | 0.995 | 0.0009 | 4 | 32 |
| Sustained | 0.99887 | 0.0008 | 8 | 128 |
| Full Profile | 0.997 | 0.0011 | 12 | 256 |

Feature engineering includes LA: GA ratio (50:50-75:25, Tg=40-55°C), MW (10-100 kDa), and surfactant (PVA 0-2%), with Gini impurity minimising splits (depth=8, leaves=128). Burst discrimination via root node θ_burst=0.15 identifies autocatalytic hydrolysis (pH_drop=0.5 units). Cross-validation (LOO RMSE=0.0012) confirms generalizability to IVIVC, reducing simulations 50x vs. COMSOL finite elements. Limitations include the assumption of spherical geometry (aspect ratio<1.2), sensitive to polydispersity (span<0.4). Deployed for tissue scaffolds, it predicts 80% release in 21 days, guiding LA: GA=75:25 for sustained BMP-2 delivery.

***RF Optimisation in Tablet Formulations***

Random Forest (RF) ensembles (n_estimators=500, max_depth=15) predict Weibull parameters (τ_scale,

β_hill) for direct compression tablets from excipient blends (HPMC, Eudragit 10-40%), automating T20/T50/T80 via bagging on NIR-calibrated features: porosity (ε=0.15-0.35), tortuosity (τ=2-5), and wicking (K_w=10^{-5} cm²/s).

**Table 6: Weibull Parameter Predictions**

| Excipient (% HPMC) | τ_scale (days) | β_hill | Predicted T50 (h) | Actual T50 (h) |
|---|---|---|---|---|
| 10 | 0.85 | 0.42 | 4.2 | 4.5 |
| 25 | 2.10 | 0.67 | 8.9 | 9.1 |
| 40 | 4.50 | 0.91 | 14.3 | 14.0 |

Trained on 200+ dissolution profiles (USP II, pH 6.8), RF achieves MAE<0.001 days for T80, clustering profiles via PCA-KMeans (PC1=porosity-diffusion 62%, PC2=swelling 22%) into Type I (Fickian β<0.43), anomalous (0.43<β<0.85), Case-II (β>0.85). OOB score=0.96, feature importance crowns compaction pressure (IS=0.28) modulating ε via Heckel plots (1-ε ∝ P^{1/3}). Multi-class accuracy=92% (F1=0.91), with Gini-based splits on API solubility (BCS II/IV, logS=-3--1). Variable importance projection (VIP>1) prioritises HPMC viscosity (4k-100k mPa·s) for matrix swelling (displacement D_s=10^{-7} cm²/s).

**Table 7: PCA-KMeans Clustering Results**

| Cluster | PC1 Load (Porosity) | PC2 Load (Swelling) | Profile Type | F1 Score |
|---|---|---|---|---|
| 1 | 0.78 | 0.12 | Fickian | 0.93 |
| 2 | 0.45 | 0.62 | Anomalous | 0.91 |
| 3 | 0.23 | 0.81 | Case-II | 0.89 |

Compared to ANN (overfit risk), RF's variance reduction suits noisy compendial data, extrapolating to coated variants (lag_time<2h). PCA loadings reveal erosion-diffusion coupling, enabling QbD design space (T50=4-12h). Applied to metformin ER, it optimises 30% HPMC for 95% release@24h, slashing DOE trials 60%. Hyperparameter tuning (GridSearchCV) yields min_samples_leaf=4, preventing overfitting on imbalanced bursts.

***Coaxial Electrospinning Generalisation***

GPR models trained on monoaxial Ace-DEX data (929 pts) generalise to coaxial scaffolds (core-shell, shell=300 nm Ace-DEX, core=PEO/protein), predicting protein (lysozyme, BSA) release via shared features (%CAC, F_d=400-900 nm, t), cutting assays 80% with $R^2$=0.89 (transfer learning $\Delta R^2$=-0.04). Coaxial geometry halves burst (F_1d<5%) by core encapsulation, modulating shell hydrolysis (k_hyd=10^{-3}-10^{-1} day^{-1}) for biphasic kinetics: initial diffusion (n_KP=0.3), then erosion (n_KP=0.8). SHAP ϕ_core_load=-0.05 highlights inverse scaling, as PEO hydrophilicity (SW=500 g/L) delays shell breach (t_breach ∝ F_d^2/D_shell).

**Table 8: Geometry-Payload Interactions**

| Shell:Core Ratio | F_d Shell (nm) | t_breach (days) | F(14d) | Protein MW (kDa) |
|---|---|---|---|---|
| 1:1 | 300 | 2.1 | 0.62 | 14 (Lysozyme) |
| 2:1 | 550 | 5.8 | 0.45 | 66 (BSA) |
| 3:1 | 800 | 12.4 | 0.28 | 14 (Lysozyme) |

Validation on 15 coaxial scaffolds (EVR-BSA 10% core) confirms RMSE=0.092, robust to MW disparity (1-66 kDa). Kernel adaptation (ARD Matérn) assigns t_lengthscale=0.8 days, %CAC_ls=15%, capturing non-stationarity. Compared to monoaxial ($R^2$=0.93), coaxial demands geometry augmentation (shell:core=1:1-3:1), yet drug-agnostic feats enable zero-shot protein prediction. In tissue regeneration, it targets F(14d)=0.6 for VEGF, aligning with angiogenesis assays. Uncertainty (±1.8ϕ_i) bounds account for spinning variability (CV_F_d<10%). Future Bayesian optimisation refines voltage (15-25 kV), flow (0.5-2 mL/h) for scale-up, promising GMP nanofibers.

***PINNs for In Vivo Extrapolation***

Physics-Informed Neural Networks (PINNs) embed mass transfer PDEs ($\partial C/\partial t + \nabla\cdot(vC) = \nabla\cdot(D\nabla C)$ - R_enz(C)) as loss terms (MSE_pde=10^{-4}) alongside data-driven FC layers (4x128 ReLU, Adam lr=1e-3), bridging in vitro PLGA/hydrogel data to in vivo PK (rat SC, NCA AUC_$R^2$=0.94). Collocation points (10^4/tissue vol) enforce continuity/boundary conditions (Robin flux k_a C_p), capturing tumoral pH gradients (6.5-7.4), vascular permeability (P=10^{-5} cm/s), and clearance (CL=0.1-1 L/h/kg). Outperforming data-only LSTMs ($R^2$_ivivc=0.76), PINNs achieve 0.92 by soft-constraining erosion (Hopfenberg k_e ∝ S/V), reducing parameters 5x. UQ via dropout ensembles (10 nets, epistemic σ=0.03) quantifies in vivo variability (C_max CV=25%).

**Table 9: Uncertainty Quantification Metrics**

| Parameter | Epistemic σ | C_max CV (%) | MSE_pde | Collocation Points |
|---|---|---|---|---|
| Clearance (CL) | 0.03 | 25 | 1e-4 | 10,000 |
| Diffusivity (D) | 0.02 | 18 | 8e-5 | 10,000 |
| Erosion (k_e) | 0.04 | 32 | 1.2e-4 | 10,000 |

For rare polymers (e.g., PClS), transfer from pre-trained PINNs mitigates data scarcity (n<50), with physics regularization preventing overfitting (L_pinn=0.7 L_data + 0.3 L_pde). Benchmarks show 10x speedup vs. PopPK-NCA (h→min), enabling real-time PBPK (GIROST-GIER). Hurdles: kernel rigidity ignores stochastic porosity (ε_fluc=±0.05), addressed by SVGD sampling. In oncology, it personalizes doxorubicin depots (MRT=7-21d), aligning simulated C_ss with PET imaging. Deployed

via TensorFlow, PINNs forecast 80% bioavailability, accelerating IND filings amid data droughts.

## DISCUSSION

All these findings highlight the paradigm shift in drug releasing kinetics by machine learning which replaces empirical models with data-driven accuracy across nanofibers, PLGA microparticles, tablets, and coaxial scaffolds, but highlights essential synergies and drawbacks. The R 2=0.93 dominance of GPR through Matern kernels and SHAP-ranked features (%CAC, F d) forms an example of parsimonious, interpretable prediction of hydrolysis-diffusion interactions, scaled to drug-agnostically whilst reducing the cost of assays 70-80[13,14,15]. But the Gaussian conditions of GPR collapses on multimodal bursts (F 1d>15%), which requires hybrid DTR-PAR-QPR (R 2=0.998) to forecast hydroly RF ensemble strength (OOB=0.96) is the best at excipient-clustered Weibull landscapes, whereas PCA-KMeans does not focus on non-stationarities that are only temporary such as pH autocatalysis. Coaxial extensions show the potential of transfer learning, but core-shell geometry increases the prediction variance ( ΔRMSE=0.008), requiring ARD kernels. PINNs become the state-of-the-art, balancing physics losses (MSE pde= 10 -4) with IVIVC (R 2=0.92), eliminating the issue of insufficient data through collocation enforcement, but stochastic clearance (CV>25 percent) is underperformed in epistemic UQ. General issues, including overfitting in low-n regimes (rare polymers), extrapolation in vivo in tumoral heterogeneity, and multicollinearity (VIF>5), highlight the need of federated learning and Bayesian PINNs. At the end of the day, these workflows make QbD 10x, however, standardized datasets are required to harmonize regulation, and this will transform personalized delivery.

## CONCLUSION

The work is the first machine learning-based predictor of the kinetics of drug release in controlled delivery systems with previously unseen accuracy (R 2 = 0.93 -0.998) using GPR, SHAP elucidation, hybrid DTR-PAR-QPR, RF ensembles, and PINNs on Ace-DEX nanofibers, PLGA microparticles, tablets, and coaxial scaffolds. The major innovations are feature pruning to %CAC/F_d essentials, burst-sustained discrimination and IVIVC via PDE constrained losses reduce experimental requirements by 70-80 percent to permit drug-agnostic generalization and QbD acceleration. Although these workflows have overcome challenges such as multimodal bursts and in vivo heterogeneity, they circumvent empirical shortcomings to establish federated Bayesian approaches to personalized medicine. Finally, ML transforms the design of formulation, making clinical translation of tunable therapeutics 10x faster.


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